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TÍTULO SOLICITADO: "Composiciones de liberación dual de un inhibidor de ciclooxigenasa-2"

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SOLICITANTE: PHARMACIA CORPORATION

APODERADO: RAMIRO CASTRO DUQUE

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, con el propósito de coadyuvar en la negación de la solicitud colombiana QQ-097-644 en trámite y como sustentación al escrito de oposición presentado en abril 28 de 2004, ruego que se tenga en cuenta el documento anexo titulado "Concepto Técnico sobre Tamaño de Partícula de Fármaco y su Relación con la Biodisponibilidad y Bioequivalencia de los Medicamentos – Métodos para Reducir el Tamaño de los Fármacos" preparado por la Facultad de Ciencias – Departamento de Farmacia de la Universidad Nacional de Colombia, en donde se da cuenta del amplio conocimiento de la técnicas de reducción de partículas y de su extendido empleo en la industria farmacéutica, casi como un paso obligatorio en cualquier proceso de pre-formulación de fármacos, en especial si se está en presencia de principios activos poco solubles, o si se desea efectivamente mejorar su biodisponibilidad.

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Así mismo, muy respetuosamente solicito que la Superintendencia considere las tesis expuestas en el documento en cuestión, y los argumentos presentados oportunamente en el escrito de oposición, en la evaluación definitiva de la solicitud de patente en referencia

Señor Superintendente,



José Luis Reyes Villamizar
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Exp 00 097 644



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CONCEPTO TECNICO SOBRE:

**Tamaño de partícula de fármacos y su relación
con la Biodisponibilidad y la Bioequivalencia de
los Medicamentos**

**Métodos para reducir el tamaño de partícula de
fármacos**

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CAPITULO 1

CONTENIDO

- 1 Introducción Generalidades de las formas farmacéuticas sólidas características del tamaño, morfología y distribución de tamaño, definiciones no oficiales del tamaño de partícula, información de equipos utilizados en la determinación del tamaño y distribución de tamaño no oficiales en farmacopea tablas de catalogación del tamaño no oficiales en farmacopea, aspectos biofarmacéuticos de la solubilidad del fármaco en el agua**
- 2 Efecto de las Propiedades Fisicoquímicas del Fármaco sobre la Velocidad de Disolución**
Solubilidad del fármaco, formación de la sal, tamaño de partícula, efecto del tamaño de partícula sobre la solubilidad, estado cristalino del fármaco
Polimorfismo
- 3 Distribución del tamaño de partícula**
Representaciones de la forma de las partículas, tamaño y distribución, El problema del muestreo de sólidos en polvo, determinación por tamizado analítico, tabla comparativa de tamaños de partícula de varios materiales Análisis por tamizado
- 4, Determinación de las propiedades de los polvos en el laboratorio**
Análisis por tamizado, , método experimental, determinación de las propiedades de flujo, método experimental, densidad real, global y apisonada, tabla comparativa d los tamices con sus aperturas nominales, tabla de comparación de ISO 12013-1 para grados de polución con polvos

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FORMAS FARMACEUTICAS DE DOSIFICACIÓN SOLIDAS

Son sistemas unitarios de entrega del fármaco para administración oral y/o peroral.

Estos sistemas de entrega de fármacos comprenden tabletas, cápsulas, gránulos y ("sachets" ("Dry syrups")

VENTAJAS DE LOS SISTEMAS

- Constituyen la forma de dosificación más utilizada por
- a) la exactitud y flexibilidad en la dosificación del fármaco
 - b) constituyen la forma de dosificación más utilizada
 - c) mayor estabilidad física y química
 - d) permitir la versatilidad en su formulación facilitando el control de liberación del fármaco
 - e) permitir el control de las características organolépticas del fármaco
 - f) facilidad de administración
 - g) permitir su fabricación a gran escala reducen los costos de elaboración

DESVENTAJAS DE LOS SISTEMAS

- a) Problemas de biodisponibilidad causados por deficiencias en su formulación, en el empaque o en su almacenamiento
- b) Problemas de deglución y potencial efecto de la irritación de la mucosa gastrointestinal causado por algunos fármacos

CARACTERIZACION DEL TAMAÑO, MORFOLOGÍA Y DISTRIBUCIÓN DEL TAMAÑO DE PARTICULAS

Durante el desarrollo de un nuevo fármaco la caracterización de su estado sólido juega un papel importante en la selección de la forma química (ej. base libre o su sal), la forma física (estado cristalino), el tamaño de partícula y su morfología, la porosidad, la superficie específica y las demás propiedades físico químicas

La selección de las propiedades físicas del fármaco contribuyen al logro de la calidad biofarmacéutica en sus aspectos de biodisponibilidad y en el aseguramiento de la cinética de liberación requerida del fármaco. Además, las propiedades mencionadas, debe recordarse que en la formulación de un sistema de entrega del fármaco sólida unitaria, se requiere asegurar la uniformidad de contenido y la estabilidad del sistema de entrega

De acuerdo con el concepto del Doctor Harry G. Britan asesor de la USP y director del Centro de Física Farmacéutica en Milford N.J. el concepto de tamaño de partícula está íntimamente ligada a los aspectos de forma y morfología, porque el diámetro de partícula involucra los factores de forma. Si tenemos en cuenta esta afirmación, no es posible considerar el tamaño de una partícula o cualquiera distribución asociada con los tamaños de un conjunto de partículas sin la consideración primaria de las características tridimensionales de la partícula en sí. Esto obedece al tamaño de la partícula que se expresa en tanto en términos de dimensión lineal derivados de su forma o en términos de su superficie proyectada o su volumen. Como podrá apreciarse algunos métodos expresan el tamaño de partícula sin tener en cuenta el concepto de la forma y en su lugar lo expresan en términos de algún tipo de tamaño equivalente al esférico.

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Como ejemplo el diámetro de superficie es el diámetro correspondiente a una esfera que tiene la misma área superficial de la partícula y el diámetro de volumen se define como el volumen de una esfera que tiene el mismo volumen de la partícula,

La Farmacopea Americana en el capítulo (776) de Pruebas Generales, correspondiente a Microscopía óptica, define y describe los parámetros de forma de las partículas.

El tamaño de partícula constituye un aspecto importante en el desarrollo de un medicamento en forma sólida puesto que esta propiedad, constituye uno de los factores determinantes de su calidad biofarmacéutica de las formas sólidas unitarias para administración peroral
En la actualidad se dispone de muchos métodos para la determinación del tamaño de partículas y su distribución de tamaño

Desafortunadamente las farmacopeas no definen el tamaño de partícula denominado sub-tamiz y se limitan tan solo a presentar pruebas generales para la determinación del tamaño por el método de tamizado analítico. Este método oficial en las Farmacopeas tan solo permite catalogar partículas con un tamaño mínimo de 45 μm . Sin embargo, la edición 28 de la Farmacopea Americana en el capítulo (811) Para la determinación de la finura de los polvos, describe un método para determinar la finura de polvos sub-tamiz, por medio de la permeación de aire para tamaños comprendidos 0.2 y 50 μm .

La Farmacopea americana en capítulo (776) Microscopía Óptica establece que este sistema se aplica a tamaños de partícula comprendidos entre 0.5 y 100 μm .

Hasta la fecha ninguna de las farmacopeas tienen un capítulo dedicado a la determinación de la distribución del tamaño de partículas por medio de medidas de difracción con Laser
La única posibilidad que se tiene para la determinación de tamaños de partícula menores a 0.5 μm , es la utilización de la Norma ISO 13320 para análisis de la distribución de tamaño de partícula por difracción con Laser

Definiciones de tamaño de partícula no oficiales en las Farmacopeas

Micronización

Proceso de elevada energía para reducción de tamaño de partícula de fármacos por vía seca
Usualmente el tamaño de un fármaco micronizado comprende el rango de tamaño de 1 a 10 μm .
www.nektar.com/content/glossary

Partícula ULTRAFINA.

Partícula con un diámetro equivalente $< 0.1\mu\text{m}$ (ISO 14644-1)

Nanopartícula

Tamaño $< a 1\mu\text{m}$

Partículas portadoras (carriers) sólidas coloidales consistentes en compuestos macromoleculares cuyo tamaño varía entre 10 y 1000 nanómetros (nm)

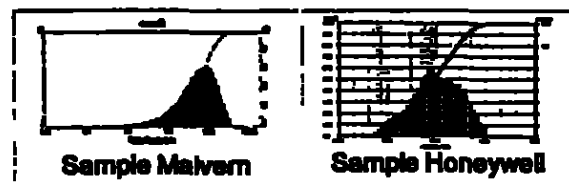
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Información sobre equipos no oficiales, utilizados en el control de tamaño y distribución de tamaño de partículas

LASER DIFFRACTION (Malvern MasterSizer and Honeywell X-100)

- Highly reproducible analysis covering a broad size range: 0.05 μm – 900 μm
- Widely utilized in many industries for quality control and development
- Analyzes in various carrier fluids as well as dry powders and aerosols

SAMPLE LASER DIFFRACTION

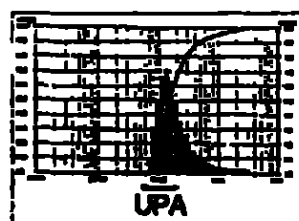


ULTRAFINE PARTICLE ANALYZER (UPA)

by Honeywell

- High-resolution sub-micron analyzer with a dynamic range of 3 μm s to 6.5 μm s
- Designed to analyze a wide range of particle concentrations
- Effectively measures most types of distributions (narrow, broad, monomodal, multimodal, etc.)

SAMPLE UPA



PHOTON CORRELATION SPECTROSCOPY (PCS)

via Nicomp C370

- Sub-micron particle size analyzer with a range of 3 μm s to approximately 2 μm s
- Classic technology within dye/pigment, emulsion, and protein industries

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AERODYNAMIC PARTICLE SIZE (Aerosizer and BAHCO)

Aerosizer (by TSI)

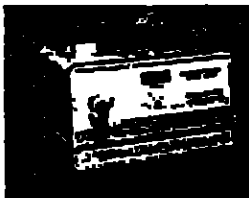
Aerodynamically measures particle size with a manufacturer's specified range of 0.1 μm -- 700 μm

Works well with very small amounts of sample

➔ Built-in auto-dispersing unit promotes full and reproducible dispersions for all dry powders

⊙ Data results reported in Number, Mass, Area, and Time of Flight formats on either aerodynamic or equivalent spherical diameter basis.

Nicomp 380/DLS Sub-micron Particle Sizer



The basic Nicomp 380 uses the principle of dynamic light scattering to measure the particle size distribution. It is the only dynamic light scattering instrument designed using a modular approach. The size range is 0.01 -- 5 μm .

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Catalogacion no oficial de tamaño de partículas

The American Institute of Chemical Engineers

Designation	Number of particles	Number per gram	Approximate size
Coarse	>100,000	>100	-
Medium Coarse	10,000	10	2
Medium fine	1,000	1	18
Fine	100	0.1	150
Superfine	25	0.025	500
Ultrafine	10	0.010	1,250
Colloid	5	0.005	2,500

EJEMPLO DE APERTURA DE TAMICES

STD ISO	STD US	STD TYLER
150µm	No 100	100 mesh
125µm	No 120	115 mesh
106µm	No 140	150 mesh
90µm	No 170	170 mesh
75µm	No 200	200 mesh
63µm	No 230	250 mesh
53µm	No 270	270 mesh
45µm	No 325	325 mesh
38µm	No 400	400 mesh
32µm	No 450	450 mesh
25µm	No 500	500 mesh
20µm	No 635	635 mesh

LA SOLUBILIDAD ACUOSA DEL FARMACO COMO FACTOR DETERMINANTE DE SU BIODISPONIBILIDAD

La solubilidad acuosa del fármaco desempeña un papel muy importante en el diseño y formulación de los medicamentos. El profesor Henning G. Kristensen del Departamento de Farmacia de la Escuela Real de Farmacia de Copenhague afirma que los fármacos utilizados en medicamentos para uso peroral deben tener una solubilidad en el agua superior a 10 mg/mL en el rango de pH comprendido entre 1 y 7, pues de lo contrario, se pueden presentar problemas en su absorción.

La solubilidad acuosa de un fármaco menor de 1 mg/mL presentará una velocidad de disolución limitada por cuanto la solubilidad y la velocidad de disolución están interrelacionadas.

Según el profesor Kristensen, más del 40% de los nuevos fármacos aprobados en la Farmacopea Europea entre los años 1992 y 1995 presentan solubilidades menores a 1 mg/mL y el 32% tienen una solubilidad menor al 0.1 %.

El planteamiento del Profesor Kristensen coincide con las opiniones de entidades por investigadores de laboratorios farmacéuticos norteamericanos como el Dr. Hauss de Eli Lilly.

Comenta el Dr. Hauss que cerca de la mitad de los nuevos fármacos obtenidos por Química Combinatoria tienen una muy reducida solubilidad en el agua.

Los químicos farmacéuticos de Investigación y Desarrollo de nuestra industria farmacéutica están de acuerdo en la afirmación que se plantea: más de un tercio de los fármacos listados en la USP 26 podrían catalogarse en la categoría de insolubles o muy poco solubles en el agua.

ALTERNATIVAS PARA CONTRARRESTAR EL PROBLEMA TECNOLÓGICO

Históricamente fue en la década de los años 60 que se planteó que cuando la solubilidad de un fármaco era inferior a 1 mg/mL, el tamaño de partícula (o área efectiva de superficie), representaba un factor importante a considerar para asegurar la biodisponibilidad del mismo.

Cabe anotar que con anterioridad a la década de los 60 J.G. Rhemold y colaboradores en 1945 observaron niveles plasmáticos más elevados con una suspensión de sulfadiazina micronizada (tamaño 1 a 3 μ m) que aquella que se venía utilizando con macrocristales del fármaco.

Con la unificación de las ciencias biofarmacéuticas en la década de los años 60 se establece la importancia que tiene la relación entre las propiedades fisicoquímicas de un fármaco en una forma de dosificación y la respuesta terapéutica observada después de su administración.

Si bien la micronización del fármaco solucionó parcialmente el problema de biodisponibilidad de fármaco de baja solubilidad, también causó problemas en formas unitarias de administración sólidas por fenómenos de aglomeración, problemas de carga estática con la consecuente segregación de las mezclas sólidas.

Se trabajó también en sistemas de administración líquida utilizando alcohol y/o propilenglicol para solubilizar el fármaco, el cual precipitaría en partículas micronizadas a nivel gástrico, al diluirse con los fluidos biológicos.

Otro sistema utilizado para subdivisión de fármacos poco solubles en agua y que tiene vigencia, lo constituyen las llamadas dispersiones sólidas cuya clasificación corresponde a:

- Mezclas eutécticas amplas
- Soluciones sólidas
- Soluciones y suspensiones vitreas
- Precipitaciones amorfas en un portador cristalino
- Formación de complejos
- Asociaciones entre algunas de las anteriores

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En la actualidad los métodos disponibles para incrementar la velocidad de disolución de fármacos de baja solubilidad en el agua corresponden a:

- Incremento del área superficial
- Formación de complejos con excipientes
- Solubilización utilizando tensioactivos
- Cambio de la forma cristalina por precipitación con polímeros hidrofílicos
- Formulaciones lipofílicas
- Preparación de dispersiones sólidas
- Formación de sales de ácidos y bases débiles
- Utilización de profármacos
- Nanoestructuración del fármaco por tecnología criogénica
- Comacronización fármaco - tensioactivo

Effect of the Physicochemical Properties of the Drug on Dissolution Rate

Factors that affect the dissolution rate of dosage forms can be classified under three main categories; first, factors relating to the physicochemical properties of the drug; second, factors relating to the dosage form, and third, factors relating to the dissolution apparatus and the test parameters. The physicochemical properties of the drug substance that affect its dissolution rate include solubility, particle size and crystalline state such as polymorphism, state of hydration, solvation and complexation

Other physical properties such as density, viscosity and wettability contribute to the general dissolution problems of flocculation, flotation and agglomeration. Adsorption characteristics of the drug have also been found to have a significant effect on the dissolution of certain drugs

Drug Solubility

Solubility of the drug substance plays a prime role in controlling its dissolution from the dosage form. According to the modified Noyes and Whitney equation

$$R = \frac{dc}{dt} = k \frac{DS}{sh} (c_s - c_t) = k_1 (c_s - c_t) \quad (4-1)$$

and, under sink condition

$$R = \frac{dc}{dt} = k_2 c_s \quad (4-2)$$

The above equations show that the aqueous solubility of the drug (c_s) is the major factor that determines its dissolution rate. According to Eq 4-2 a plot of R , the dissolution rate, vs c_s should yield a straight line which passes through the origin and has a slope equal to k_2 .

Hamlin, *et al.*,¹ studied 45 compounds representing many different chemical class

es and a wide range of solubilities to demonstrate that the initial dissolution rates of these substances directly are proportional to their respective solubilities. Under their experimental conditions, the authors found that, $R = 2.24c_s$. Using this empirical relationship it was suggested that it is possible to predict the approximate initial rates of dissolution of a broad range of compounds when their solubility values are known. Furthermore, the solubility data may be used as a rough predictor of the likelihood of any future problems with bioavailability. For example, it has been advocated² that a minimum aqueous solubility of 1% is required to avoid potential solubility-limited absorption problems. Parrott, *et al.*,³ investigated the effect of solubility of benzoic acid on its dissolution rate from compressed tablets. Figure 4-1 shows that the dissolu-

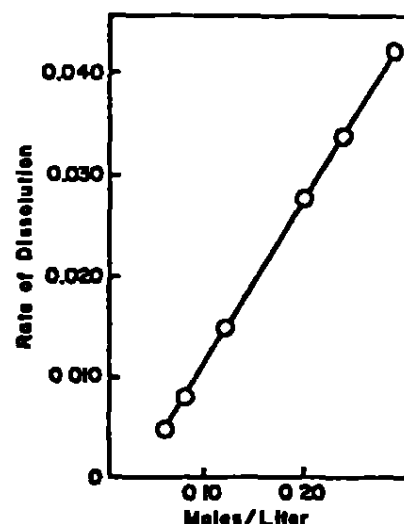


Fig 4-1 Influence of the solubility of benzoic acid on the dissolution rate in sodium sulfate solutions [Reproduced from Parrott, *et al.*, *J Pharm Sci*, 44, 269 (1955)]

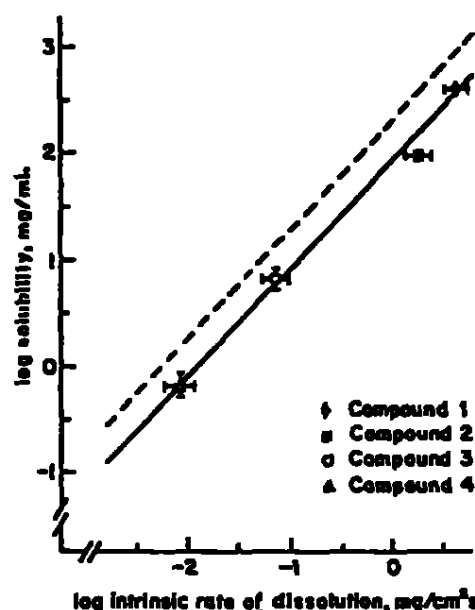


Fig 4-2. Correlation between solubilities and intrinsic rates of dissolution at infinite rotation speed. --- centric disk — vertical disk. [Reproduced from Nicklasson, *et al*, *Acta Pharm Suec*, 15, 25 (1982).]

tion rate of the acid was dependent linearly upon the solubility of the acid in the particular solvent as would be expected theoretically from Eq 4.2. Later findings by Nelson and Shah⁴ and Nicklasson, *et al*,^{3,5} confirmed the close association between the intrinsic dissolution rate of the drug and its solubility. Figure 4-2 shows a log log plot of the solubilities of several drugs vs their corresponding intrinsic rates of dissolution at infinite rotation speed. It is evident from the graph that compounds with high solubilities exhibit significantly higher dissolution rates.

Solubilities of drug compounds in various aqueous/organic solvent systems also have been of interest in dissolution studies especially during the preformulation stage. Discussion rates of cholesterol have been shown to be proportional directly to the measured solubilities in organic solvents. Nicklasson and Brodin³ suggested that for very poorly soluble drugs it might be preferable to use solvent mixtures during the

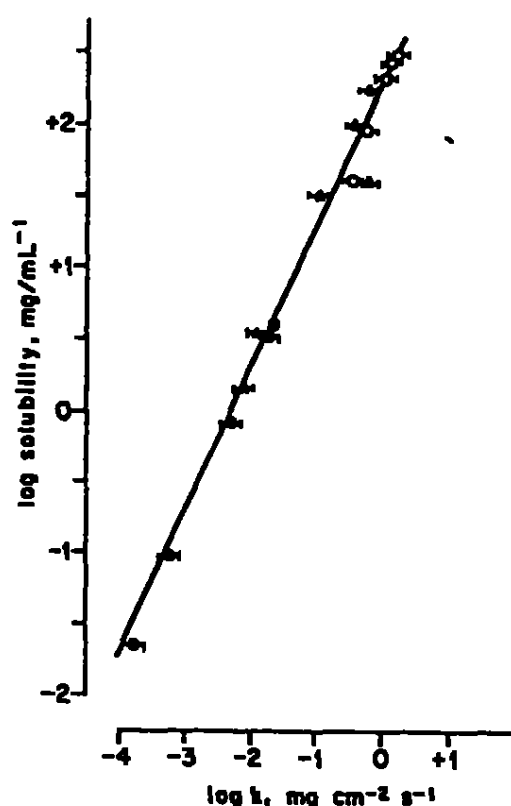
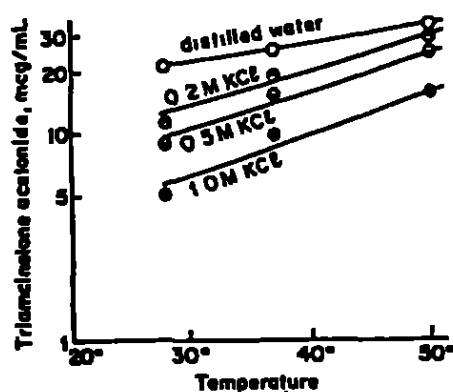


Fig 4-3 Relationship between solubility and intrinsic rate of dissolution for different substances in the water-ethanol binary system. The symbol with in parenthesis denotes the solubility data obtained for dextropropoxyphene napsylate in ethanol after 20 hr [Reproduced from Nicklasson, and Brodin *Int J Pharm*, 18, 149 (1984)]

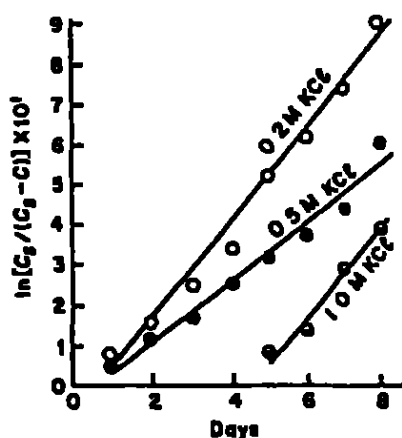
Key: O alaproclate hydrochloride; Δ dextropropoxyphene napsylate; ● oxazepam.

early formulation stage of new drug candidates, instead of increasing the aqueous sink volume. The authors studied the solubilities and intrinsic dissolution rates for alaproclate hydrochloride, oxazepam and dextropropoxyphene napsylate in binary mixtures of water and ethanol. Figure 4.3 shows that a log log plot exhibits a linear relationship between the solubilities and the corresponding intrinsic dissolution rates with a slope of 1.0.

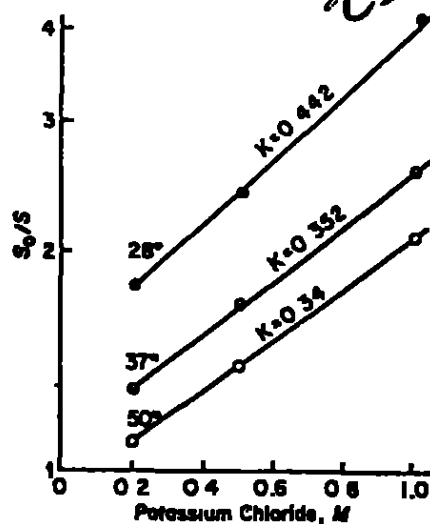
Investigation of the effect of neutral ionic and nonionic compounds on the solubility and dissolution rates of drugs have also been conducted. Parrott *et al*,³ observed



a



b



c

Fig 4-4. a. Solubility of triamcinolone acetonide in dissolution media containing potassium chloride as a function of temperature b. Triamcinolone acetonide dissolution in potassium chloride solutions at speed 7 (308 rpm) and 28° plotted in accordance with the integrated form of the modified Noyes-Whitney equation c. Setchenow plots for triamcinolone acetonide in potassium chloride solutions [Reproduced from Block and Patel, *J Pharm Sci*, 62, 617 (1973).]

that the dissolution rate of benzoic acid decreased when various concentrations of sodium chloride, sodium sulfate and dextrose were added to the dissolution medium. Sodium chloride was noticed to have the least effect, and sodium sulfate the greatest effect on decreasing the dissolution rate. Addition of urea, on the other hand, enhanced the dissolution of benzoic acid, probably because of complex formation. The effect of sodium chloride on the solubility and dissolution rate of triamcinolone acetonide was investigated by Block and Patel.⁹ The authors confirmed Parrott's finding as they noted a marked decrease in both solubility and dissolution rate of the drug in potassium chloride solutions (Figs 4-4a and 4-4b).

"Salting out" coefficients were calculated using the empirical Setchenow equation^{10,11} for the effect of an electrolyte on the solubility of a nonelectrolyte

$$\log S_0/S = kc \quad (4-3)$$

where S_0 is the solubility of the nonelectrolyte in pure solvent, S is the solubility of the nonelectrolyte in the electrolyte solution of a given molar concentration c , and k is the salting-out coefficient. Setchenow plots of the solubility data are shown in Fig 4-4c, along with the respective slopes (k values) for each system. The values ranged from 0.3–0.4 which significantly are higher than those previously reported¹² for other nonelectrolytes such as diacetone alcohol (0.03–

0.14), mesityl oxide (0.02–0.18) and certain barbiturates¹³ (0.04–0.21). The salting out effect, however, tends to decrease at higher temperatures.

Salt Formation

Salt formation is one of the most common approaches used to increase drug solubility and dissolution rate.^{14–19} Higuchi, *et al.*,¹⁴ reported increased dissolution rates for benzoic acid when certain bases and buffers were added to the aqueous solvent. Nelson¹⁷ studied the dissolution rates of several weak acids and their sodium salts in aqueous solutions having pH values corresponding to those of the gastrointestinal fluids. In all cases, the dissolution rates of the salts were greater than those of the free acids.

It should be pointed out, however, that after attaining a certain value of base strength, the dissolution rates of solid weak acids become essentially independent of the base concentration. Instead, it becomes a linear function of the product of the base concentration and the base diffusion coefficient. Higuchi^{18,19} showed that in most cases the diffusion controlled dissolution behavior of monophasic solids in reactive media may be predicted by knowledge of the appropriate solubility equilibrium and the effective diffusion coefficients of the species in solution (the diffusion coefficients for most drugs of similar density would not expect to vary greatly²⁰ since the diffusion coefficients vary approximately as the cube root of the molecular weight, according to the Stokes-Einstein equation).

For situations involving more than one phase,^{18–19} such as when dissolving disks exhibit simultaneous surface deposition of new phases, the problem becomes complex. In these cases, Higuchi¹⁹ showed that there appeared to be two kinds of dissolution behavior for the sodium salt. When the buffer concentration was high and the pH was low an acid coat may form after a brief period and the dissolution rate becomes similar to that of the acid phase itself. In Fig 4.5a, the solubility results for tolazamide acid in

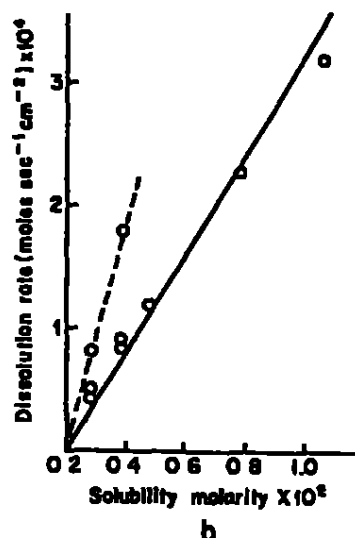
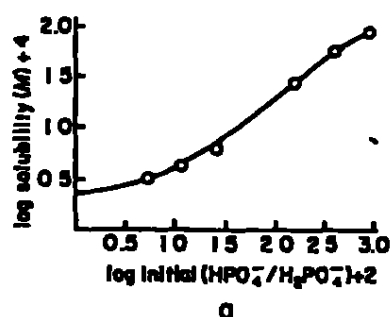
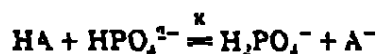


Fig 4-5. a: Solubility of tolazamide acid at 30°C as a function of the buffer salt-to-acid ratio. Total buffer concentration is 0.10M. Smooth curve is theoretical curve based on $(HA)_0 = 2.1 \times 10^{-4}M$ and $K = 9.0$. b: The dissolution rates of tolazamide acid (circles on solid line) as a function of the total solubility C_s . The dissolution rates of sodium tolazamide in the same buffer following surface conversion to the acid are given by the circles on the broken line. [Reproduced from Higuchi, *et al.*, *J Pharm Sci*, 54, 8 (1965).]

phosphate buffers are presented as a function of the initial $(HPO_4^{2-})/(H_2PO_4^-)$ ratio. The smooth curve is theory based where $(HA)_0$ is the solution concentration of the unionized tolazamide acid in equilibrium with the solid and K is defined by the equation



In Fig 4.5b the dissolution rates of sodium tolazamide in 0.1M and 0.2M phosphate

buffers are plotted as a dashed line and compared with the data from the tolazamide acid experiments. These values were within a factor of 2 of the rates for tolazamide acid. Thus, the coat which formed over the sodium salt phase must have been relatively impermeable to diffusion, and to some extent, it must have been "self-healing" as it dissolved away.

Higuchi¹⁹ reported another kind of behavior which occurred in the intermediate region, when the impermeable coat of the redeposited acid on the disk surface dissolved and dissolution appeared to occur simultaneously from both phases and flaking became noticeable. Finholt and Solvang²¹ noticed that initially the same high drug concentration was obtained for both the sodium salt and free acid of phenobarbital in tablets using 0.1N HCl and diluted human gastric juice. However, the precipitation of the free acid in excess of solubility took place at a much slower rate in gastric juice than in HCl acid, probably because of the presence of surfactants.

The preceding results have a large bearing on the question of the relative availability of solid acidic drugs and their more soluble sodium salts. It has always been assumed that the sodium salts dissolve faster than their corresponding insoluble acids and consequently became the preferred choice for drug formulators to assure bioavailability. This may be the case for several drugs,¹⁷ e.g., sodium and potassium salts of penicillin G, sodium salts of sulfa drugs, phenytoin and barbituates, however, on many occasions, the reverse was found to be true. That is, the dissolution of the sodium salt was slower than that of the weak acid. In a comparative study of the dissolution rates of phenobarbital and its sodium salt, Solvang and Finholt²² found that the rate of dissolution of the sodium salt was consistently less than the acid form both in 0.1N HCl and diluted human gastric juice. The wet granulation and compression processes decreased the dissolution rate of the pure sodium salt, while they increased that of

phenobarbital acid. The increase, in the case of the acid form, was more pronounced in diluted gastric juice than in 0.1N HCl, mainly because of the lower surface tension of the gastric juice and therefore its better wettability and solvent penetration characteristics. The reason for the lower tablet dissolution rate of the freely soluble sodium phenobarbital, as compared to the tablets of the poorly soluble acid form, was the result of the difference in disintegration time. Although the sodium salt tablets disintegrated rapidly in water, they did not disintegrate in the acidic media; instead, they swelled and dissolved slowly from the surface. The phenobarbital acid tablets, however, disintegrated very rapidly in acidic media as well as in water.

Solvang and Finholt tried dry granulation (or direct compression) in order to increase the dissolution rate of the sodium phenobarbital tablets in the acidic media, but no improvement over the wet granulation procedure was observed. The situation is similar for weak base drugs. Strong acid salts, such as the hydrochlorides and sulfates, are the most common forms used for weak bases such as epinephrine, tetracycline and alkaloidal bases due to their high solubility. However, Miyazaki, *et al.*,²³ confirmed that the free bases of chlortetracycline, demethylchlortetracycline and methacycline were more soluble than the corresponding hydrochloride salts at the gastric pH values, due to the common ion suppression of the solubility product equilibrium. Furthermore, the free bases of chlortetracycline and methacycline, yielded higher drug levels in the body fluids of rats and humans than the hydrochloride salt, indicating better bioavailability.²⁴

The suppression action of the common ion effect on solubility and dissolution rate was also demonstrated²⁵ for papaverine HCl. Using an acetate buffer, the solubility of the salt increased with decrease in pH as is normally expected for weak bases. However, when a HCl sodium acetate buffer was employed, a solubility maximum was ob-

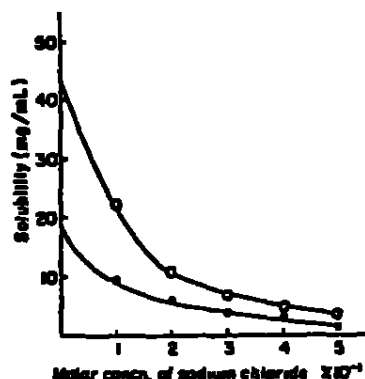


Fig 4-6a. Effect of sodium chloride concentration on the aqueous solubility of papaverine-HCl at 37°C. [Reproduced from Miyazaki, et al, *Chem Pharm Bull* 29 3414 (1981)]

Key: —○—, water —●— 0.1N HCl

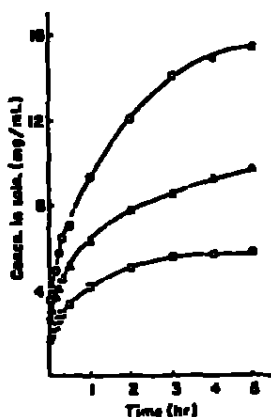


Fig 4-6b. Dissolution behavior of papaverine-HCl in 0.1N HCl at 37°C in the presence and absence of sodium chloride [Reproduced from Miyazaki et al, *Chem Pharm Bull*, 29 3414 (1981)]

Key: —○—, 0.1N HCl —▲—, 0.5% NaCl in 0.1N HCl —□—, 0.9% NaCl in 0.1N HCl

tained at pH 3.7. Similarly, the dissolution rates of the free bases of papaverine, trihexphenidyl, and isoxsuprine were much higher than the hydrochloride salts at the pH range of the stomach (pH 1.0–1.4).

Miyazaki, et al.²⁵ confirmed the inhibitory action of the chloride ion on the solubility and dissolution rate of papaverine HCl not only *in vitro* (using a medium rich in chloride ion) but also *in vivo*. When the drug was administered to rats with 0.9% NaCl it resulted in a decrease in the drug

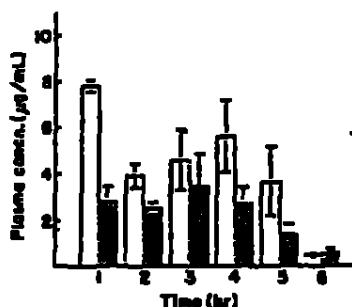


Fig 4-6c. Effect of chloride ion on the plasma drug levels following oral administration of papaverine-HCl suspensions to rats. [Reproduced from Miyazaki, et al, *Chem Pharm Bull*, 29 3414 (1981).]

Key: □ water ■ 0.9% NaCl

blood level from that obtained when the drug was administered alone. The authors interestingly suggested that it may be possible to formulate sustained release preparations of papaverine HCl by combination with NaCl (Figs. 4-6a, 4-6b, and 4-6c). The common ion effect was also demonstrated²⁷ for other amine hydrochloride salts such as phenazopyridine HCl, cyproheptadine HCl, and bromhexine HCl. These findings are of extreme importance for the research pharmacist who has to decide which form of the active ingredient to use in formulating a new drug.

Concerns over slow dissolution and poor bioavailability traditionally have been limited to the sparingly soluble free acids. According to the above discussion, the concerns should be extended equally to the freely soluble salts as well. This also points to the importance of selecting the proper dissolution medium, if a meaningful *in vitro/in vivo* comparison is sought.

Particle Size

Equation 4-1 shows a direct relationship between the surface area of the drug and its dissolution rate. Since the surface area increases with decreasing particle size, higher dissolution rates may be achieved through reduction of the particle size. Under sink conditions, according to Eq. 4-2, a plot of dissolution rate vs time should give a straight line with a slope of k . However,

given various samples of the same drug with different particle sizes, the number of drug particles and hence the surface area would differ. This in turn results in a difference in the dissolution rate constant k . Consequently, Wagner²⁸ related the apparent first order kinetics under sink conditions to the fact that a percent dissolved value at time t may be equivalent to the percent surface area generated at the same time, i.e., the first order kinetics actually is not due to dissolution *per se*, but rather to the distribution of the available surface area, which is dependent on the drug particle size.

The effect of particle size has been demonstrated by the superior dissolution rate and higher absorption efficiency observed after micronization, as opposed to the regularly milled form, of certain sparingly soluble drugs such as griseofulvin,²⁹⁻³² chloramphenicol³³ and various salts of tetracycline.³⁴ Review articles on the effect of particle size on drug availability have been published by Levy³⁵ and Fincher.³⁶

Reliable investigation of the particle size effect on the dissolution of sparingly soluble drugs has, on many occasions, been hindered by the problems of flotation and flocculation. Finholt, *et al.*,^{37,38} could not differentiate dissolution rates of different particle size acetylsalicylic powders in 0.1N HCl containing 0.2% polyacrylate 80. Lin, *et al.*,³⁹ also encountered similar problems in their attempt to establish a rank order in the dissolution rates of different particle size powders.

Ismat Ullah and Cadwallader⁴⁰ designed a special dissolution apparatus to overcome these problems and were able to establish a rank order for *in vitro* dissolution times of different particle size salicylic acid powders (Fig 4-7a). In studying the effect of particle size reduction on the dissolution rate of griseofulvin, Ismat Ullah and Cadwallader⁴¹ reported that the presence of a sink phase (e.g., organic solvent) and the introduction of samples in the form of suspensions were necessary to obtain appropriate rank order in the dissolution rates of mi-

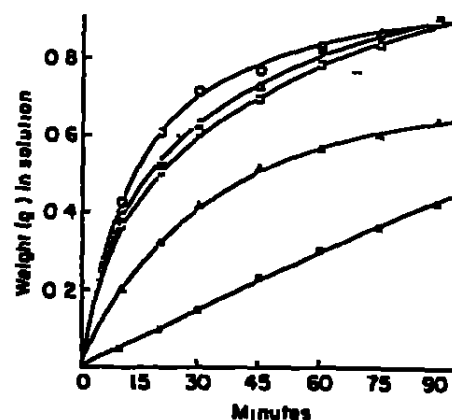


Fig 4-7a. Effect of particle size on dissolution of salicylic acid under sink conditions using four propellers at 30 rpm and 37°C [Reproduced from Ismat Ullah and Cadwallader *J Pharm Sci*, 59, 979 (1970)]

Key: O 200/230 mesh; Δ 120/140 mesh; □ 80/80 mesh; ▲ 40/60 mesh; ■ 20/30 mesh.

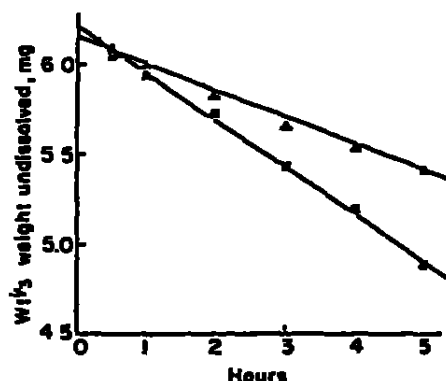


Fig 4-7b. Plots of $Wt^{1/3}$ vs time [Reproduced from Ismat Ullah and Cadwallader *J Pharm Sci*, 60, 230 (1971).]

Key: Δ regular milled griseofulvin powder; ■ micronized griseofulvin powder

cronized and regularly milled powders. The authors were able to plot their data, according to a modified Hixson and Crowell cube root law in order to obtain dissolution rate constants for two different particle size griseofulvin powders (Fig 4-7b). Regarding the effect of particle size on the dissolution of granules and tablets, Finholt, *et al.*,³⁷ showed that a rank order can be established for the dissolution rates of phenobarbital granules manufactured from different size powders (Fig 4-8a). Similarly, Solvang and

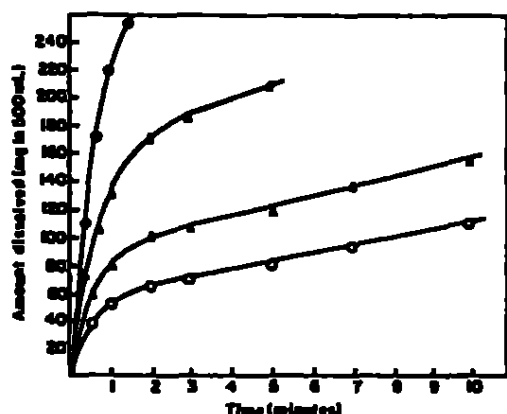


Fig 4-8a. Effect of particle size of phenobarbital on dissolution rate of the drug from granules. [Reproduced from Finholt, *et al*, *Medd Norsk Farm Selsk*, 28, 17 (1968)]

Key: $\circ$ particle size, 0.07-0.15 mm; Δ particle size, 0.15-0.25 mm; $\triangle$ particle size, 0.25-0.42 mm; $\square$ particle size, 0.42-0.71 mm.

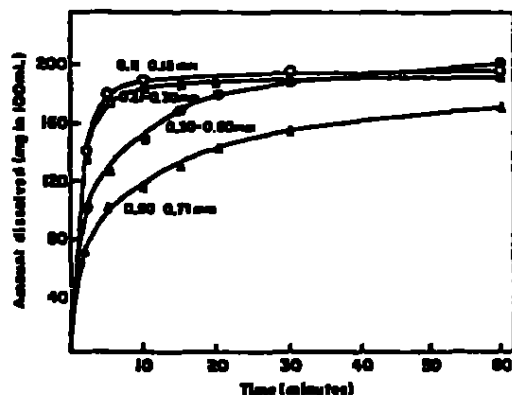


Fig 4-8b. Effect of particle size of phenobarbital on dissolution rate of the drug from tablets, in diluted gastric juice (surface tension 40.5 dynes cm^{-1} pH 1.50). [Reproduced from Solvang and Finholt, *J Pharm Sci*, 59, 51 (1970)]

Finholt⁴² demonstrated the same pattern for phenobarbital tablets (Fig 4-8b) Tuladhar, *et al*,⁴³ however, pointed out that control of particle size of the drug substance may not be sufficient to control the dissolution rate of the drug from tablets if particle bonding or crushing of the drug occurs during the tableting process

In addition, it has been found that micronization of sparingly soluble drugs to reduce particle size, is by no means a guaran-

tee of better dissolution and bioavailability. Micronization of hydrophobic powders, as Finholt³⁷ found, can lead to aggregation and flotation when the powder is dispersed in the dissolution medium. Lötter, *et al*,⁴⁴ also found that for drugs that are more hydrophobic than the ones studied by Finholt, larger aggregates and clusters of particles can exist even in the drug powder before compression. Furthermore, these clusters or aggregates are not dispersed easily in the dissolution medium as they tend to float to the surface or settle to the bottom. As a result, widely divergent data for the same drug may be obtained between different studies and within the same study. It should be recognized, therefore, that the mere increase in the surface area of a drug does not always guarantee an equivalent increase in dissolution rate. Rather, it is the increase in the "effective" surface area, or the area exposed to the dissolution medium, and not the absolute surface area that is directly proportional to the dissolution rate. Finholt, *et al*,³⁷ raised this point after he demonstrated that the dissolution rate of aspirin, phenobarbital and phenacetin powders actually decreased after reduction of their particle sizes. This was explained by the fact that because these drugs have hydrophobic surfaces, they tend to adsorb air at the surface and inhibit their wettability. Increase in the surface area causes a parallel increase of the air adsorbed and a decrease in the surface area available to the dissolution medium and, therefore, the dissolution rate decreases. This inhibitive effect, however, could be eliminated by evacuating the surface of the tablets from all adsorbed air as Wurster and Seitz⁴⁵ have shown, or by adding a trace amount of a surfactant to the dissolution medium, which does exactly the same as the evacuation process by lowering the interfacial barrier³⁷ (Fig 4 9a). In the case of granules or tablets made from these drugs, however, Finholt³⁷ showed that the reduction in the particle size of the drug generally causes a significant increase in the dissolution rate (Figs 4 9b and 4 9c). This

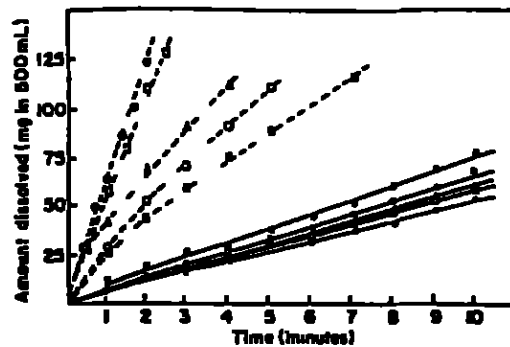


Fig 4-8a. Effect of particle size on rate of dissolution of phenacetin [Reproduced from Finholt, et al, *Medd Norsk Farm Selsk* 28, 17 (1966).]

Key: ○ particle size, 0.11–0.15 mm; □ particle size, 0.15–0.21 mm; ▲ particle size, 0.21–0.30 mm; ◇ particle size, 0.30–0.50 mm; ⊗ particle size, 0.50–0.71 mm; — dissolution medium, 0.1N HCl; - - - dissolution medium, 0.1N HCl containing 0.2% Tween 80

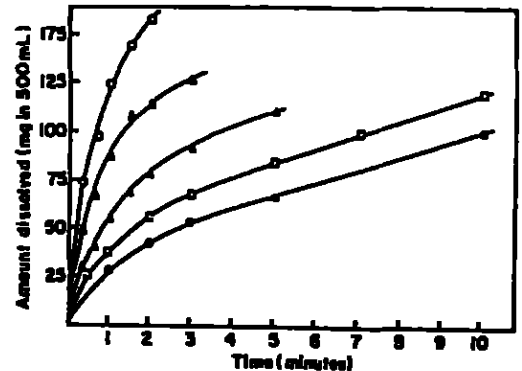


Fig 4-8b. Effect of particle size of phenacetin on dissolution rate of the drug from granules [Reproduced from Finholt, et al, *Medd Norsk Farm Selsk* 28, 17 (1966).]

Key: ○ particle size, 0.11–0.15 mm; ▲ particle size, 0.15–0.21 mm; △ particle size, 0.21–0.30 mm; □ particle size, 0.30–0.50 mm; ⊗ particle size, 0.50–0.71 mm.

was explained by the suggestion that mixing of the drug with the usual hydrophilic diluents and with subsequent granulation, makes the surface of these hydrophobic drugs more hydrophilic. *In vivo* conditions also exhibit excellent wetting properties due to the presence of natural surfactants, such as the bile salts, and thus allows the increase in the effective surface area with particle size reduction of the drug. Finholt's³⁷ findings agreed with previously published data by Kornblum and Hirschhorn⁴⁶ who compared the dissolution rates at pH 1.2 of a spray-dried and air-attritioned quinaolinone compounds. The authors found that the air-attritioned powder with particle size of 1–5 μ m, dissolved more slowly than the spray-dried powder with particle size of 1–15 μ m. The data was also substantiated more recently by Macek⁴⁷ in 1975, and by Brossard⁴⁸ in 1981.

Also, physical properties of the drug particles other than size, though indirectly, influence the effective surface area by modifying the shear rate of the fresh solvent that comes in contact with the solid. These properties include the particle shape and the density. Hanson⁴⁹ discussed the flow dynamics effects on the surface area and cautioned that in some cases mutual interfer-

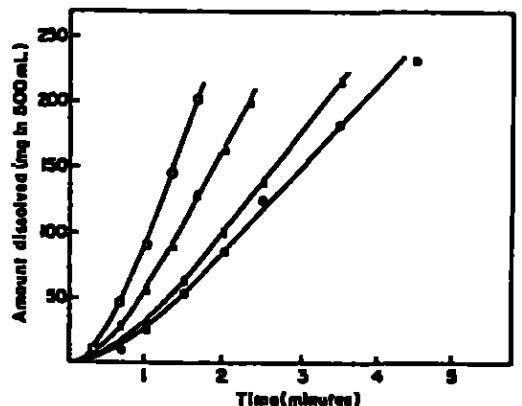


Fig 4-8c. Effect of particle size of phenobarbital on dissolution rate of the drug from tablets [Reproduced from Finholt, et al, *Medd Norsk Farm Selsk* 28, 17 (1966).]

Key: ○ particle size, 0.07–0.15 mm; ▲ particle size, 0.15–0.25 mm; △ particle size, 0.25–0.42 mm; ◇ particle size, 0.42–0.71 mm.

ences in the motion of particles, changes in electrical potential between particles, molecular layers of solvent tightly bound around particles, as well as many other influences, can retard dissolution upon reduction of particle size. Therefore, the common generalization that size reduction of drug particles enhances dissolution should not be accepted without qualification and caution.

Effect of Particle Size on Solubility

Another mechanism by which the reduction in particle size improves dissolution is through enhancement of the drug solubility (c_s). It should be pointed out that Eq 4-1 has an inherent limitation in assuming that c_s is independent of the particle size. Actually c_s and the surface area can be correlated by the Ostwald-Freundlich equation

$$\ln S = \frac{2M\gamma}{\rho RT} \frac{1}{r} = \frac{\alpha}{r} \quad (4-4)$$

where

$$\alpha = \frac{2M\gamma}{\rho RT}$$

and M is the molecular weight, ρ is the density, γ is the interfacial tension or surface free energy of the solid and r is the radius of the particle.

From Eq 4-4, it can be shown that

$$S = S_\infty e^{\alpha/r} \quad (4-5)$$

Equation 4-5 shows that the log of solubility is inversely proportional to particle radius. Therefore, S can be viewed as the solubility of the micro particles while S_∞ can be viewed as the solubility of the macro particles. However, it is obvious that the particle radius has to be reduced to a micro level before it can effect a change in solubility. This extreme reduction in particle size usually cannot be achieved through regular milling or even micronization procedures, however, other methods have been recommended. One of these methods is the formation of a "solid-solution" or "molecular dispersion" where the molecules of the sparingly soluble drug are either dispersed interstitially in a water soluble drug or replaced in its crystal lattice.

Another technique which also produces extremely small particles, but still larger than those produced by a solid solution, is by dispersion of the drug into a soluble carrier such as a polyvinylpyrrolidone solution. These techniques usually are utilized for the enhancement of the dissolution rate of insoluble drugs and will be discussed later in more detail (Chapter 13).

Crystalline State of the Drug

The solid phase characteristics of drugs, such as amorphicity, crystallinity, state of hydration, solvation, and polymorphic structures have been shown to have a significant influence on the dissolution rate. Wildermann⁵⁰ and Gross⁵¹ were the first to report on these influences when they noted that specific crystalline faces produced changes in the rate of dissolution of certain compounds.

According to Halebian,⁵² crystalline modification of solid drug substances can be either polymorphs or molecular adducts. Solvate forms, stoichiometric types of adducts, are not molecular compounds but are identified as complexes that incorporate solvent molecules in their crystal lattice. Hydrates are the most common solvate forms of drug compounds. As early as 1931, Roller^{53,54} observed that anhydrous calcium sulfate has greater aqueous solubility (1.45 times) than the hydrated form. Roller, however, reported that under certain conditions, the dissolution rate of the hydrate was higher than the anhydrous form. This later was disputed because thermodynamically the anhydrous forms of drugs are more active than the hydrates and consequently, as shown by Shefter and Higuchi,⁵⁵ the anhydrous forms have greater solubility and dissolve faster than the hydrated forms.

Wurster and Taylor⁵⁶ suggested that Roller's results may have been distorted by entrapped air at the particle surface. Also, in support of Shefter and Higuchi's thermodynamic argument, Poole, *et al*,^{54,57} found that anhydrous ampicillin has higher aqueous solubility and faster dissolution rate than ampicillin trihydrate (Fig 4 10a). In addition, bioavailability studies in dogs and humans showed that the mean blood serum concentration of anhydrous ampicillin, following the oral intake of commercial capsules or suspensions to be higher significantly than those obtained for the hydrated crystalline form (Fig 4 10b). Other reports⁵⁸⁻⁶⁰ however suggested that Poole's

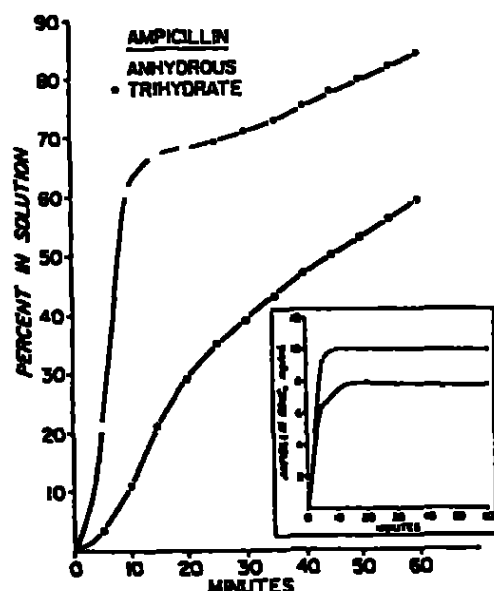


Fig 4-10a Dissolution of ampicillin in distilled water at 37°C from trade capsule formulations *inset*: Solubility of ampicillin anhydrous and ampicillin trihydrate in distilled water at 37°C [Reproduced from Poole *Curr Ther Res* 10, 292 (1968)]

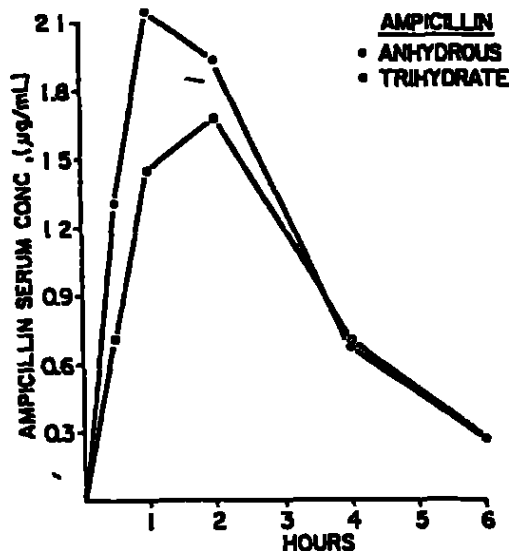


Fig 4-10b. Mean blood serum concentrations of ampicillin in human subjects after oral administration of 250 mg doses of the oral suspensions [Reproduced from Poole *Curr Ther Res*, 10, 292 (1968)]

bioavailability studies were conducted on commercial products and thereby formulation factors may have been responsible for the differences in bioavailability. In order to clarify these conflicting reports Ali and Farouk⁵⁹ evaluated the *in vivo* performance in man of two identical formulations of pure ampicillin anhydrous and trihydrate. In addition, two commercial dosage forms of the anhydrous and the trihydrate forms were included in the study. Examination of the urinary excretion data indicated that ampicillin from the experimental capsules containing the pure anhydrous form (with no excipients) was absorbed at both a faster rate and to a greater extent than from either of the experimental capsules containing the trihydrate form, or the two commercial capsules. Approximately two times as much ampicillin was excreted from the pure anhydrous form as compared with the pure trihydrate drug. Nevertheless, the bioavailability of the commercial capsules containing the anhydrous form was less than that of the pure experimental drug, but in case of the trihydrate form, the reverse was true. In other words, formulation of the drug for commercial use has helped to improve the bioavailability of the trihydrate form, but decreased the *in vivo* performance of the anhydrous form. This may explain the findings of Mayersohn and Endrenyi,⁶⁰ Hill, et al,^{58a} and Cabana, et al^{58c}.

Smidt, et al,⁶⁰ investigated the dissolution kinetics of theophylline monohydrate and anhydrous theophylline in buffer solutions under sink conditions. The study again confirmed that the anhydrous form generally dissolves faster than the hydrated form, however, the course of the dissolution process of the anhydrous drug was found to be rather complex. Three phases were identified (a) a pretransformation phase in which the anhydrous theophylline dissolves at a fast rate, (b) the transformation phase, during which the dissolution rate drops to the level of the theophylline monohydrate dissolution rate, and (c) steady state, at which the dissolution rate of the anhydrous

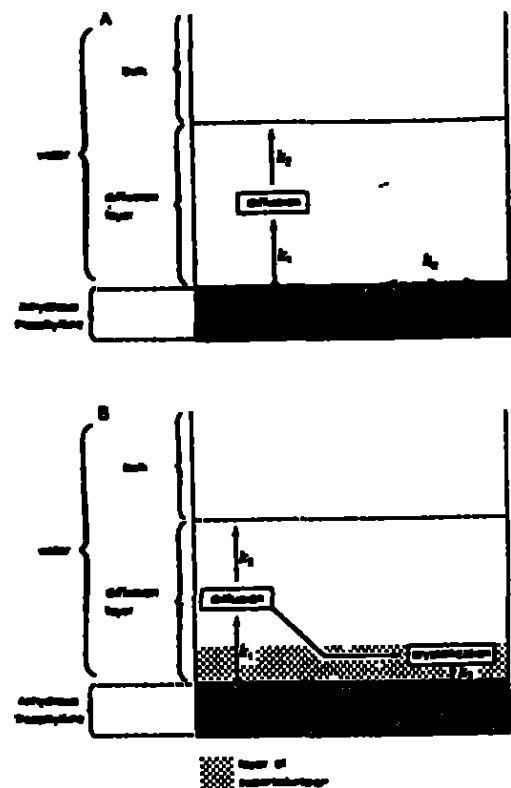


Fig 4-10c. Dissolution of anhydrous theophylline in buffer solutions. (A) Direct conversion of the surface the surface of anhydrous theophylline is converted to the monohydrate by immediate reaction after contact with water (B) indirect conversion of the surface theophylline crystallizes on the anhydrous surface via diffusion from a layer of supersaturation [Reproduced from Smidt, *et al*, *J Pharm Sci*, 75, 497 (1986).]
 Key: (k_1) rate constant of dissolution reaction; (k_2) rate constant of convective diffusional transport; (k_3) rate constant of surface transformation; (k_4) rate constant of crystallization.

theophylline equals the dissolution rate of theophylline monohydrate (Fig 4-10c) The presence of theophylline monohydrate crystals at the dissolving surface was confirmed by IR spectrometry and microscopic examination (Fig 4 10c) Carbamazepine an antiepileptic drug that exists in an anhydrous form and as a dihydrate was reported by Stahl⁶¹ to have a crystalline structure that is dependent highly on temperature and relative humidity Memard, *et al*,⁶² as well as others,⁶³⁻⁶⁵ showed that the absorption from the suspension formulation of

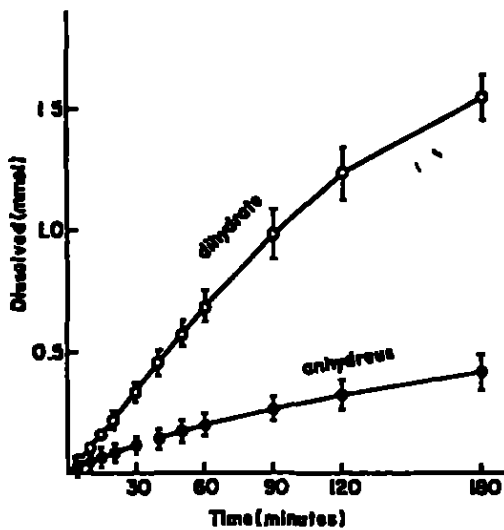


Fig 4-10d. Dissolution behavior of carbamazepine anhydrous (—○—) and dihydrate (—□—) in 0.1M hydrochloric acid. [Reproduced from Kahela, *et al*, *Int J Pharm*, 14, 103 (1983)]

this drug, where the dihydrate form is used, is faster than that from tablets where the anhydrous form is utilized. Although the fine particle size of the suspension may have been an important factor, Kahela, *et al*,⁶⁶ have suggested that the difference in absorption might also be attributed partly to the different crystal modifications. In their study of the dissolution and serum levels of the two crystalline forms (the anhydrous and the dihydrate) of carbamazepine, the authors found that when 0.01M HCl is used as the medium, the dihydrate dissolved faster than the anhydrous form (Fig 4 10d) On the other hand, when 0.1% wetting agent was added to the medium, the dissolution patterns changed (Fig 4-10e) Absorption data also showed that the dihydrate appeared in the serum at a faster rate than the anhydrous form These observations of crystal transformations previously have been reported by others^{67,68} More important, the observation by Kahela regarding the inhibiting effect of the surfactants on the crystal growth in aqueous media was in agreement with a similar finding by Moustafa *et al*,⁶⁹ for succinylsulfathiazole Allan, *et al*⁷⁰ too has reported earlier, that eryth

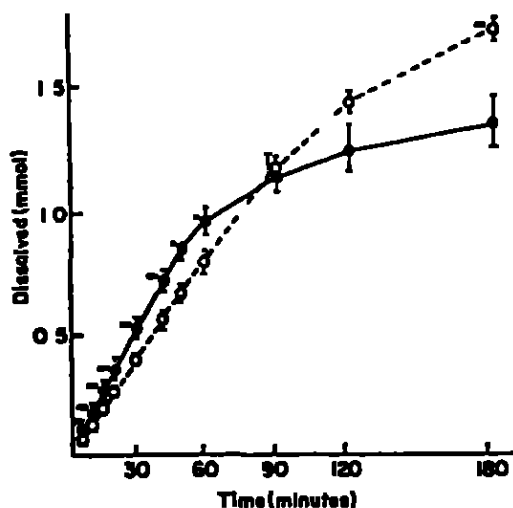


Fig 4-10e Dissolution behavior of carbamazepine anhydride (—) and dihydrate (---) in 0.1M hydrochloric acid with 0.01% polysorbate 80 [Reproduced from Kahela, *et al* *Int J Pharm*, 14, 103 (1983)]

romycin dihydrate dissolves faster in a phosphate buffer of pH 7.5 than the less hydrated or anhydrous forms. Although these findings appear contradictory to the general principle based on the thermodynamic stability of the anhydrous and hydrated forms, the contrast, according to Kahela, *et al*,⁶⁶ is only apparent. The wettability of the solid phase and particle-particle interactions are the real reasons for their findings. In this case, crystal growth of the anhydrous forms in 0.1N HCl, as well as its transformation in solution to the dihydrate, which is the only stable form in aqueous media, are probably the reasons for the faster dissolution of the dihydrate. In presence of the wetting agent, the crystal growth appeared to be inhibited, though temporarily, and consequently faster dissolution for the anhydrous is observed initially.

Six crystalline forms of fluprednisolone were studied by Haleblan, *et al*.⁷² Of these forms, three were anhydrous, two were monohydrates and one was a *tert*-butylamine di solvate. Figure 4-11 shows that, in general, the anhydrous forms dissolved faster than the hydrated and di solvate

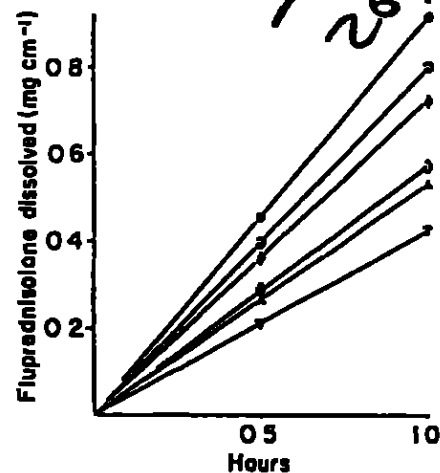


Fig 4-11 Dissolution of various phases of fluprednisolone in water at 23° [Reproduced from Haleblan *et al*, *J Pharm Sci*, 60, 1485 (1971)]
Key: ● Form I; ○ Form II; ○ Form III; ▽ α-monohydrate; △ β-monohydrate; ♦ *tert*-butylamine di solvate.

forms. This *in vitro* result was also substantiated by an *in vivo* study where solid pellets of the drug were implanted subcutaneously in the abdominal region of rats. Animal weight loss and adrenal gland atrophy were utilized as two biological responses to measure the drug bioefficacy. Nogami, *et al*,⁷³ in 1969, investigated the dissolution behavior accompanying simultaneous phase changes of *p*-hydroxybenzoic acid and phenobarbital which transformed to their respective hydrates. The maximum concentrations of the anhydrous forms were 1.5 times the respective solubilities of the hydrates, mainly due to a higher initial dissolution that accompanies the transformation of the dispersed anhydride to the hydrate form. This concentration, however, decreases gradually until it reaches the equilibrium state. Nogami explained that this convex curve shows that the bulk liquid is supersaturated with respect to the solubility of the hydrate (Figs 4-12a, 4-12b, and 4-12c).

It is also interesting to note that, amorphous (noncrystalline) forms of drugs, in general, tend to dissolve faster than crystalline materials. Mullins and Macek⁷⁴ showed that the amorphous form of novobiocin has a greater solubility and higher dissolution

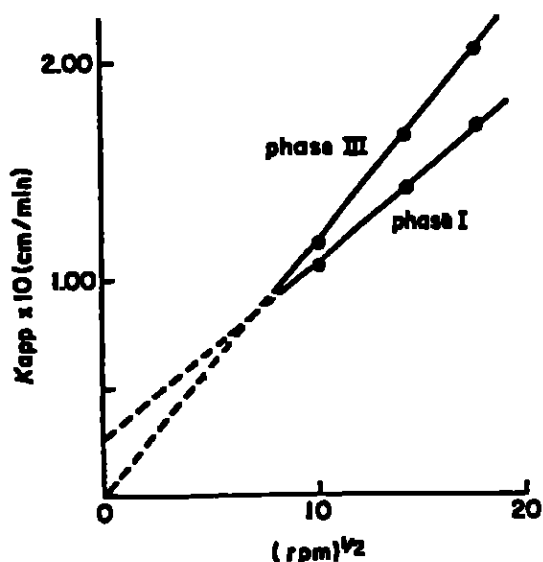


Fig 4-12a. Dependence of apparent dissolution rate constant, K_{app} , of barbitol polymorphs in water on the rotating velocity of disk at 30° [Reproduced from Nogami *et al*, *Chem Pharm Bull*, 17 28 (1969).]

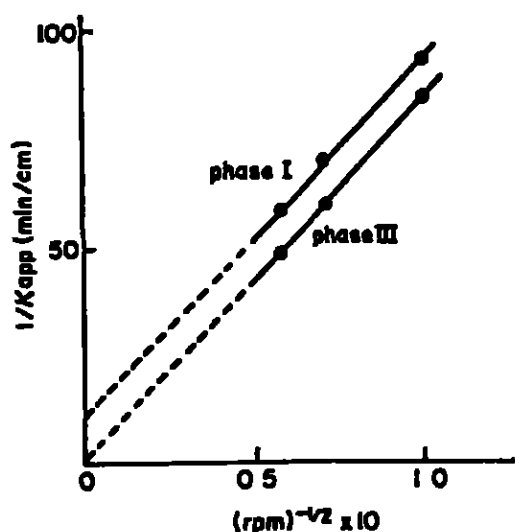


Fig 4-12b. Plots of the reciprocal of apparent dissolution rate constant $1/K_{app}$ vs that of square root of rotating velocity at 30° [Reproduced from Nogami *et al*, *Chem Pharm Bull*, 17 28 (1969).]

rate than the crystalline form (Fig 4-13a) Blood level studies confirmed such findings where administration of the amorphous form yielded about 3-4 times the concen-

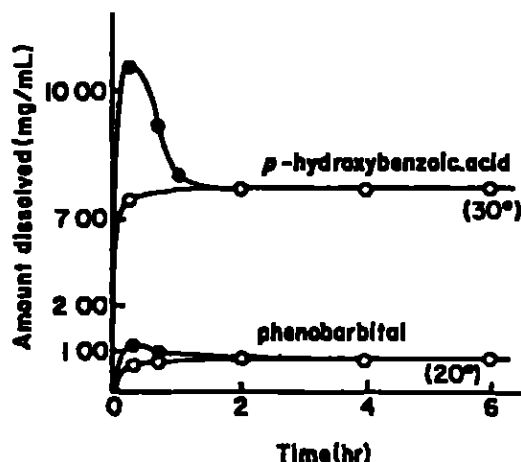


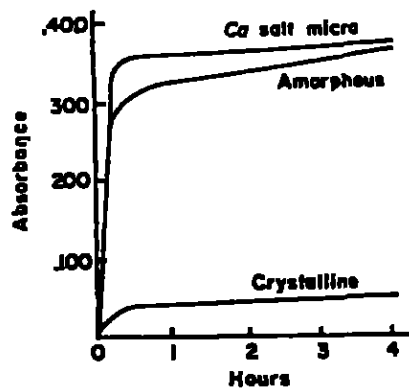
Fig 4-12c. Dissolution behaviors of anhydrous and of its hydrate by dispersed amount method. Sample amount: *p*-hydroxybenzoic acid 0.7 g, phenobarbital 0.2 g in 50 mL water [Reproduced from Nogami *et al*, *Chem Pharm Bull*, 17 501 (1969).] Key: —●—, Anhydrous —○—, hydrate.

tration of that found after the administration of the crystalline form (Fig 4-13b) Similar differences,⁷⁵ though less dramatic, were demonstrated for griseofulvin, phenobarbital, cortisone acetate and chloramphenicol.

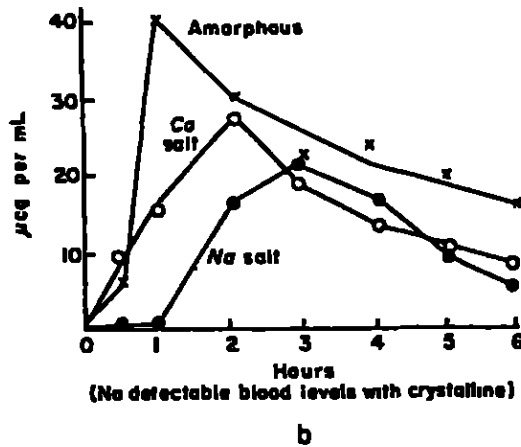
Polymorphism

The existence of polymorphic structures is another important variant of the crystalline forms that can effect greatly the dissolution rate behavior of drugs. For thermodynamic reasons,⁷⁶ compounds that exhibit crystal polymorphism should possess different fugacities (thermodynamic activities) that vary according to the crystalline modification. Accordingly, the dissolution rate and bioavailability may depend, to a large extent, on the dissolution characteristics of the specific polymorphic forms utilized in the formulation. Because many of the polymorphic crystalline structures exhibit vast ranges of solubility and rates of solution polymorphism has been a major source of dose to dose variability of the bioavailability of several drug compounds.

In general, the metastable (high activation energy) polymorphic forms have better



a



b

Fig 4-13. a: Rate of dissolution (as absorbance values) for various forms of novobloclin. b: Blood level vs time data for the various forms of novobloclin [Reproduced from Goldberg Academy of Pharm. Sci 2215 Constitution Ave NW Washington, DC 20037 Graph is based on data from Mullens, and Macek J Am Pharm Assoc Sci Ed, 49 245 (1960).]

dissolution than the stable forms. Hamlin, et al,⁷⁷ in 1962, showed distinct dissolution rates for the two polymorphs of methylprednisolone. These differences, however, disappeared at higher agitation speeds. Wurster and Taylor⁷⁸ later found similar results for three different polymorphs of methylprednisolone. Levy and Procknal⁷⁹ also confirmed Hamlin's finding that the difference in the dissolution rate of the two polymorphs of methylprednisolone disappear at higher agitation rate, and attributed

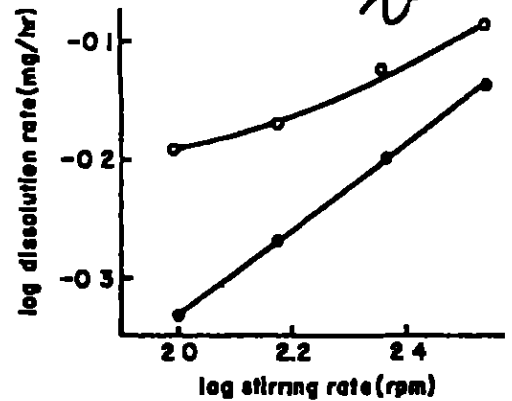


Fig 4-14. Dissolution rates of methylprednisolone polymorph I (●) and polymorph II (○) from rotating disks (1.27 cm²) as a function of rate of disk rotation [Reproduced from Levy and Procknal, J Pharm Sci 53, 656 (1964)]

such behavior to an intrinsic property of the drug and not to effects caused by a particular apparatus or methodology (Fig 4-14). Higuchi, et al,^{80,81} studied this phenomenon and found a correlation between the rates of reversion of the metastable polymorphic form to the stable one during dissolution and the crystal growth rates of the stable form (Figs 4-15a and 4-15b). When the rate of the crystal growth of the stable form is slow, there is a little tendency for polymorphic reversion during dissolution. Based on their studies of the dissolution behavior of the polymorphic mixtures of sulfathiazole (Fig 4-16) and methylprednisolone in different solvents, the authors proposed their "mixture theory" to interpret their data and to provide an explanation for the loss of sensitivity in distinguishing the difference in dissolution rates of polymorphs at high agitation speeds. Figure 4-16a shows a schematic diagram of the three stages (left to right) of the dissolution process. It is assumed that initially the mixture is uniform and no reversion occurs. As dissolution proceeds by diffusion across the effective liquid diffusion layer of thickness h , only form II dissolves initially, i.e., at time zero C' , the solution concentration at the tablet boundary and solution interface, is equal to C_s^{II} , the solubility of form II. At later times C_s^{II}

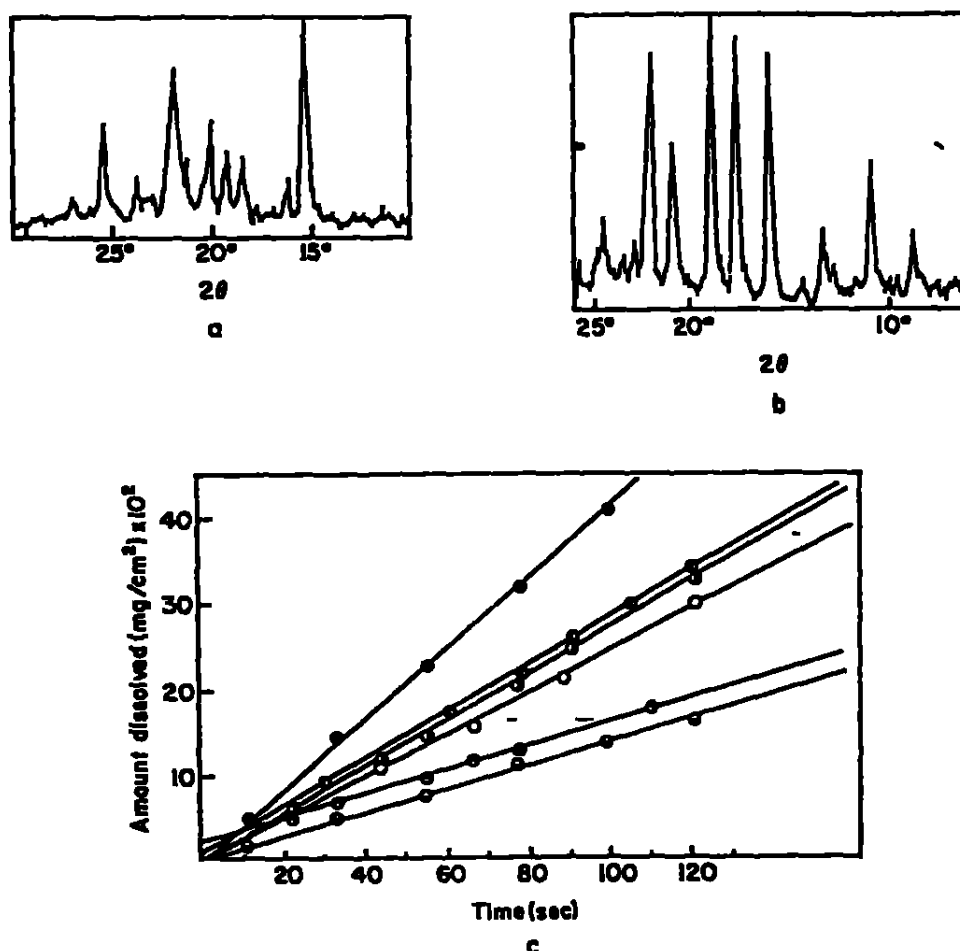


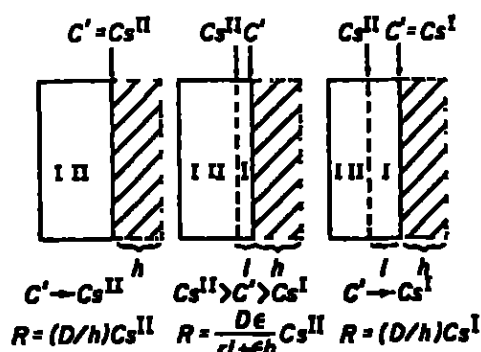
Fig 4-15 a- X-ray recording of sulfathiazole form I b- X-ray recording of sulfathiazole's form II c- Dissolution rates of sulfathiazole (form I) and form II and mixture of 80 % I and 20 % II) at two agitation speeds in *n*-propyl alcohol [Reproduced from Higuchi, *et al*, *J Pharm Sci*, 56, 200 (1967).]

Key: ○ form I (A); □ mixture (A); △ form II (A); ○ form I (B); □ mixture (B); △ form II (B); A, diffusion layer thickness = 5.82×10^{-3} cm; B, diffusion layer thickness = 2.84×10^{-3} cm.

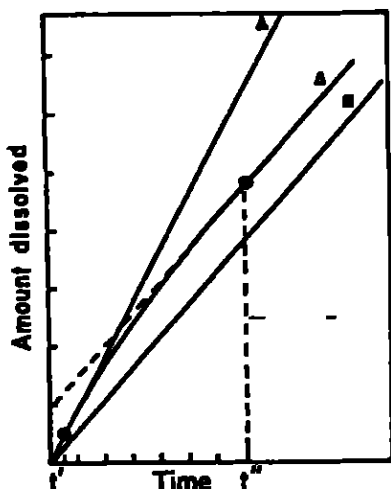
$> C' > C_s^I$, and finally at steady state, $C' \approx C_s^I$, and both forms I and II dissolve at rates proportional to their percentages in the original mixture. The results of these considerations are illustrated in Fig 4-18b where t' is the point where deviation of the mixture curve from the pure form II curve begins to become important and t'' is the point at which the rate of dissolution of the mixture becomes equal to the rate for pure form I. Higuchi, *et al*³⁰ derived the mathematical treatment for the model that fits their data and that of Hamlin's to the theo-

retical equation. Phenylbutazone too, has been reported to exist in several polymorphic forms. Matsumaga, *et al*,³² reported the existence of three polymorphs and Ibrahim, *et al*,³³ reported four polymorphic forms. Müller however, showed that two of forms reported by Ibrahim are actually solvates and reported the existence of two new ones.

Tuladhar, *et al*,³⁴ prepared and characterized five different polymorphic forms of phenylbutazone using differential scanning calorimetry. The authors observed inter-



a



b

Fig 4-18 a Mixture theory model. b: Comparison of dissolution rate of the two polymorphs and a mixture according to theory [Reproduced from Higuchi *et al*, *J Pharm Sci*, 56, 200 (1967)]

Key: Δ B; $\triangle$ mixture; $\square$ A

conversion between polymorphs on grinding. Based on the equilibrium solubility and intrinsic dissolution rates data of the various polymorphic forms (Fig 4-17), the authors concluded that the dissolution process could be described by the Berthoud model. This model, which is also known as the consecutive process concept, was first proposed by Berthoud⁸⁵ in 1912, and was then highlighted by Wurster and Taylor⁷⁸ to explain their prednisolone findings. Because all molecules originating from differ-

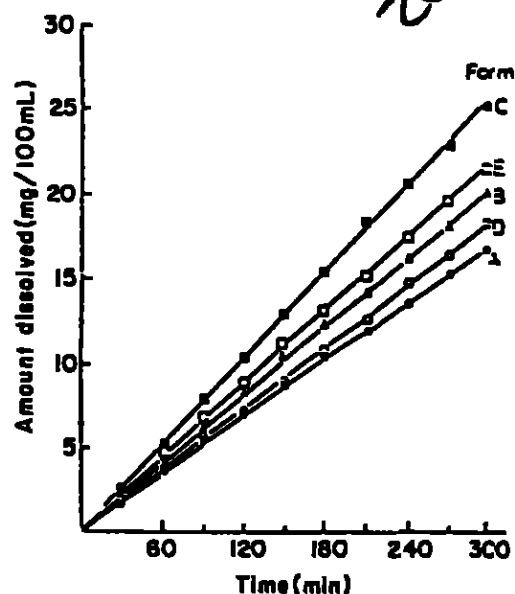


Fig 4-17 Comparison of dissolution rates of phenylbutazone crystal forms in 0.2M phosphate buffer pH 7.5 at 37°C and 100 rev min⁻¹ [Dissolution Properties of Phenylbutazone Polymorphs. Reproduced from Tuladhar *et al*, *J Pharm Pharmacol*, 35, 208 (1983)]

Key: $\bullet$ Form A, $\triangle$ Form B, $\blacksquare$ Form C, $\circ$ Form D, $\square$ Form E

ent crystalline forms exist in the same state in solution, they should have the same diffusion coefficient and the same dissolution-rate constants. As this relationship is not followed in the case of many different solvated and polymorphic forms, Wurster and Taylor⁷ proposed the consecutive process, where a phase reaction at the interface is suggested to take place, followed by the transport away from the interface. Nogami, *et al*,^{73,86} utilized the same concept to explain their findings regarding the different dissolution rate constants for three barbitol polymorphs and proposed the existence of a double diffusion layer for the material transport. Combining this concept with Levich's⁸⁷ equation, they were able to calculate the rate constant of the interfacial chemical reaction and that of the transport process. Figure 4-18 explains this double layer concept.

Other polymorphic forms have been reported for a wide variety of drugs. Aguiar⁸⁸

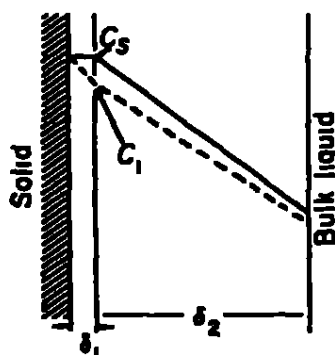


Fig 4-18a Schematic diagram of concentration profile on the dissolution process of solids. C_s , saturated concentration; C_1 , effective concentration; δ_1 , thickness of effective or saturated concentration layer; δ_2 , thickness of diffusion layer [Reproduced from Nogami, *et al*, *Chem Pharm Bull*, 17, 24 (1969).]

demonstrated a dramatic difference in dissolution and bioavailability between two distinct polymorphic forms of chloramphenicol. Shibata, *et al*,⁸⁰ characterized different polymorphic forms of cimetidine, and Rowe and Anderson⁸⁰ described the stability of the various polymorphs of tolbutamide.

Behme, *et al*,⁹¹ pointed out that prediction of the relative stability of a pair of polymorphic solids can be facilitated greatly if the polymorphs are characterized as either monotropic or enantiotropic. For monotropic solids, the higher melting form has the lower free energy at all temperatures and consequently is more stable at all temperatures. For enantiotropic solids, their relative stabilities depend on the temperature of the system relative to the transition temperature. However, as the number of polymorphs increases, the interpretation of data becomes difficult. Burger and Ramberger⁹² recommended the use of an energy-temperature diagram to facilitate the interpretation process. Their "heat of fusion rule" states that the higher melting form has the lower heat of fusion; the two forms are usually enantiotropic; otherwise they are monotropic. Behme, *et al*,⁹¹ utilized such a rule in their interpretation of the

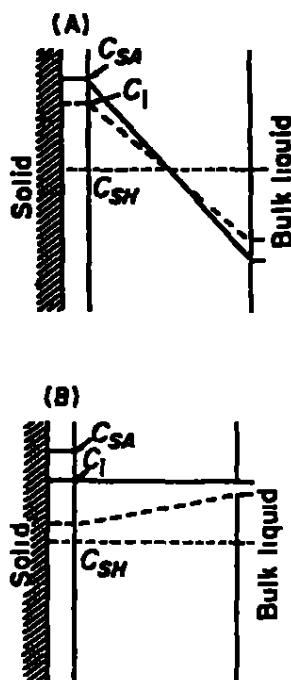


Fig 4-18b. Schematic diagram of concentration profiles on the dissolution process of solids. C_{SA} , saturated concentration of anhydrous; C_1 , effective concentration on solid surface; C_{SH} , saturated concentration of hydrate [Reproduced from Nogami, *et al*, *Chem Pharm Bull*, 17, 499 (1969).]

stability data of three polymorphic forms of gepirone hydrochloride, an investigational anxiolytic drug.

It is interesting to note that from one standpoint, the presence of different polymorphic forms of the same drug can lead either to satisfactory or problematic consequences. If the existence of multiple crystalline modifications is unrecognized in a particular formulation, it may result in too wide a range of dose-to-dose variation in the drug bioavailability. On the other hand, Higuchi, *et al*,⁹⁰ as well as others⁹³ have advocated, and successfully demonstrated, the utilization of a polymorph of significantly greater thermodynamic activity, than that of the stable crystalline modification to provide better dissolution characteristics and higher blood levels for an otherwise poorly absorbed drug.

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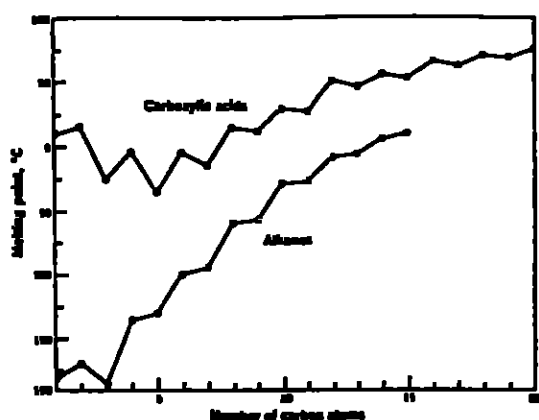


Fig. 2-6. The melting points of alkanes and carboxylic acids as a function of carbon chain length (Modified from C. R. Noller, *Chemistry of Organic Compounds*, 2nd Ed., Saunders, Philadelphia, 1957, pp. 40-149).

The melting points of normal carboxylic acids also show this alternation, as seen in Figure 2-6. This can be explained as follows. Fatty acids crystallize in molecular chains, one segment of which is shown in Figure 2-7. The even carbon acids are arranged in the crystal as seen in the more symmetric structure I, whereas the odd numbered acids are arranged according to structure II. The carboxyl groups are joined at two points in the even carbon compound, hence, the crystal lattice is more stable and the melting point is higher.

The melting points and solubilities of the xanthines of pharmaceutical interest, determined by Guttman and Higuchi,⁹ further exemplify the relationship between melting point and molecular structure. Solubilities, like melting points, are strongly influenced by intermolecular forces, as will be discussed later in Chapter 10. It will be observed by reference to Table 2-6 that methylation of theophylline to form caffeine, and lengthening of the side chain from methyl (caffeine) to propyl in the 7 position results in a decrease of the melting points and an increase in solubilities. These effects presumably are due to a progressive weakening of intermolecular forces.

Polymorphism. Some elemental substances, such as carbon and sulfur, may exist in more than one crystal-

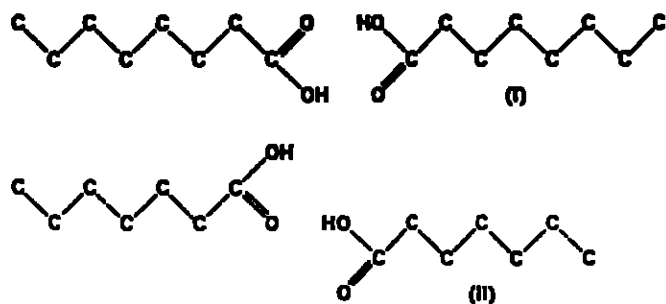


Fig. 2-7. Configuration of fatty acid molecules in the crystalline state (Modified from A. E. Bailey, *Melting and Solidification of Fats*, Interscience Publishers, New York, 1950, p. 120).

TABLE 2-6 Melting Points and Solubilities of Some Xanthines*

274
268

Basic structure

Compound	Melting Point (°C uncorrected)	Solubility in Water at 30° C (mole/liter × 10 ³)
Theophylline (R = H)	270-274	4.5
Caffeine (R = CH ₃)	238	13.3
7-Ethyltheophylline (R = CH ₂ CH ₃)	156-157	17.6
7-Propyltheophylline (R = CH ₂ CH ₂ CH ₃)	99-100	104.0

*From D. Guttman and T. Higuchi, *J. Am. Pharm. Assoc. Sci. Ed.* 46, 4, 1957.

line form and are said to be *polymorphic*. Polymorphs generally have different melting points, x-ray diffraction patterns, and solubilities, even though they are chemically identical.

Nearly all long-chain organic compounds exhibit polymorphism. In fatty acids, this results from different types of attachment between the carboxyl groups of adjacent molecules, which in turn modify the angle of tilt of the chains in the crystal. The triglyceride, tristearin, proceeds from the low-melting metastable alpha (α) form through the beta prime (β') form and finally to the stable beta (β) form, having a high melting point. The transition cannot occur in the opposite direction.

Theobroma oil or cacao butter is a polymorphous natural fat. Since it consists mainly of a single glyceride, it melts to a large degree over a narrow temperature range (34°-36° C). Theobroma oil is capable of existing in four polymorphic forms, the unstable gamma form melting at 18°, the alpha form melting at 22°, the beta prime form melting at 28°, and the stable beta form melting at 34.5° C. Riegelman¹⁰ has pointed out the relationship between polymorphism and the preparation of cacao butter suppositories. If theobroma oil is heated to the point at which it is completely liquefied (about 35° C), the nuclei of the stable beta crystals are destroyed and the mass does not crystallize until it is supercooled to about 15° C. The crystals that form are the metastable gamma, alpha, and beta prime forms and the suppositories melt at 23° to 24° C or at ordinary room temperature. The proper method of preparation involves melting cacao butter at the lowest possible temperature, about 23° C. The mass is sufficiently fluid to pour, yet the crystal nuclei of the stable beta form are not lost. When the mass is chilled in the mold, a

stable suppository, consisting of beta crystals and melting at 34.5° C, is produced

Polymorphism has achieved significance in recent years owing to the fact that different polymorphs exhibit different solubilities. In the case of slightly soluble drugs, this may affect the rate of dissolution. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug. Agular et al.¹¹ have shown the polymorphic state of chloramphenicol palmitate to have a significant influence on the biologic availability of the drug. Khalil et al.¹² reported that form II of sulfamer, an antibacterial agent, was more active orally in humans than form III, although marketed pharmaceutical preparations were found to contain mainly form III.

Polymorphism can also be a factor in suspension technology. Cortisone acetate has been found to exist in at least five different forms, four of which were found to be unstable in the presence of water and which change to a stable form.¹³ Since this transformation is usually accompanied by appreciable caking of the crystals, these should all be in the form of the stable polymorph before the suspension is prepared. Heating, grinding under water, and suspension in water are all factors that affect the interconversion of the different cortisone acetate forms.¹⁴

It is difficult to determine the crystal structure and molecular conformations of different polymorphs of a single drug and the reports of such work are not common. Azibi et al.¹⁵ studied two polymorphs of spiperone, a potent antipsychotic agent used mainly in the treatment of schizophrenia. The chemical structure of spiperone is shown in Figure 2-8a, and the molecular conformations* of the two polymorphs, I and II, are shown in Figure 2-8b. The difference between the two polymorphs is in the positioning of the atoms in the side chains, as seen in Figure 2-8b, together with the manner in which each molecule binds to neighboring spiperone molecules in the crystal. The results of the investigation showed that the crystal of polymorph II is made up of dimers (molecules in pairs), whereas polymorph crystal I is constructed of nondimerized molecules of spiperone. In a later study, Azibi et al.¹⁶ examined the polymorphism of a number of drugs to ascertain what properties cause a compound to exist in more than one crystalline form. Differences in intermolecular van der Waals forces and hydrogen bonds were found to produce different crystal structures in antipsychotic compounds such as haloperidol (Fig. 2-9) and bromperidol. Variability in hydrogen bonding also contributes to polymorphism in the sulfonamides.¹⁷

Goldberg and Becker¹⁸ studied the crystalline forms of tamoxifen citrate, an antiestrogenic and antineoplas-

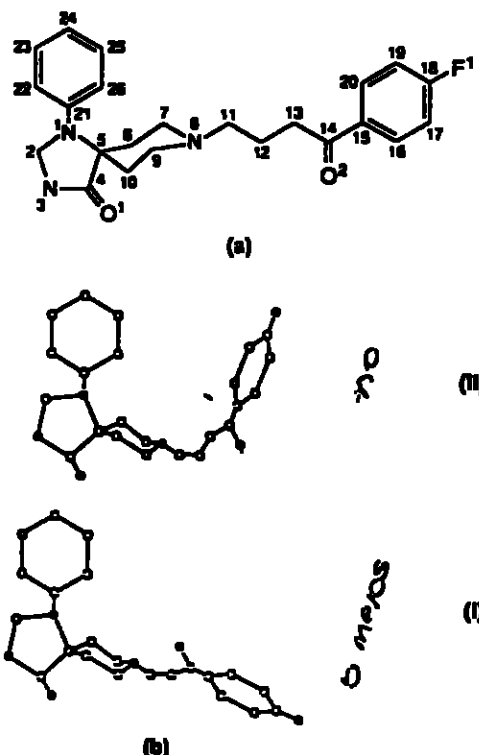


Fig. 2-8. (a) Structure and numbering of spiperone. (b) Molecular conformation of two polymorphs I and II of spiperone (M. Azibi et al. J. Pharm. Sci. 72:222, 1983. Reproduced with permission.)

tic drug used in the treatment of breast cancer and postmenopausal symptoms. The structural formula of tamoxifen is shown in Figure 2-10. Of the two forms found, the stable polymorph, referred to as form B, is held in its molecular conformation in the solid state by hydrogen bonding. One carboxyl group of the citric acid moiety donates its proton to the nitrogen atom on an adjacent tamoxifen molecule to bring about the hydrogen bonding and to stabilize the molecular crystal of form B. The other polymorph, known as form A, is a metastable polymorph of tamoxifen citrate, its molecular structure being less organized than that of the stable B form. An ethanolic suspension of polymorph A spontaneously rearranges into polymorph B.

Lowes et al.¹⁹ made physical, chemical, and x-ray studies of carbamazepine. Carbamazepine is used in the treatment of epilepsy and trigeminal neuralgia (severe pain in the face, lips, and tongue). The β polymorph of the drug can be crystallized from solvents of high dielectric constant, such as the aliphatic alcohols. The α polymorph is crystallized from solvents of low dielectric constant, such as carbon tetrachloride and cyclo-

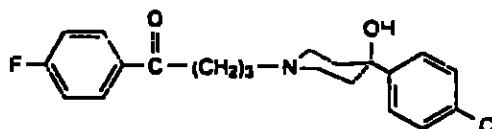


Fig. 2-9 Haloperidol.

*The arrangement of the atoms in a particular stereoisomer gives the configuration of a molecule. On the other hand, conformation refers to the different arrangements of atoms resulting from rotations about single bonds.

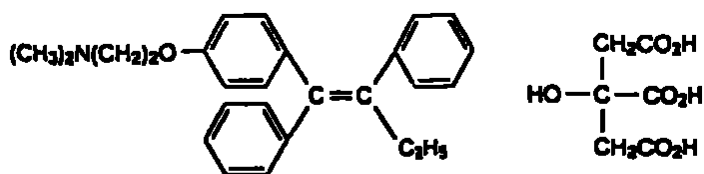


Fig. 2-10. Tamoxifen citrate

hexane. A rather thorough study of the two polymorphic forms of carbamazepine was made using infrared spectroscopy (p 89), thermogravimetric analysis (p 49), hot-stage microscopy, dissolution rate (p 330-332), and x-ray powder diffraction (p 30). The hydrogen-bonded structure of the α polymorph of carbamazepine is shown in Figure 2-11a, together with its molecular formula (Fig 2-11b).

Estrogens are essential hormones for the development of female sex characteristics. When the potent synthetic estrogen ethynylestradiol is crystallized from the solvents acetonitrile, methanol, and chloroform saturated with water, four different crystalline solvates are formed. Ethynylestradiol has been reported to exist in several polymorphic forms. However, Ishida et al.²⁰ have now shown from thermal analysis, infrared spectroscopy, and x-ray studies that these forms are crystals containing solvent molecules and thus should be classified as *solvates* rather than as polymorphs. Solvates are sometimes called *pseudopolymorphs*.²¹

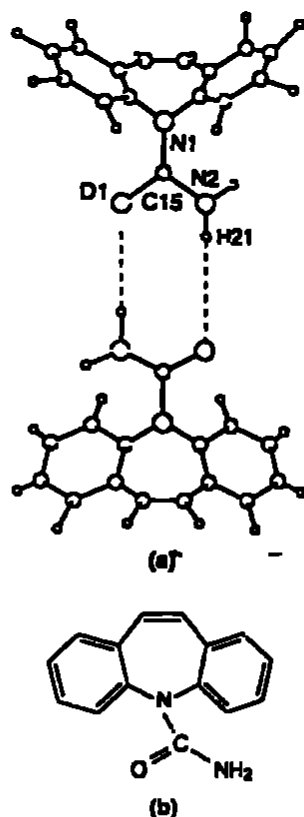


Fig. 2-11 (a) Two molecules of the polymorph α -carbamazepine joined together by hydrogen bonds. (M. M. J. Lowes, et al. J. Pharm. Sci. 76:744, 1987. Reproduced with permission.) (b) Carbamazepine.

Other related estradiol compounds may exist in true polymeric forms.

Behme et al.²² reviewed the principles of polymorphism with emphasis on the changes that the polymorphic forms may undergo. When the change from one form to another is reversible, it is said to be *enantiotropic*. When the transition takes place in one direction only—for example, from a metastable to a stable form—the change is said to be *monotropic*. Enantiotropism and monotropism are important properties of polymorphs, as described by Behme et al.²²

The transition temperature in polymorphism is important because it helps to characterize the system and determine the more stable form at low temperatures. At their transition temperatures, polymorphs have the same free energy, identical solubilities in a particular solvent, and identical vapor pressures. Accordingly, plots of logarithmic solubility of two polymorphic forms against $1/T$ provide the transition temperature at the intersection of the extrapolated curves. Often the plots are nonlinear and cannot be extrapolated with accuracy. For dilute solutions, in which Henry's law (p 152) applies, the logarithm of the solubility ratios of two polymorphs can be plotted against $1/T$, and the intersection at a ratio equal to unity gives the transition temperature.²³ This temperature can also be obtained from the phase diagram of pressure versus temperature and by using differential scanning calorimetry.²⁴ An example of the solubility method is given as Problem 2-20.

Biles,²⁵ as well as Halebian and McCrone,²⁶ have discussed in some detail the significance of polymorphism and solvation in pharmaceutical practice.

Amorphous Solids. Amorphous solids may be considered as supercooled liquids in which the molecules are arranged in a random manner somewhat as in the liquid state. Substances such as glass, pitch, and many synthetic plastics are amorphous solids. They differ from crystalline solids in that they tend to flow when subjected to sufficient pressure over a period of time, and they do not have definite melting points. In Chapter 17, it will be learned that the rheologist classifies as a solid any substance that must be subjected to a definite shearing force before it fractures or begins to flow. This force, below which the body shows elastic properties, is known as the *yield value*.

Amorphous substances, as well as cubic crystals, are usually *isotropic*; that is, they exhibit similar properties in all directions. Crystals other than cubic are *anisotropic*, showing different characteristics (electric conductance, refractive index, rate of solubility) in various directions along the crystal.

It is not always possible to determine by casual observation whether a substance is crystalline or amorphous. Beeswax and paraffin, although they appear to be amorphous, assume crystalline arrangements when heated and then allowed to cool slowly. Petrolatum, as already mentioned, contains both crys-

talline and amorphous constituents. Some amorphous materials, such as glass, may crystallize after long standing

Whether or not a drug is amorphous or crystalline has been shown to affect its therapeutic activity. Thus the crystalline form of the antibiotic novobioicin acid is poorly absorbed and has no activity, whereas the amorphous form is readily absorbed and therapeutically active.²⁷

THE LIQUID CRYSTALLINE STATE

Three states of matter have been discussed thus far in this chapter: gas, liquid, and solid. A fourth state of matter is the *liquid crystalline state* or *mesophase*. The term *liquid crystal* is an apparent contradiction, but it is useful in a descriptive sense since materials in this state are in many ways intermediate between the liquid and solid states.

Structure of Liquid Crystals As seen earlier, molecules in the liquid state are mobile in three directions and can also rotate about three axes perpendicular to one another. In the solid state, on the other hand, the molecules are immobile, and rotations are not possible.

It is not unreasonable to suppose, therefore, that intermediate states of mobility and rotation should exist, as in fact they do. It is these intermediate states that constitute the liquid crystalline phase, or mesophase, as the liquid crystalline phase is called.

The two main types of liquid crystals are termed *smectic* (soap- or grease-like) and *nematic* (thread-like). In the smectic state, molecules are mobile in two directions and can rotate about one axis (Fig. 2-12a). In the nematic state, the molecules again rotate only about one axis but are mobile in three dimensions (Fig.

2-12b). A third type (cholesteric crystals) exist but may be considered as a special case of the nematic type.

The smectic mesophase is probably of most pharmaceutical significance since it is this phase that usually forms in ternary (or more complex) mixtures containing a surfactant, water, and a weakly amphiphilic or nonpolar additive (see Chapter 18).

In general, molecules that form mesophases (1) are organic, (2) are elongated and rectilinear in shape, (3) are rigid, and (4) possess strong dipoles and easily polarizable groups. The liquid crystalline state may result either from the heating of solids (thermotropic liquid crystals) or from the action of certain solvents on solids (lyotropic liquid crystals). The first recorded observation of a thermotropic liquid crystal was made by Reinitzer in 1888 when he heated cholesteryl benzoate. At 145° C, the solid formed a turbid liquid (the thermotropic liquid crystal), which only became clear, to give the conventional liquid state, at 179° C.

Properties and Significance of Liquid Crystals. Because of their intermediate nature, liquid crystals have some of the properties of liquids and some of solids. For example, liquid crystals are mobile and thus can be considered to have the flow properties of liquids. At the same time they possess the property of being birefringent, a property associated with crystals. In birefringence, the light passing through a material is divided into two components with different velocities and hence different refractive indices.

Some liquid crystals show consistent color changes with temperature, and this characteristic has resulted in their being used to detect areas of elevated temperature under the skin that may be due to a disease process. Nematic liquid crystals are sensitive to electric fields, a property used to advantage in developing display systems. The smectic mesophase has applica-

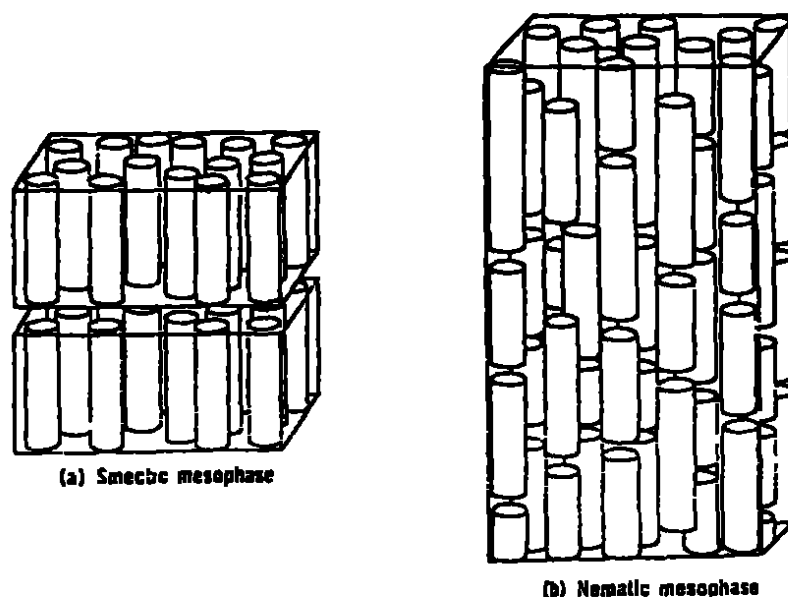


Fig. 2-12 Liquid crystalline state (a) Smectic structure (b) nematic structure

276
270

Factors Affecting the Rate of Dissolution of Solid Dosage Forms

There are several factors, other than those related to the physicochemical characteristics of the active ingredient that may affect the dissolution rate and bioavailability of solid dosage forms. These generally can be discussed under five major categories: formulation factors, processing factors, packaging and storage factors, the dissolution apparatus and the test parameters. Although the magnitude and significance of these effects must be determined individually for each product, the following discussion of earlier and current findings can serve as a guideline for the pharmaceutical scientists, especially during the initial stages of formulation design and product development.

Formulation Factors

It has been shown that the dissolution rate of pure drugs can be altered significantly when mixed with various adjuncts during the process of manufacturing solid dosage forms. These adjuncts are added to satisfy certain pharmaceutical functions and may include diluents (fillers), dyes, binders, granulating agents, disintegrants and lubricants. Generically identical tablet and capsule products, manufactured by different pharmaceutical houses, were found to exhibit significant differences in the dissolution rates of their active ingredients. Nelson and Schaldemose,¹ Levy,²⁻⁵ Varley,⁶ and others⁷⁻¹¹ showed that some tablet and capsule formulations can lead to a marked decrease in the dissolution and bioavailability of drugs from solid dosage forms. Such findings during the 1960's, especially in the case of digoxin and tolbutamide tablets, as well as chloramphenicol and tetracycline HCl capsules (all lifesaving drugs), were the

main triggering factors that compelled drug regulatory agencies and compendial authorities to institute the dissolution test as a legal requirement for most solid dosage forms.

Diluents (Fillers)

Diluents are used to give the powder bulk, so that a tablet of an acceptable size is produced.

Levy, *et al.*,⁵ in 1963, studied the effect of starch, one of the most commonly used diluents, on the rate of dissolution of salicylic acid tablets manufactured by the dry, double compression process. Increasing the starch content from 5 to 20% resulted in a three-fold increase in the dissolution rate (Fig 5-1). This was attributed to better and more thorough disintegration (starch is an excellent disintegrant). Finholt, *et al.*,⁷ in

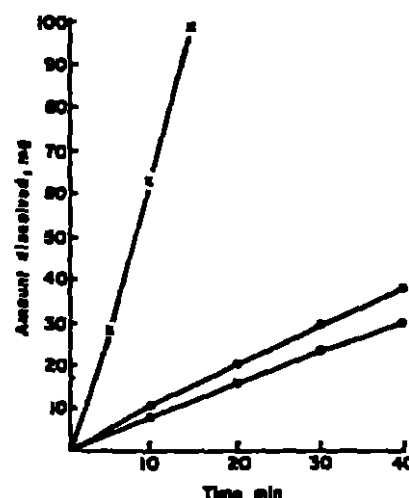


Fig 5-1 Effect of starch content of granules on dissolution rate of salicylic acid contained in compressed tablets [Reproduced from Levy *et al.*, *J Pharm Sci* 52, 1050 (1963)]

Key: ○ 5% ○ 10% × 20% starch in granules.

1966, investigated the same phenomenon utilizing phenobarbital tablets. It was found that only when the drug was mixed with the starch and then dry granulated, were fast disintegrating granules obtained. Dry granulation alone did not improve the dissolution rate. They suggested that the hydrophobic drug crystals acquire a surface layer of fine starch particles that impart a hydrophilic property to the granular formulation and thereby increase the effective surface area and hence the dissolution rate.

Yen,⁸ in 1964, studied the effect of different diluents on the dissolution rate of the sparingly soluble drug triamterene when manufactured by wet granulation. Four fillers were tried: starch, lactose, glycine and *terra alba*. The results showed significantly better dissolution rates with the first three diluents, all hydrophilic powders, but hard and less soluble granules were obtained with *terra alba* as diluent.

In another study by Marlowe and Shargaw,⁹ the use of starch as a diluent was shown to produce sodium salicylate tablets with a much faster dissolution rate than when lactose was used. Different types of starch were studied by Underwood and Cadwallader¹⁰; however, the type of dissolution apparatus utilized for testing was found to affect the ranking of the different starch varieties employed. With stirring type of agitation, the order was, potato starch > corn > arrowroot > rice; with the oscillating type of agitation, a different order was observed, corn > rice > arrowroot > potato.

Disintegrant

A disintegrant is used to cause the tablet to disintegrate when exposed to an aqueous environment.

The studies of Solvang, *et al*¹¹ and Finholt, *et al*¹² showed that starch not only is an excellent diluent but also a superior disintegrant due to its hydrophilicity and swelling property. Varley⁶ reported a significant decrease in the serum level of tolbutamide when the amount of Vee-gum used as a

disintegrant in the tablets was reduced by 50%. Other workers¹³ evaluated the effects of different types of disintegrants on the dissolution rate of phenobarbital tablets. A water insoluble brand of sodium carboxymethylcellulose (Nymcel), was found to be less effective than Primojel, a sodium glycolate of potato starch. It may be pointed out that care should be taken in investigating the possibility of adsorption of some drugs to the surface of certain diluents and disintegrants. Highly adsorbent substances, e.g., bentonite, should be avoided in tablet formulations of drugs used in very small doses, such as cardiac glycosides, alkaloids, synthetic estrogens and steroids. These substances can be adsorbed permanently so that only a fraction would be available after administration. Yen⁸ found that triamterene was adsorbed by the disintegrant Vee-gum.

The deleterious effect of lubricants, especially magnesium stearate, on the effectiveness of disintegrants has been highlighted by Bolhuis, *et al*,^{14,15} Lerk, *et al*,^{16,17} Shah and Mlodzeniec,¹⁸ and DeBoer, *et al*.¹⁹ The lubricant forms a thin hydrophobic film around the tablet excipients, thereby inhibiting the penetration of water into the tablet pores and delaying disintegration. Bolhuis, *et al*,¹⁵ showed that the efficacy of potato starch as a disintegrant is decreased by an increase in the mixing time of the tablet ingredients with magnesium stearate. However, Proost, *et al*,²⁰ pointed out that because the hydrophobic film formed by the lubricant never envelopes the disintegrant particles completely, the swelling is not inhibited at the surface of the tablet where the disintegrant particles are in direct contact with water. Working with diazepam tablets (Table 5.1) the authors demonstrated that with disintegrants of a moderate swelling capacity such as potato starch, the disintegration and dissolution rates depend to a large extent on the mixing time of the drug/excipient preblend with the lubricant magnesium stearate. In this case the disintegration also was largely in

Table 5 1—Diazepam Tablet Formulations with Variable Swelling Capacities of Diluents

Ingredient, % (w/w)	Formulation			
	P-2	P-30	S-2	S-30
Diazepam	2.5	2.5	2.5	2.5
Dicalcium phosphate dihydrate	77	77	93	93
Potato starch	20	20		
Sodium starch glycolate			4	4
Magnesium stearate	0.5	0.5	0.5	0.5
Mixing time with magnesium stearate (min)	2	30	2	30

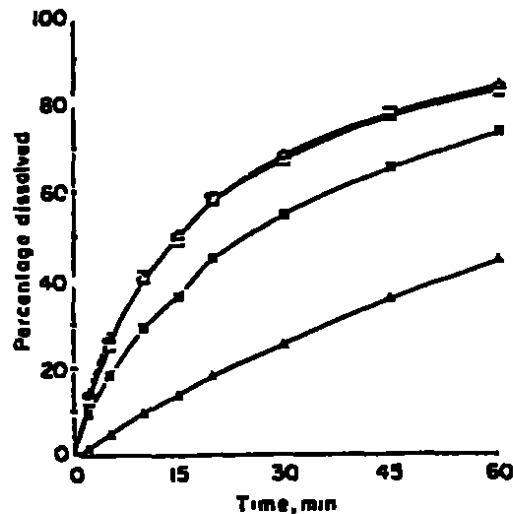


Fig 5-2 Dissolution profiles of diazepam determined with the rotating basket at 100 rpm. [Reproduced from Proost, *et al*, *Int J Pharm*, 13, 267 (1983)]
Key: ■ P-2; ▲ P-30; □ S-2; △ S-30 (abbreviations see Table 5-1).

fluenced by mechanical means such as the dissolution apparatus and agitation rate. On the other hand, when disintegrants with a strong swelling capacity, such as sodium starch glycolates, were used the disintegration and dissolution rates hardly were affected by the time of mixing with magnesium stearate. In this case, the surface structure was disrupted completely, permitting water to penetrate into the tablet and hence, effecting rapid disintegration and dissolution without the aid of mechanical means (Fig 5-2).

Binders and Granulating Agents

Substances added to impart cohesive or binding qualities to the powdered drug for

mulation, in order to insure that the tablet remains intact after compression, are called binders or granulating agents. These materials include gelatin solution, starch, sugar natural and synthetic gums such as gum acacia, gum tragacanth, polyethylene glycols, polyvinylpyrrolidone, Veegum and carboxymethylcellulose.

Wet granulation, in general, has been shown to improve dissolution rates of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules. Solvang and Finholt¹¹ determined the rate of dissolution of phenobarbital, phenacetin and prednisolone before and after granulation and compression into tablets. In all cases, the dissolution rate was faster with the granules than for the pure drug. The rate of release was also faster after compression than that obtained for the uncompressed granules (Fig 5 3a). This was attributed to the better wettability of the tablets and also to the fact that some deformation or crushing of the granules occurs during compression, thus increasing the effective surface area, a finding reported earlier by Higuchi, *et al*.²¹⁻²⁴ The authors showed that with normal tablet compression, deformation of the granules takes place but without the particles breaking up. The particles are changed from being almost spherical to being nearly disk shaped and hence their surface area is increased.

Regarding the most suitable binding agent, Solvang and Finholt¹¹ showed that phenobarbital tablets granulated with gelatin solution dissolved much faster in human gastric juice than those prepared with sodium carboxymethylcellulose or polyethylene

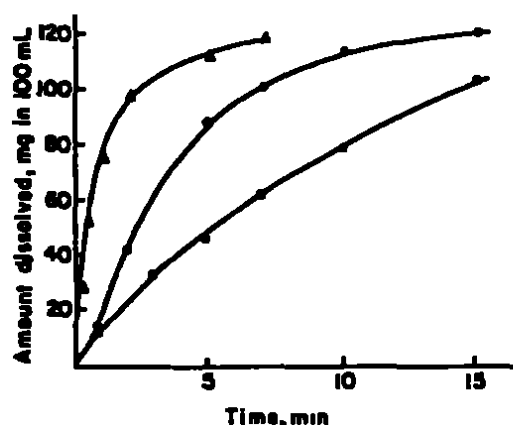


Fig 5-3a. Rate of dissolution of phenacetin from powder granules and tablets in diluted gastric juice (surface tension 42.7 dynes cm^{-1} pH 1.85) [Reproduced from Solvang and Finholt, *J Pharm Sci* 59, 50 (1970).]

Key: O phenacetin powder Δ phenacetin granules, ● phenacetin tablets.

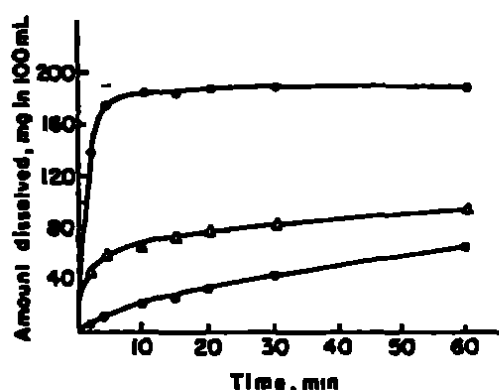
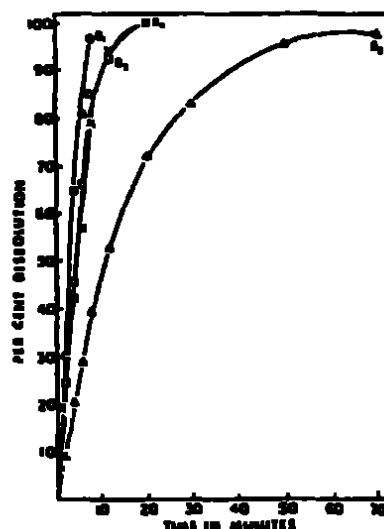


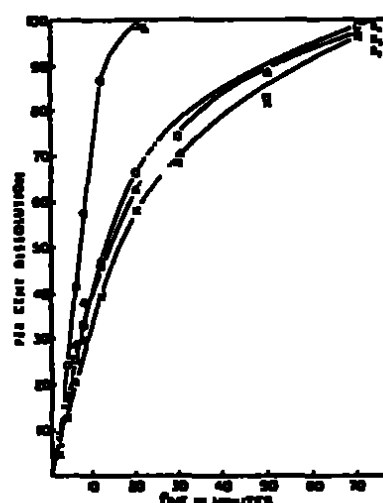
Fig 5-3b. Dissolution rate of phenobarbital tablets in diluted gastric juice (surface tension 39.4 dynes cm^{-1} pH 1.50). [Reproduced from Solvang and Finholt, *J Pharm Sci* 59, 50 (1970)]

Key: ● gelatin binder Δ CMC O polyethylene glycol 6000.

glycol 6000 as a binder (Fig 5 3b) They suggested that gelatin imparts hydrophilic characteristics to the hydrophobic drug surface, whereas sodium carboxymethylcellulose is converted in the low pH gastric juice to its less soluble acid form. In case of polyethylene glycol it was proposed that it forms a poorly soluble complex with phenobarbital probably during the dissolution test. This fact was reported earlier by Higuchi and Lach³⁵ and later by Singh *et al*³⁶ who found that the complex ratio is 45:5 mg



a



b

Fig 5-4. a: Comparison of filler-binders in a tablet formula containing starch, hydrogenated vegetable oil and 3.5 S-C hardness b: Comparison of filler-binders in a tablet formula containing no starch, magnesium stearate and 6.5 S-C hardness [Reproduced from Marlowe and Shangraw, *J Pharm Sci* 56, 500 (1967)]

Key: B₁ spray-dried lactose; B₂ ethylcellulose and lactose; B₃ acacia mucilage and lactose; B₄ starch paste and lactose

of polyethylene glycol 4000/100 mg of phenobarbital at 37°C and pH 5.3

Finholt, *et al*² reported similar results using sulfadiazine and phenacetin as test drugs, when the fastest dissolution rate was obtained with drugs granulated with gelatin

as opposed to CMC and carbowax 6000 Marlowe and Shangraw⁹ compared the effect of various fillers and binders on the dissolution rate of experimental tablet batches and found that formulations containing spray dried lactose dissolved faster than other formulations. The slowest dissolution was obtained when ethyl cellulose was used in combination with lactose (Figs 5-4a and 5-4b). The retarding effect of ethyl cellulose was confirmed by Jacob and Plein⁷⁷ who compared the dissolution rates of phenobarbital tablets manufactured with gelatin as well as other popular binders such as gum acacia, ethyl cellulose and hydroxymethylcellulose. The authors reported that gelatin produced the best dissolution behavior, whereas the use of the cellulose derivatives resulted in tablets with poor dissolution characteristics. On increasing the amount of gelatin, however, tablets with decreased dissolution rate (and increased hardness) were obtained. Yen⁸ reported similar results on increasing the amount of gelatin used as binder.

Lubricants

Tablet granulations usually can not be compressed without the addition of small quantities of materials called lubricants that enhance their processing characteristics. Lubricants improve the flow of the tablet granulation, reduce interparticle friction and prevent adhesion of the tablet material to the surface of the dies and punches of the compressing machine. Lubricants also facilitate the ejection of the tablets from the die cavities.

During the mid 50s, Takeru Higuchi²¹⁻²³ and his colleagues at the School of Pharmacy, University of Wisconsin published an important series of articles on the physics of tablet compression. In their discussion of the theoretical aspects of tablet lubricants, they categorized them into two major groups: the first called the fluid (or hydrodynamic) type, such as hydrocarbons (mineral oil and paraffin), and the second known as the boundary type lubricant, such as the

metallic stearate salts and talc, considered to be the best lubricants. These investigators, however, warned that the addition of lubricants, such as talc and magnesium stearate, to granulations tended to prolong markedly the tablet disintegration time. They explained that the lubricant usually forms a water repellent coat around individual granules, which appeared to remain almost intact during the compression process. The lubricant did not mix intimately with the granular content during compression, but usually was confined only to the surface and the intergranular regions. The retarding effect of this water repellent film formed by the lubricant later was shown³⁸ to be the most important factor in influencing the rate of dissolution of solid dosage forms. It greatly inhibits the wettability of the tablet and decreases the penetrability of the dissolution medium thereby reducing the effective surface area and dramatically prolonging the process of dissolution.

Both the amount and the method by which the lubricant is added to the granulation can affect greatly its performance and reduce its unwanted waterproofing properties. The lubricant should be added only in small amounts (1% or less) and should be divided finely by passing it through a 100-mesh nylon cloth onto the granulation. The blend then should be tumbled or mixed gently for only a very short time. Prolonged mixing of the lubricant with the granulation may significantly affect the hardness, disintegration and dissolution times of the resulting tablets. Lubricants that cannot be pulverized efficiently, such as stearic acid, can be dissolved in an organic solvent, such as ether, and sprayed over the granules. Levy and Gurntow²⁸ investigated the effects of different types of lubricants on the dissolution rate of salicylic acid tablets. They found that magnesium stearate, a hydrophobic lubricant, retarded the dissolution rate of salicylic acid tablets, while a water-soluble surface active lubricant, sodium laurylsulfate enhanced the dissolution rate significantly (Figs 5-5a and 5-5b). Investi-

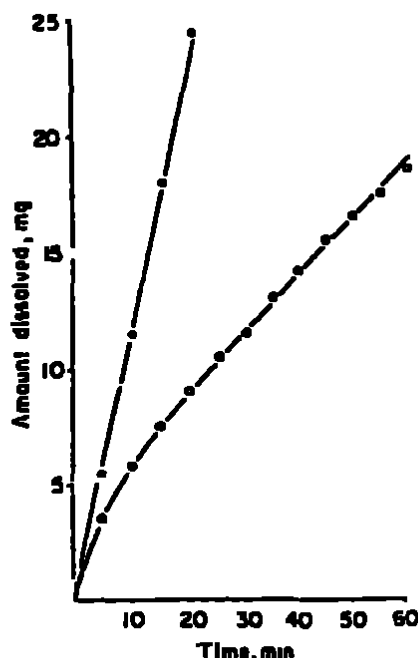


Fig 5-5a. Effect of magnesium stearate on dissolution rate of salicylic acid from rotating disks made from fine salicylic acid powder [Reproduced from Levy and Gurnow *J Pharm Sci*, 52 1140 (1963)]
Key O 3% magnesium stearate; ● no lubricant added.

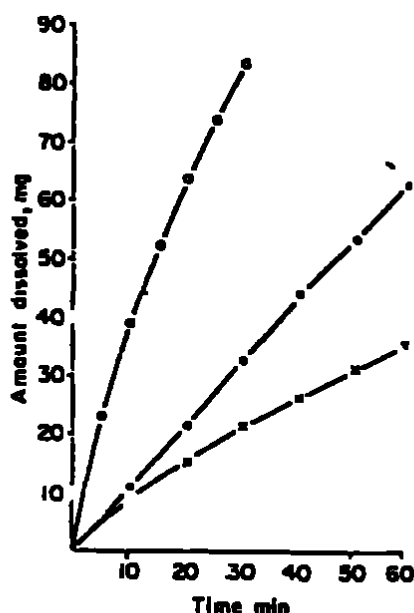


Fig 5-5b Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula A). [Reproduced from Levy and Gurnow *J Pharm Sci* 52 1140 (1963)]
Key X, 3% magnesium stearate; ● no lubricant; O 3% sodium lauryl sulfate.

gating the mechanism of retardation they suggested that hydrophobic lubricants, such as magnesium stearate, aluminum stearate, stearic acid and talc, decrease the effective drug solvent interfacial area by changing the surface characteristics of the tablets which results in reducing its wettability, prolonging its disintegration time and decreasing the area of the interface between the active ingredient and solvent. The enhancing effect of sodium lauryl sulfate, on the other hand, was suggested to be due, in part to an increase in the microenvironment pH surrounding the sparingly soluble weak acid and to increased wetting and better solvent penetration into the tablets and granules as a result of lowering the interfacial tension between the solid surface and the solvent. This conclusion was in agreement with observation by Wuster and Seitz²⁰ who found that dissolution of pellets with artificial pores increased when sodium lauryl sulfate was added to the dis-

solution medium. The fact that sodium lauryl sulfate is a water-soluble lubricant was not considered a factor in improving the dissolution rate, since sodium stearate, an other water soluble lubricant, was found to have a retarding effect on the dissolution rate. Other water soluble lubricants did not fare any better. Carbowax 6000 was tried by Yen⁸ and found to produce triamterene tablets with slower dissolution rates than those manufactured with magnesium stearate. Marlow and Shangraw⁹ tried another water-soluble lubricant, containing carbowax 4000, with sodium salicylate tablets, and this also was found to produce tablets with slower dissolution rates than those made with magnesium stearate.

Jammet, *et al*³¹ investigated the effect of different lubricants on the dissolution rate of phenobarbital tablets and found that the optimum concentration of magnesium stearate is about 1% or less. Increasing its quantity to 1.5% resulted in tablets with decreased dissolution rate. Ironloye and

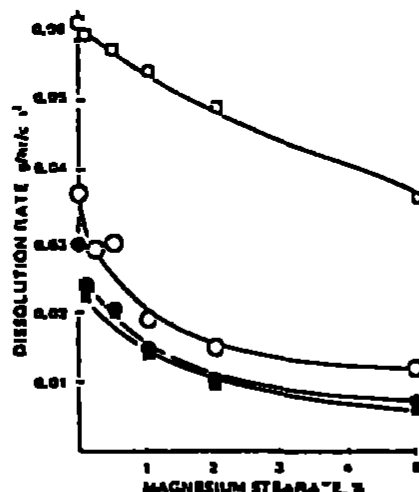


Fig 5-6a. Effect of concentration of magnesium stearate on dissolution rate of 80/100-mesh materials compressed at 1135 kg [Reproduced from Iranloye and Parrott *J Pharm Sci*, 67 535 (1978)]

Key: ○ salicylic acid; □ aspirin, ● salicylic acid from equimolar mixture of aspirin and salicylic acid; ■ aspirin from equimolar mixture of aspirin and salicylic acid.

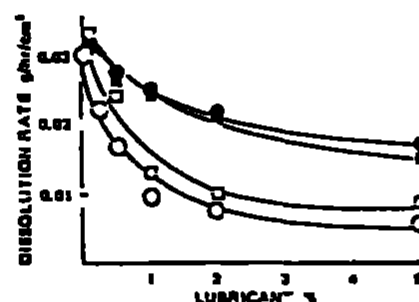


Fig 5-6b Effect of concentration of calcium stearate and glyceryl monostearate on dissolution rate of 80/100-mesh equimolar mixture of aspirin and salicylic acid compressed at 1135 kg [Reproduced from Iranloye and Parrott, *J Pharm Sci*, 67 535 (1978)]

Key: ○ salicylic acid with calcium stearate; □ aspirin with calcium stearate; ● salicylic acid with glyceryl monostearate; ■ aspirin with glyceryl monostearate.

Parrott³² compared the effect of several hydrophobic lubricants on the dissolution rate of aspirin and salicylic acid tablets. The authors found that an increase in concentration of magnesium stearate, calcium stearate, glyceryl monostearate or stearic acid decreased the dissolution rates of disks of an equimolar mixture of aspirin and salicylic acid (Figs 5 6a and 5 6b) With mag

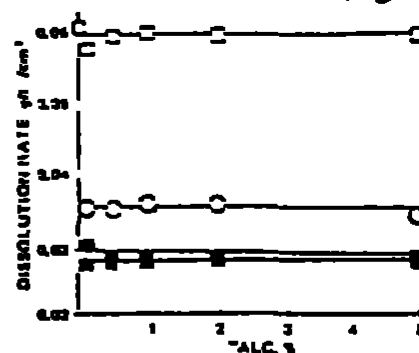


Fig 5-6c. Effect of concentration of talc on dissolution rate of 80/100-mesh materials compressed at 1135 kg [Reproduced from Iranloye and Parrott, *J Pharm Sci*, 67 535 (1978)]

Key: ○ salicylic acid; □ aspirin, ● salicylic acid from equimolar mixture of aspirin and salicylic acid; ■ aspirin from equimolar mixture of aspirin and salicylic acid.

nesium stearate, a concentration of 0.5% decreased the dissolution rates of salicylic acid and aspirin by 33 and 27%, respectively, whereas stearic acid at 1% decreased the dissolution rate by 7 and 10%, respectively. Talc on the other hand, behaved differently. As shown in Fig 5-6c, the dissolution rates of disks compressed from salicylic acid, aspirin and an equimolar mixture of aspirin and salicylic acid essentially were independent of the talc concentration, up to 5%. It was suggested that the stearates soften and spread under compression to produce a more prominent coverage of the matrix than talc.

Iranloye and Parrott³² also confirmed Levy's and Guntow's finding that the use of water soluble lubricants, such as polyethylene glycol 4000, does not enhance the dissolution rate since a lubricant must be simultaneously a water-soluble and surface active agent (e.g., sodium lauryl sulfate) to produce an enhancement. Finholt, *et al*,⁷ however, reported that while sodium lauryl sulfate enhanced the release of phenobarbital from granules it had little effect on the dissolution from tablets. The use of paraffin and silicone as lubricants and their effect on dissolution was discussed by Igwilo and Pilpel³³ and others.^{34,35} Addition of these lubricants produced a parallel increase in disintegration and dissolution time (Fig 5-7)

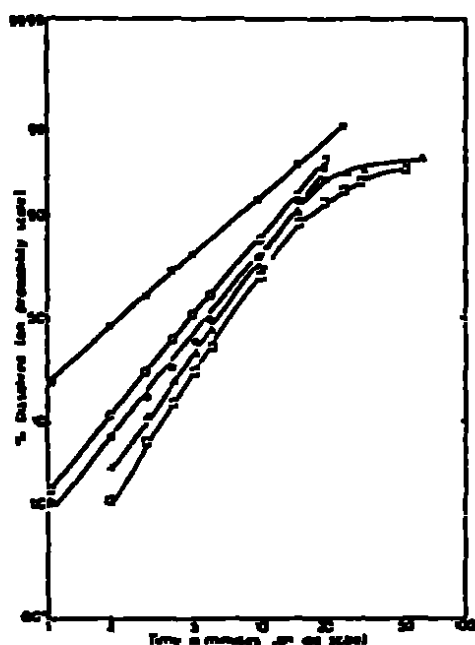


Fig 5-7 Wagner plot on dissolution tests of tablets compressed at 20°C containing 0.0–10.0 $\times 10^{-3}$ mol/g of light liquid paraffin [Reproduced from Igwilo, and Pilpel *Int J Pharm*, 15, 73 (1983).]

Key: $\star$ lactose "blank" (0.0×10^{-3} mol-g $^{-1}$); $\bullet$ 0.5×10^{-3} mol-g $^{-1}$; $\circ$ 1×10^{-3} mol-g $^{-1}$; Δ 5.0×10^{-3} mol-g $^{-1}$; $\square$, 10.0×10^{-3} mol-g $^{-1}$

This was attributed to the fact that paraffins and silicones not only reduce the wettability of the surface of a tablet by increasing its contact angle with water but also reduced the interparticle friction and change the nature, shape and size distribution of the capillaries which conduct water into it. The presence of a paraffin or silicone in the tablet voids makes the internal surface more hydrophobic and reduces the number of capillaries which are contributing to the transport of water, thereby decreasing dissolution rate.

Evaluating all factors, metallic stearates are considered the best lubricants, so long as they are used in very small amounts (<1%) and mixed with the matrix for a very short time. However, if an enhancing effect in the dissolution characteristics of hydrophobic granules is desired, a surface active water-soluble lubricant such as sodium lauryl sulfate, may be tried.

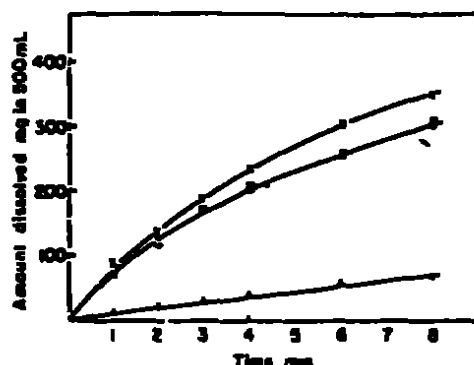


Fig 5-8. Effect of Polysorbate 80 on the dissolution rate of phenacetin from granules. [Reproduced from Finholt, "Dissolution Technology" published by the Industrial Pharmaceutical Technology Section of the Academy of Pharm Sci p 133 (1974), edited by Leeson and Carstensen.]

Key: Δ phenacetin granules; ∇ phenacetin granules II with 0.1% Polysorbate 80 added, dissolved in the granulating solution; $\square$ phenacetin granules II with 1% Polysorbate 80 added, dissolved in the granulating solution; $\times$ phenacetin granules II with 0.1% Polysorbate 80 sprayed on the dried granules.

Effects Of Other Tablet Additives

Effect of Surfactants In Formulations on the Dissolution Rate

The addition of surface-active substances to hydrophobic tablet formulations had been shown, in some cases, to enhance the dissolution rate of poorly soluble drugs. This is due to the lowering of the interfacial tension between the solvent and the solid surfaces of the tablet and granules, thereby increasing the effective surface area, which in turn results in a faster dissolution rate. Solvang and Finholt¹¹ have shown that the addition of polysorbate 80, a nonionic surfactant, to phenacetin granules increased the dissolution rate (Fig 5-8). The increase was more pronounced when the surfactant was sprayed on the granules than when it was dissolved in the granulating agent. Cantt *et al.*^{12,13} also reported that the addition of surfactants to certain tablet formulations resulted in better absorption of the poorly soluble drug. Although this was attributed initially to a physiologic effect, it later was shown that the low concentration of the surfactant could not account for such

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274 81

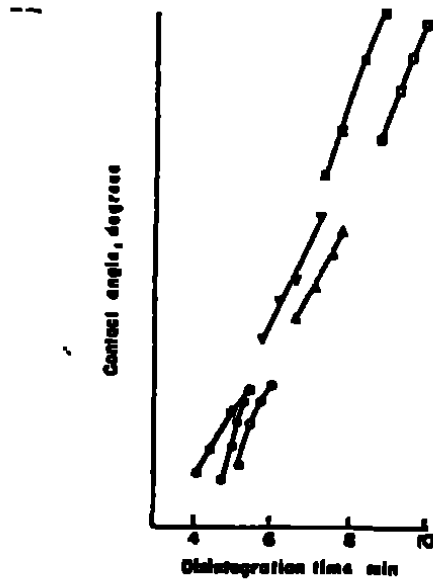


Fig 5-9a. Correlation of contact angle of water on the powder compacts containing $0.5-10.0 \times 10^{-3} \text{ mol g}^{-1}$ of paraffins and silicones with the disintegration time (min) of the corresponding tablets compressed at 20°C [Reproduced from Igwilo and Pilpel *Int J Pharm*, 15, 73 (1983)]

Key: $\bullet$ light liquid paraffin; $\circ$ liquid paraffin; Δ white soft paraffin; $\square$ paraffin; $\star$ silicone dc 200/20; ∇ silicone dc 200/50; $\boxplus$ silicone dc 350

a mechanism. Rather, the increase in absorption was found to be due to a dosage form effect. The surfactant enhances the dissolution rates of the drugs contained in the compressed tablets and thereby causes them to be more rapidly and completely absorbed. Igwilo and Pilpel³³ pointed out that the water penetrates through the matrix capillaries as a result of the pressure difference, Δp , which exists across the entrance to each capillary according to the equation of Carman³⁸

$$\Delta p = \frac{Y \cos \theta}{m} \quad (5-1)$$

where Y is the surface tension of water, θ is its contact angle on the capillary surface and m is the ratio of the cross sectional area of the capillary to its perimeter. It is clear that the slowest penetration occurs when Δp is minimum (i.e., when θ is 90°). Figure 5-9 illustrates this relationship between the contact angle and the disintegration time as

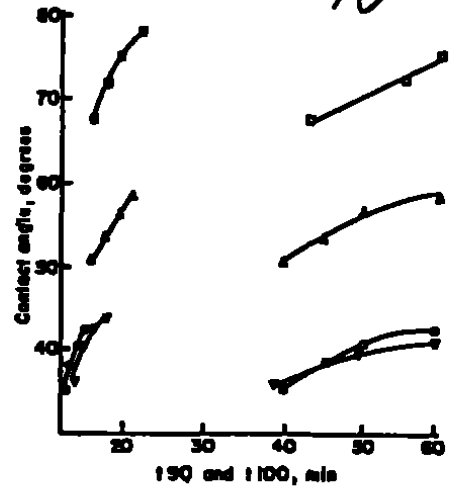


Fig 5-9b. Correlation of contact angle of water on the powder compacts containing $0.5-10.0 \times 10^{-3} \text{ mol g}^{-1}$ of paraffins with t_{50} and t_{100} of the corresponding tablets compressed at 20°C . [Reproduced from Igwilo and Pilpel *Int J Pharm*, 15, 73 (1983)]

Key: Light liquid paraffin: $\bullet$ t_{50} , $\circ$ t_{100} ; Liquid paraffin: ∇ t_{50} , ∇ t_{100} ; White soft paraffin: Δ t_{50} , Δ t_{100} ; Paraffin wax: $\boxplus$ t_{50} , $\square$ t_{100} .

well as the dissolution time of lactose tablets, using paraffin and silicones as lubricants. The presence of these hydrophobic substances in the tablet voids increases the contact angle and reduces the number of capillaries which contribute to the transport of water. Newton, *et al.*,³⁹ demonstrated that the addition of 1% of the surface active agent, sodium lauryl sulfate, increased the dissolution rate of the hydrophobic drug ethinamate filled into capsules at a high and at a low packing capacity. When discussing the effects of surfactant additions to tablet formulations, it is important to differentiate between the enhancement of dissolution rate by lowering the surface tension and increasing penetrability which requires only small amount of surfactants, and the micelle solubilization of a drug which requires significantly larger amounts of the surface active agent.^{40,41}

Kakemi, *et al.*,⁴² demonstrated that the rectal absorption of sulfisoxazole was increased when the compound was solubilized with polysorbate 80. Ravin *et al.*⁴³ reported

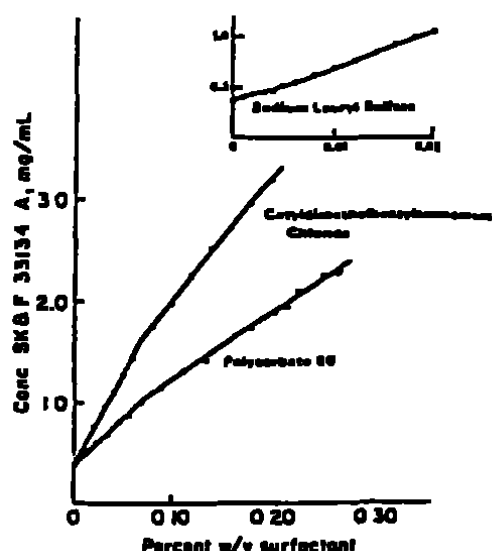


Fig 5-10. Effect of surfactant concentration on the solubility of SK&F 33134-A [Reproduced from Ravin, *et al*, *J Pharm Sci* 58, 1242 (1969)]

that the aqueous solubility of SK&F 33134-A, an experimental antifungal agent, was increased in the presence of sodium lauryl sulfate, cetyltrimethylbenzylammonium chloride or polysorbate 80 (Fig 5-10), the effect being proportional to concentration. A two-fold increase in availability was also observed for SK&F 33134-A when the compound was administered in polysorbate 80 solution to bile-cannulated rats, as compared to a tragacanth suspension. Although, in many instances, the apparent increase in aqueous solubility has some effect on the availability of the drug, results have been at times anomalous. An example, is the data reported by Levy and Reuning⁴⁴ where the solubilization of salicylic acid with polysorbate 80 led to a decrease in the absorption of the drug. Therefore, care should be taken in utilizing different types of surfactants in large concentrations especially because of the toxicity effects some of these compounds may impart to the formulation.

Effects of Certified Water-Soluble Dyes on the Dissolution Rate

The inhibiting effects of low concentrations of various certified water soluble dyes

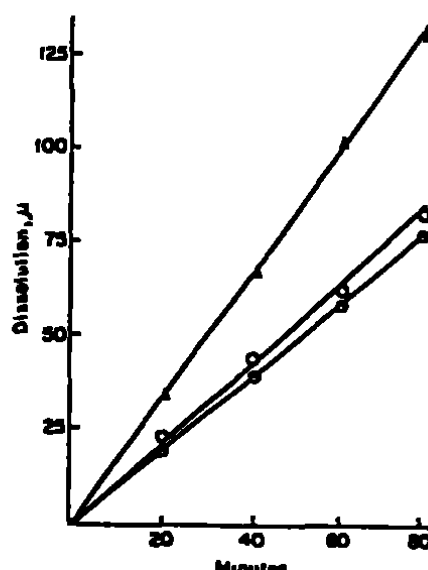


Fig 5-11a Single-crystal dissolution of sulfathiazole as a function of time. Effect of water soluble dyes on the dissolution rate of drugs. [Reproduced from Piccolo and Tawashi *J Pharm Sci*, 60 59 (1971).]

Key: ○ In distilled water; ▲ In 0.04M solution of sodium cholate; □ In 0.04M solution of sodium cholate containing 5 mg/mL FD&C Blue No. 1

on the dissolution rates of several crystalline drugs was first demonstrated by Piccolo and Tawashi.^{44,46} The dissolution rate of a single crystal of sulfathiazole was found to decrease significantly in the presence of FD&C Blue No. 1. The inhibiting effect was related to the preferential adsorption of the dye molecules on the primary dissolution sources of the crystal surfaces. Similar effects were also observed when compressed disks of sulfathiazole were used⁴⁷ (Fig 5-11a). Piccolo and Tawashi found that the dyes inhibit the micellar solubilization effect of sodium cholate on sulfathiazole, an effect which could lead to the impairment of the drug absorption through the micellar solubilization by the bile salts in the intestine (Fig 5-11b). This later was confirmed⁴⁸ *in vivo* on human volunteers (Fig 5-11c). Other *in vitro* studies^{47,49} showed similar inhibitory effects by a relatively large number of the existing certified water soluble dyes on the dissolution rate of diethylstilbestrol. The authors also showed that cat

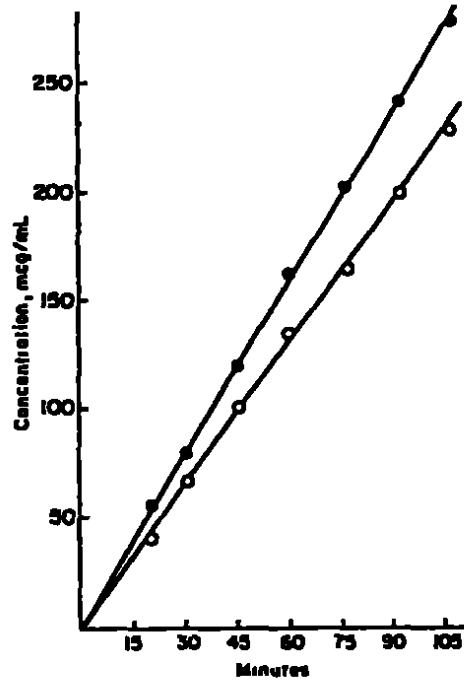


Fig 5-11b. Dissolution behavior of sulfathiazole compressed disks. Effect of water soluble dyes on the dissolution rate of drugs [Reproduced from Piccolo and Tawashi *J Pharm Sci*, 60, 59 (1971)]
Key: ● compressed disks of drug crystals alone; ○ compressed disks of drug crystals containing 5 mg FD&C Blue No. 1

ionic dyes are more reactive in lower concentrations than are anionic dyes, probably due to higher adsorption intensity at the primary dissolution sources on the crystal surface

Dyes also have been implicated⁴⁰⁻⁴³ with interactions and other stability problems. Prillig⁴³ investigated the effect of colorants on the solubility of modified cellulose polymers such as hydroxypropyl methyl cellulose and sodium ethyl cellulose sulfate. Free film solubility studies showed that six dyes significantly altered the solubility of the polymers tested. Figure 5-12 shows that the dissolution rate of riboflavin tablets decreased when FD&C Red No. 3 dye was incorporated in the film coat. Riboflavin urine excretion studies confirmed that several of the certified dyes may adversely affect *in vivo* product performance. Because these cellulose polymers have considerable use in tablets, gels and suspension prepara-

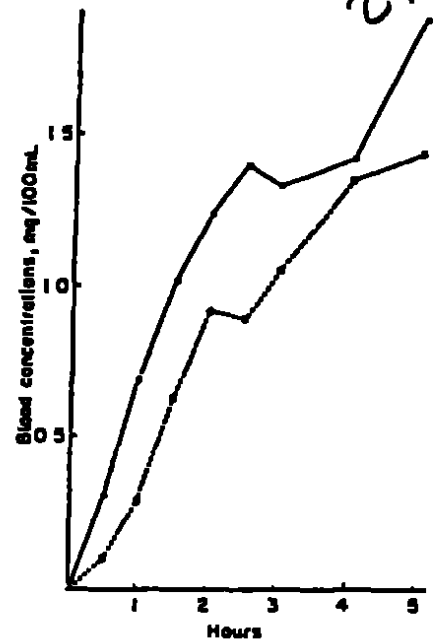


Fig 5-11c. Blood concentrations of free sulfathiazole following oral administration of 1 g sulfathiazole crystals. [Reproduced from Tawashi and Piccolo *J Pharm Sci*, 61, 1857 (1972)]
Key: ○ In presence of FD&C Blue No. 1; ● In absence of FD&C Blue No. 1

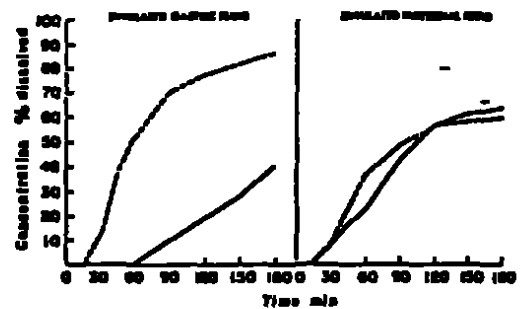


Fig 5-12. Riboflavin dissolution rate study on hydroxypropylmethylcellulose coated tablets USP XVII disintegration apparatus, 37° (without plastic disks). Effect of colorants on the solubility of modified cellulose polymers. [Reproduced from Prillig *J Pharm Sci*, 58, 1245 (1969)]
Key: ---, control; —, film with FD&C Red No. 3 dye.

tion, the above findings are of particular importance for the formulator

Effect of Coating Components on Tablet Dissolution

Coating ingredients, especially shellac, cellulose acetate phthalate, etc, also have

significant effects on the dissolution rates of coated tablets. However, these effects are related mostly to the disintegration and/or the solubilization of the coat itself rather than the inner core of the dosage form.

Effects of the Processing Factors on Dissolution Rates of Tablets

Many processing methods used in tablet manufacturing greatly influence the dissolution rates of the active ingredients. The method of granulation, size, density, moisture content and age of the granules, as well as the compression force utilized in the tableting process, all contribute to the dissolution rate characteristics of the final product.

Method of Granulation

Several studies have shown clearly that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs (Figs 5-13a and 5-13b). The use of fillers and diluents, such as starch,⁵ anhydrous⁴⁴ and spray-dried lactose^{55,56} and microcrystalline cellulose,⁵⁷ tends to increase the hydrophilicity of the active ingredients and improve their dissolution characteristics. In this regard, the wet granulation procedure traditionally was considered as a superior method compared to the dry or double compression procedure. With the advent of newer tableting machines and materials, however, it became more evident that the careful formulation, proper mixing sequence and time of addition of the several ingredients are the main criteria that affect the dissolution characteristics of the tablets, and not the method of granulation *per se*. Marlowe and Shangraw⁶ studied the dissolution of sodium salicylate tablets prepared by both wet granulation and direct compression procedures (Fig 5-14). They found that tablets prepared by direct compression with spray-dried lactose uniformly exhibited more rapid and complete dissolution profiles compared to those prepared by wet granulation. The presence of a disintegrant (starch) in the dry compression formula was

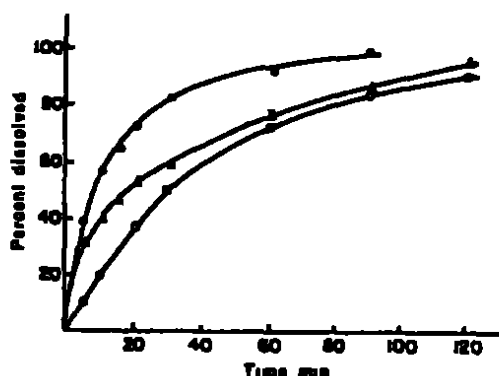


Fig 5-13a. Rate of dissolution of phenobarbital from powder granules and tablets in diluted gastric juice (surface tension 46.4 dynes cm^{-1} , pH 1.95). [Reproduced from Solvang and Finholt, *J Pharm Sci*, 59: 50 (1970)]

Key: ○ phenobarbital powder; ▲ phenobarbital granules; ● phenobarbital tablets.

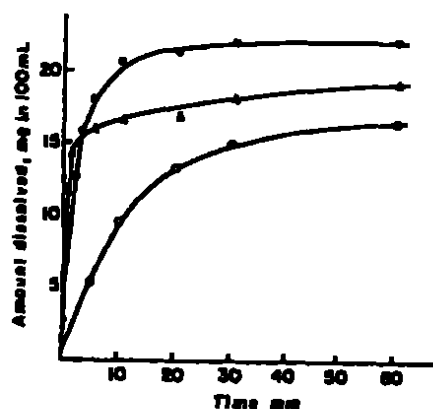


Fig 5-13b. Rate of dissolution of prednisone from powder granules and tablets in diluted gastric juice (surface tension 41.1 dynes cm^{-1} , pH 1.50). [Reproduced from Solvang and Finholt, *J Pharm Sci*, 59: 50 (1970)]

Key: ○ prednisone powder; ▲ prednisone granules; ● prednisone tablets.

essential for good dissolution. In the case of wet granulation, the use of acacia mucilage and lactose gave the fastest dissolution, while the use of ethyl cellulose and lactose consistently gave very slow and incomplete dissolution. Tablet hardness did not have a significant effect in either method, although it seemed to be of some importance for those formulations containing starch. Finholt, *et al.*,⁷ reported another comparative study utilizing phenobarbital tablets

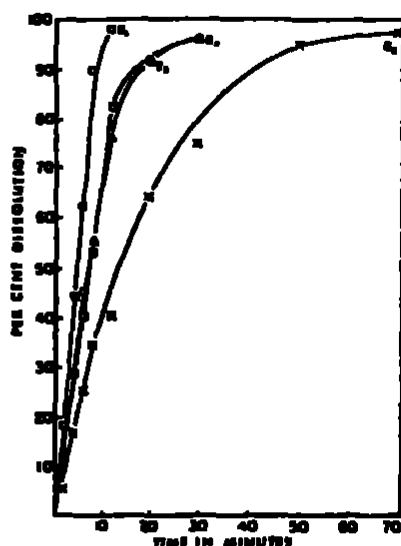


Fig 5-14. Dissolution rate of sodium salicylate tablets. [Reproduced from Marlow and Shangraw *J Pharm Sci*, 56, 500 (1967)]

Key: O B₁—direct compression with spray dried lactose; X B₂—wet granulation with ethylcellulose and lactose; A, B₃—starch mucilage and lactose; □ B₃—starch paste and lactose.

that were manufactured by both wet granulation (with gelatin) and by dry granulation. Other formulation items such as fillers and lubricants were the same. Both manufacturing procedures gave comparable rates of release provided that a disintegrant (starch) was incorporated and mixed with the drug before dry granulation. A significantly slower rate was obtained if the drug was dry granulated first and the disintegrant was added later. Levy, *et al.*⁵ studied the effect of the size of granules on the dissolution rate of salicylic acid tablets and found that the dissolution rate increased with a decrease in granule size, but not proportional to the increase in the apparent surface area of the granules (Fig 5-15a). They also found that the dissolution rate decreased significantly with the increase in the age of the granules (1-5 weeks) (Fig 5-15b).

Although wet granulation is employed widely, the method has several drawbacks. The liquid present may cause crystal bridge formation and lower the activity of micronized drugs,⁵⁸ or at times, provides the vehicle for chemical changes such as hydrolysis and

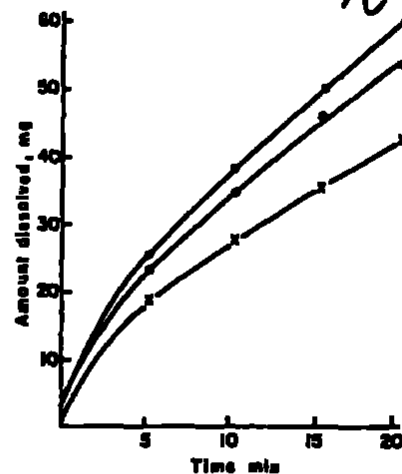


Fig 5-15a. Effect of granule size on dissolution rate of salicylic acid contained in compressed tablets. [Reproduced from Levy *et al*, *J Pharm Sci*, 52, 1048-1049 (1963)]

Key: ● 18-20 mesh; □ 20-40 mesh; X, 40-60 mesh granules.

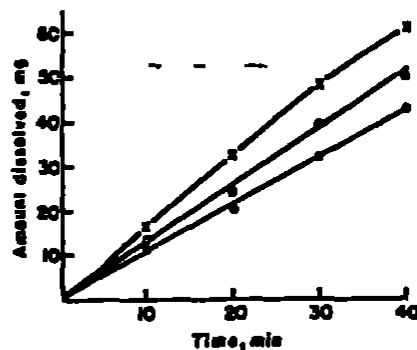


Fig 5-15b. Effect of granule age on dissolution rate of salicylic acid contained in compressed tablets [Reproduced from Levy *et al*, *J Pharm Sci*, 52, 1048, 1049 (1963)]

Key: ● one week; □ 3 weeks; X 5 week old granules.

degradation. Also, in the subsequent drying step, the use of heat and air may decompose thermolabile drugs and affect content uniformity through selective solute migration.⁵⁹ In addition due to the several equipment components required and the time and labor consumed, wet granulation is more costly than other granulation procedures.⁶⁰ Because of this Ho and Hersey^{61,62} introduced a novel method of granulation based on the fact that agglomeration usually occurs spontaneously after prolonged

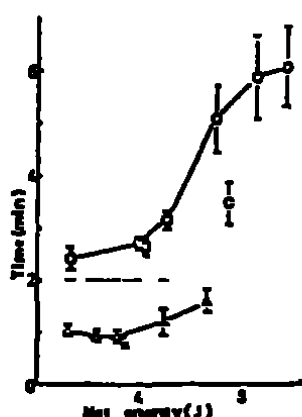


Fig 5-16a Dissolution (T86 7%) of paracetamol tablets prepared at different energy levels O Paracetamol tablets prepared by wet granulation method Δ Paracetamol tablets prepared by APOC method [Reproduced from Ho *et al*, *J Pharm Pharmacol* 32 160 (1980)]

grinding of several drugs in a ball mill. The method, called Agglomerative Phase of Commiution, "APOC," was found to produce mechanically stronger tablets with a higher dissolution rate than those compacted from granules made by the conventional wet granulation method, irrespective of the compaction energy used (Fig 5 16a). A possible mechanism for the increased dissolution rate is the increased internal surface area of the granules produced by the APOC method. Krycer and Hersey⁶³ also showed that agglomeration of ground particles during prolonged comminution in a vibratory ball mill is an irreversible process that forms granules of excellent binding quality. The authors compared⁶⁴ the dissolution characteristics of granules produced by a preliminary compression, "PC," technique and those produced by the APOC method. Four materials were utilized as models, lactose, sucrose, sodium chloride and paracetamol. While the granules produced by the PC method dissolved faster than pure crystals of the drug, the POC granules had the fastest dissolution rate (Fig 5 16b).

Hasegawa *et al*,⁶⁵ studied the factors that affect the dissolution properties of digoxin tablets. They noted that the dissolution of tablets prepared by the powder dilu-

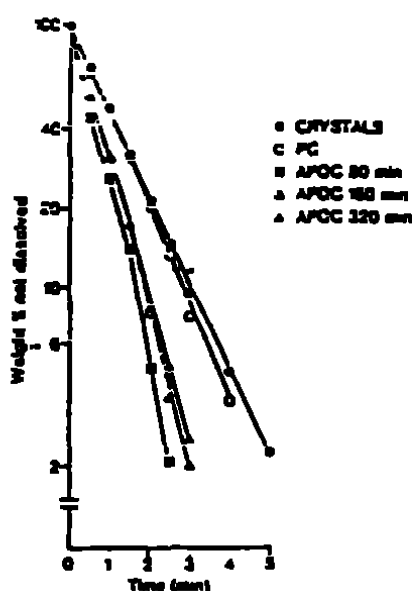


Fig 5-16b Dissolution profiles of paracetamol granules and crystals sized between 355 and 500 μm , according to Wagner's plot. Each point is the average of five determinations. [Reproduced from Krycer and Hersey *Int J Pharm Technol Prod Manuf* 2(2), 51 (1981)]

tion method was influenced to a great extent by the difference in mean particle size of the digoxin powder, while the release of digoxin from the tablets produced by the solvent deposition method showed a fast dissolution rate compared with the tablets made by powder dilution without depending on the difference in batch.

Nixon and Hassan⁶⁶ discussed the factors affecting the dissolution of thiabendazole tablets prepared from, or containing, microcapsules. The microcapsules were prepared from a suspension of the drug in 2% gelatin solution which was stirred at 300 rpm and 40°C, with an equal volume of 2% acacia solution. After adjusting the pH to 4, about 10 mL of formaldehyde solution was added and the temperature reduced to 5°C with continued stirring. The microcapsules then were filtered and washed with isopropyl alcohol. Because of the nonbinding nature of the microcapsule walls it usually is necessary to use additives during tableting—and their effect on the drug release was examined by the authors. The addition of

stearic acid as lubricant led to an increase in the disintegration as well as the dissolution times, but no break in the dissolution profile parallel with disintegration was exhibited. Starch produced fast disintegration but no significant effect on dissolution, however, the dissolution of uncompressed microcapsules was affected. It also was noticed that higher compression pressures produced a slower initial release rate, but after 45 min approximately 95% of the drug was released. It was suggested that the initial slow release rate probably is due to an increased difficulty of fluid penetration into the compressed mass. Nevertheless, after disintegration, a faster dissolution rate, compared to the uncompressed microcapsules, may result because of some damaged microcapsule walls, though none were visible. Balancing this effect, however, is the effect normally found when diffusion occurs from a depot. As the depot approached exhaustion, there is always a decrease in the rate of release. This agreed with previous findings by Luzzi, *et al*,⁶⁷ who reported that the dissolution rate of sodium phenobarbital was inversely proportional to tablet hardness. Similarly Jalsenjak, *et al*,⁶⁸ reported that tableting slowed down the release of sodium phenobarbital from ethylcellulose microcapsules.

In manufacturing tablets by the conventional wet granulation method, there are many interdependent factors that affect the property of granules and hence the dissolution rate of the produced tablets. Although recent advances in tablet manufacturing technology and the introduction of high speed shear mixers and granulating equipment have helped to minimize several in-process variables, still, the systematic control of variables such as the type and time of mixing of the granules, method time and temperature of drying, blending time with the lubricant, age of the granules, moisture content of the granules at the time of compression and the tablet crushing strength is of vital importance to ensure the production of tablets with consistent dissolution

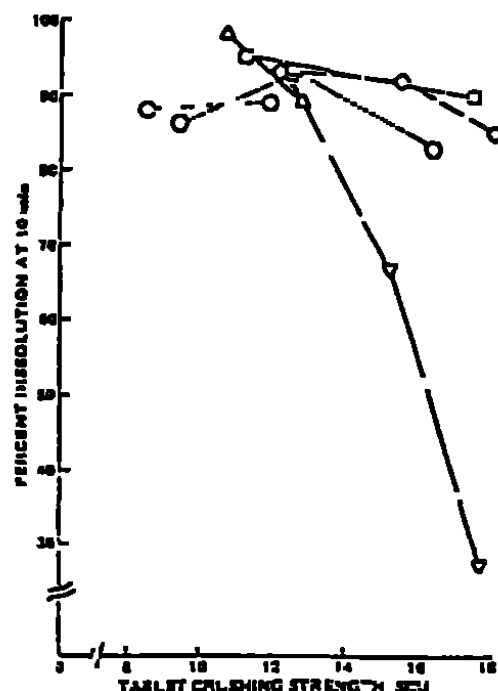


Fig 5-17 Plots of percent *in vitro* drug dissolution at the 10-min time point as a function of the tablet crushing strength at different granulation moisture contents. The moisture contents at the time of compression were (O) 0.9% (Δ) 1.6% (▽) 2.0% (□) 3.0% (◇) 3.6% (○) 4.3% [Reproduced from Chowhan, *et al*, *J Pharm Sci*, 71: 1371 (1982)]

characteristics. Chowhan, *et al*,⁶⁹⁻⁷³ studied the effect of moisture content and crushing strength on ticlopidine hydrochloride tablet friability and its dissolution. It was shown⁷² that at lower moisture content (1-2%), the drug dissolution is related strongly to the tablet crushing strength. The higher the tablet crushing strength, the lower the percent drug dissolved and vice versa. However, at higher moisture content (3-4%), the dissolution of the drug showed very little relationship to the crushing strength of the tablets (Fig 5-17). In a later study,⁷³ Chowhan and Chatterjee⁷⁰ studied the characteristics of granules produced in a high speed shear mixer in lieu of the planetary mixers used in their previous studies. The authors reported that granulations made in a high speed shear mixer generally are less porous than those made in a planetary one. They also found that by utilizing a

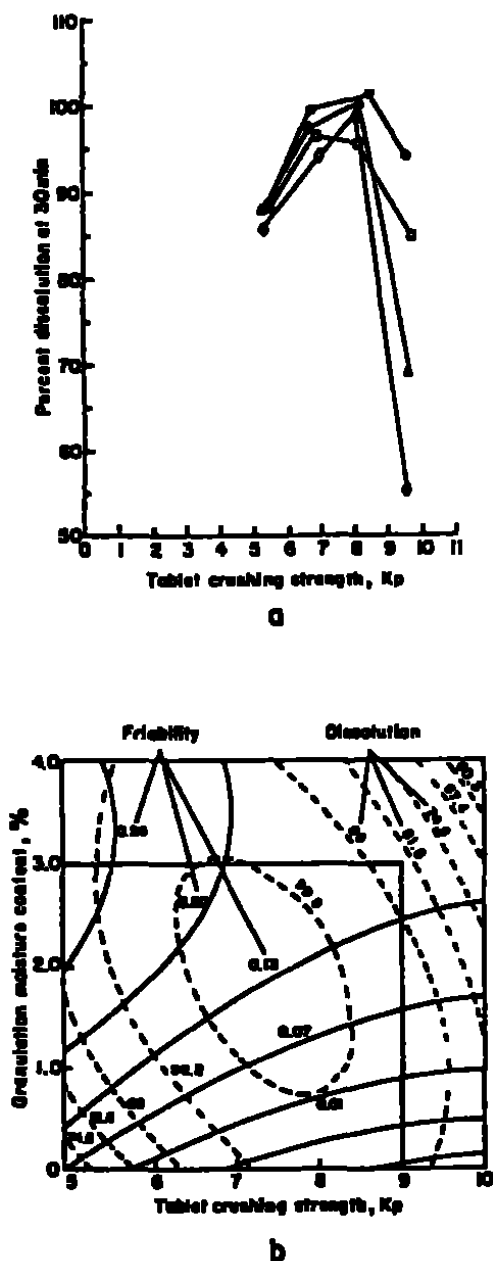


Fig 5-18 a: Plots of tablet crushing strength vs *in vitro* drug dissolution at the 30 min time point at different moisture contents for the extra deep concave punch-tip face geometry. The moisture contents in the granulation at the time of compression were (○) 1.2% (Δ) 2.1% (□) 3.0% (◇) 4.0%. b: Contour overlays showing the superimposed contour plots of tablet friability and *in vitro* drug dissolution for the deep concave punch-tip face geometry. The area within the boundaries represents the ranges in which process specifications for tablet crushing strength and granulation moisture content could be established [Reproduced from Chowhan and Chatterjee, *Int J Pharm Technol Prod Manuf* 5(2): 6 (1984)]

general quadratic response surface model, the optimum *in vitro* dissolution, corresponding to the tablet crushing strength and granulation moisture, was a simple maximum (Fig 5-18a). Tablet friability, however, exhibited a minimum-maximum response surface precluding an absolute optimum. Dissolution rate also varied with changes in punch-tip face geometry, at different crushing strengths containing different granulation moisture contents. Chowhan and Chatterjee, demonstrated that the response surface contour plot for the *in vitro* drug dissolution consisted of elliptical level curves with an elliptical paraboloid surface. The contour overlays of the friability and dissolution contour plots indicated a region where both friability and dissolution requirements could be satisfied by controlling the in-process variables, such as granulation moisture content and tablet crushing strength (Fig 5-18b).

Effects of Compression Force on Dissolution Rate

In early studies of the physics of tablet compression, Higuchi²¹ pointed to the great influence of the compressional force employed in the tableting process on the apparent density, porosity, hardness, disintegration time and average primary particle size of compressed tablets. Higuchi, *et al*,²¹ utilized a sulfathiazole granulation as a model to show that there is a logarithmic relationship between the compressional force and the apparent density or porosity of the tablets. The percent porosity was calculated by the equation

Percent porosity =
$$\left(1 - \frac{\text{apparent density of tablet}}{\text{true density of tablet}} \right) \times 100 \quad (5-2)$$

Apparent density of the tablet is the quotient of its weight and its geometric volume—True tablet density refers to the density of the compact solid mixed ingredients of

which the tablet is composed, excluding the entire pore volume that are larger than spacings of molecular or atomic dimensions, which exist in the crystal lattices of the solid ingredients. The porosity of the tablet may improve dissolution by facilitating solvent penetration, but, the entrapment of air in these pores inhibits the wettability of the tablet in dissolution media with high surface tension, such as water and 0.1 M HCl. This effect however, could be minimized by deaerating the dissolution medium or by using a surfactant. Higuchi's studies also showed that a linear relationship exists between hardness and the logarithm of the compressional force and between the logarithm of the disintegration time and the compressional force. The specific areas of the compressed tablet, a key factor in determining the dissolution rate, were found to undergo marked changes during the compressional process, exhibiting a pronounced maximum at about 2,500 lb for $\frac{3}{8}$ -in. tablets.

The interdependence of these factors and their significant influence on dissolution, project a complex and variable relationship between the compression of the tablet force and the rate of dissolution of the drug (Fig 5-19). There is always a competing relationship between the enhancing effect due to the increase in surface area through the crushing effect and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness and, consequently, a decrease in solvent penetrability. The high compression also may inhibit the wettability of the tablet due to the formation of a firmer and more effective sealing layer by the lubricant under the high pressure and temperature that usually accompany a strong compressive force.

Therefore, the curve profile of the compression force of the tablet vs dissolution rate can take one of several shapes. Levy, et al,⁵ reported that salicylic acid tablets, manufactured by double compression (to avoid the effect of binders used in wet granulation), showed an increase in dissolution rate with an increase in precompression

pressure (Fig 5-20). This was considered to be due to the fracturing of drug particles at a higher slugging pressure, yielding smaller primary particles and increasing the effective surface area. This confirmed the early findings by Higuchi, et al,⁷⁴ with aspirin tablets and also a finding by Nelson⁷⁵ that aspirin tablets manufactured at very high compression were absorbed much faster by humans than those made at a lower pressure. Yen⁸ studied several formulations of triamterene tablets and found that both maxima and minima were exhibited in the dissolution rates as a function of the tablet hardness, which is directly related to the compression force. Ganderton, et al,⁷⁶ found that by increasing the compression force used for penindione tablets prepared by wet granulation, the disintegration time progressively decreased with increasing pressure. Dissolution rate, however, followed a more complex course, decreasing at lower pressure (better bonding), then increasing at higher pressure (crushing effect) and decreasing again with further increase in pressure because of extra rebonding and formation of denser tablets with poorer dissolution characteristics.

Armstrong and Griffith⁷⁷ and Armstrong and Haines-Nutt⁷⁸ tried to explain these nonlinear relationships in dissolution rate and compression force via a thorough measurement of the specific surface area of compacts of several different granulations as a function of compression force using a nitrogen adsorption method. It was found that a maximum existed in this function for each granulation used. This demonstrated the credibility of the previous theoretical concepts that have been advanced for the explanation of this nonlinear and complex relationship between dissolution rate and compression force, i.e., the existence of an optimum ratio of bonding to cleavage or crushing of the drug crystals that occurs during the compression event. Jacob and Plein⁷⁹ studied the effect of hardness on phenobarbital tablets and found that dissolution decreased with the increase in tablet hardness.

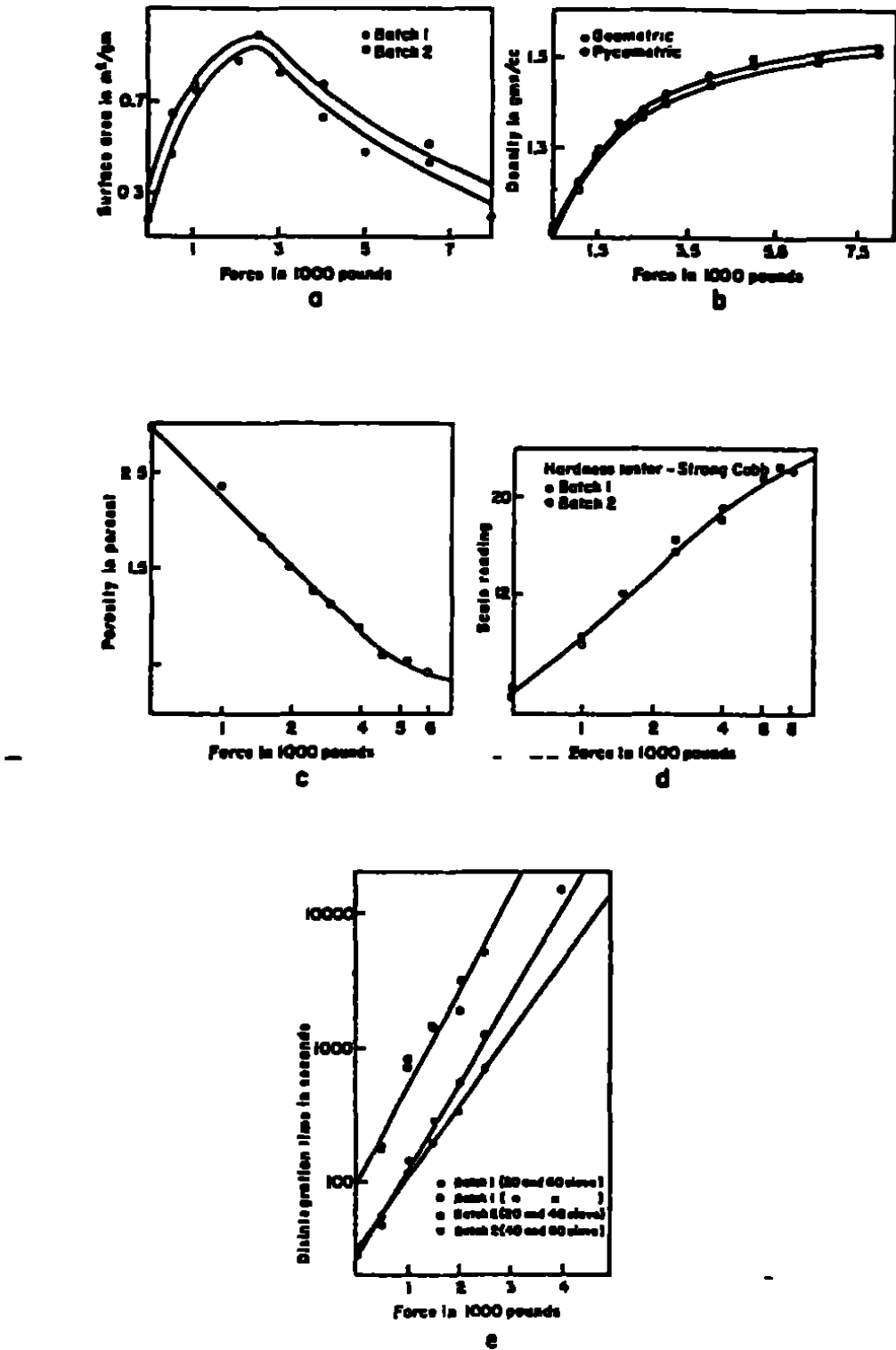


Fig. 5 19 The effect of compressional force on a the specific surface area of sulfathiazole tablets b on the apparent density of sulfathiazole tablets c on the porosity of sulfathiazole tablets d on the hardness of sulfathiazole tablets e on the disintegration time of sulfathiazole tablets [Reproduced from Higuchi *et al* J Am Pharm Assoc Sci Ed XLII, 194 (1953)]

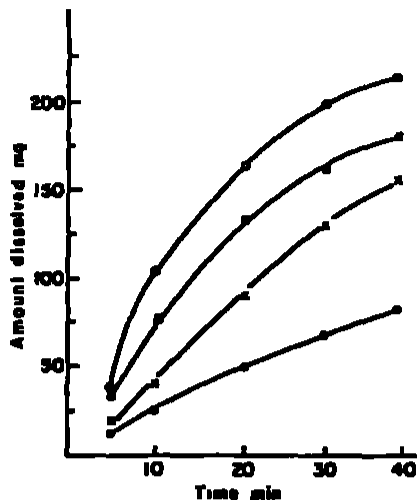


Fig 5-20. Effect of precompression pressure on dissolution rate of salicylic acid contained in compressed tablets [Reproduced from Levy *et al* *J Pharm Sci*, 52 1047 (1963)]
Key: ● 715 kg; × 1430 kg; ■ 2860 kg; ◊ 5730 kg pressure per cm² (Average of five tablets each, formula D.)

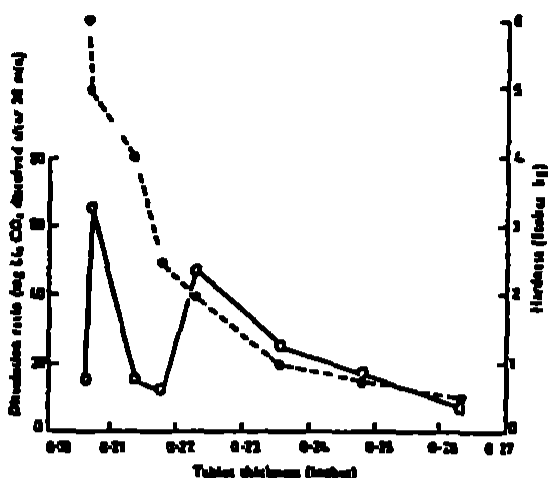


Fig 5-21. Dissolution rate (O—O) of Li₂CO₃ tablets containing 8 mg per tablet of PVP as a function of tablet thickness for tablets of constant weight (left-hand scale). Hardness (●—●) of same tablets with varying thickness (right-hand scale). [Reproduced from Smith, *et al*, *J Pharm Pharmacol* 23, 538 (1971)]

Hardness determinations usually are made throughout the compression process to determine the need for any pressure adjustments on the compression machine. If the tablet is too hard, the tablet may not disintegrate in the required time, and if it is too soft, it could not withstand handling during coating, packaging and shipping. The hardness test indicates the resistance of the tablet to chipping, abrasion or breakage during processing operations. This is accomplished by measuring the force, in kilograms, required to break the tablet when a force is applied diametrically. Another test for tablet resilience is the friability determination. The friabilator evaluates the ability of the tablet to withstand abrasion during a tumbling process. Based on these findings, Smith, *et al*,²⁰ agreed with Ganderton's interpretation that the complex dissolution behavior in response to variable compression force demonstrates the existence of a nonlinear relation between force and the ratio of bonding to cleavage occurring during the compression event. The data seem contradictory because they do not follow a simple mechanistic interpretation. Consequently the authors suggested that the

data can be explained only in terms of the dependency of dissolution rate on the changes in particle size or specific surface area during tablet compression. Dissolution rate should decrease when particle bonding is the predominant factor during compression and should increase when particle cleavage is predominant. Further, the ratio of cleavage to bonding would not be related linearly to the compression force. The authors assessed the roles of tablet hardness and compression force used and the resulting dissolution characteristics of lithium carbonate tablets with various concentrations of polyvinylpyrrolidone (PVP) as binder. Figure 5-21 shows that two maxima were exhibited, one at lower compression force (greater thickness) and a second at a higher compression force. The authors suggested that the low compression force maxima are related to the structure and crushing characteristics of the granules and therefore to the concentration of the binder. Up to this maximum, fission of the granular structure results in increased dissolution release rates with increasing pressure. With increasing pressure compact fusion or bonding occurs

which markedly reduces dissolution rate (a minimum) At still higher pressure, increase in dissolution rate may reoccur as a result of a new relative dominance of a cleavage component. This phase was considered to be dependent mainly on the inherent compression characteristics of the drugs and the formulations, and not the binder

Carless and Sheak⁸¹ showed that during compression of powders of different particle size, there was a critical size where the phenomenon of bonding and cleavage of particles within the tablet balanced each other Changes in particle size distribution after compaction were studied by measurement of the changes in the particle size distribution after disintegration which, according to Kitamori and Makino,⁸² can elucidate whether particle bonding or cleavage occurs within the tablet during compression

Tuladhar, *et al*,^{83,84} studied the effect of polymorphism on the dissolution/compression force relationship Utilizing two polymorphic forms of phenylbutazone as a model, the authors assessed the relative change in the particle size of the drug during compression by comparing the dissolution rates of the drug particles before and after compression (a change in the particle size of the drug will be reflected by a change in the dissolution rate) When the excipient was Avicel,⁸⁵ the critical particle size of polymorph A was approximately 90 μm , however, with lactose, the value was higher The critical particle size for polymorph B was approximately 600 μm when either Avicel[®] or lactose was used With a low drug concentration (10%) in the tablet, the diluent prevented the drug particles from bonding together Lactose had an abrasive action on polymorph A compared with Avicel but had no effect on the more ductile form B When the contact time of compression was decreased from 20 to 0.26 sec, the 6 μm particles of drug exhibited less bonding at the shorter time but with larger particle size, the effect was independent of the com

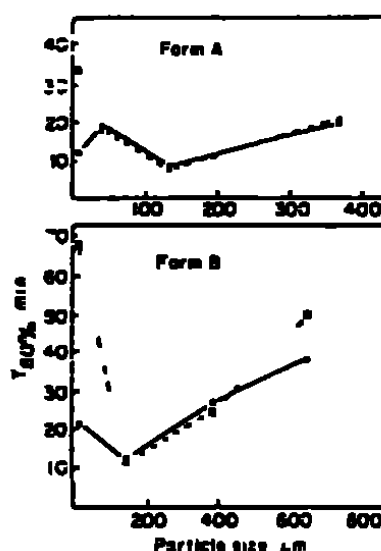


Fig 5-22. Effect of rate of compression on dissolution of phenylbutazone tablets. Polymorphic Form A and Form B - - - - 0.26 sec contact time - - - 29 sec contact time [Reproduced from Tuladhar *et al*, *J Pharm Pharmacol*, 35, 269 (1983)]

pression rate (Fig 5-22) Therefore, the study shows that the effect of the compression rate will be important for time-dependent materials when the degree of elastic/plastic flow will be affected by the rate of application of stress (under high compression rate, the elastic properties predominate, while at low compression rate plastic flow can lead to increased bonding) This is clear from the finding that the dissolution rate of the more plastic crystal form B increased by a greater extent than the less plastic crystal form A as the contact time was reduced from 29 to 0.26 sec.

Several authors^{85,86} tried to interpret the complex relationship between the compression force and dissolution as a reflection of the changes in relative density that occur during compression. The relative density is defined according to Lewis and Train⁸⁵ as the ratio of compact density to density of the solid material The authors showed that at increasing compression forces the relative density of tablets becomes greater until a maximum is reached. The force at which the maximal relative density is obtained depends on the composition of the tablet formulation Polderman and Braakman⁸⁷

Table 5-2—Relation Between Compression Force, Relative Density and Dissolution Time

	Compression force, kg	Relative density	Dissolution time, sec	CV
1	230	0.81	1400	14.0
2	260	0.82	965	11.2
3	290	0.83	680	15.0
4	318	0.85	440	16.3
5	430	0.89	135	16.0
6	500	0.90	110	14.2
7	520	0.91	110	12.4
8	650	0.94	129	11.4
9	900	0.96	250	10.5
10	1140	0.97	380	8.0
11	1350	0.97	435	2.9
12	1640	0.97	440	3.4
13	1800	0.97	440	2.1
14	2000	0.97	440	3.8

Note: CV (the coefficient of variation) is given only for the dissolution time and not for the relative density since this is always less than 0.5% [Reproduced from Foidart and Brashers, *J Pharm Pharmacol* 20, 323 (1968).]

compared the dependence of both the dissolution time and the relative density on the force of compression for sodium chloride tablets. In Table 5-2, the average values for the 90% dissolution times and the relative densities at 14 different compression forces are listed. The data show that the dissolution time becomes almost constant at about the same compression force at which the relative density becomes constant, the dissolution profile exhibits a minimum. This behavior, however, was not the same with other tablet formulations where an initial decrease was not found.

From the above discussion, it is apparent that a full dissolution/compression study for each granulation formulation is essential to determine the compression parameters that will assure good dissolution characteristics and adequate bioavailability.

The Effect of Formulation and Processing Factors on the Dissolution Rate of Capsules

Compared to tablets, capsules traditionally have received considerably less attention regarding the effects of different formulation and processing factors on their dissolution rate. This may be due to the popular misconception that encapsulation is rather

a simple pharmaceutical manipulation that imparts little, if any, change on the physical properties of the active ingredients. Disintegration tests were not specified for capsules, since it was known that the shell dissolved rapidly in the gastrointestinal tract and, therefore, the release of the drug was expected to be fast and complete. Nelson⁸⁸ ranked the bioavailability of the oral dosage forms in the order: solution > suspension > powder-filled capsule > compressed tablet > coated tablet. Wagner, *et al*,^{89,90} found that soft gelatin capsules have better bioavailability than the powder-filled capsules and are about equivalent to emulsions (Fig 5-23a). Later on, however, it was recognized that, in spite of rapid breakdown upon ingestion, capsules could have severe bioavailability problems. Tannenbaum, *et al*,⁹¹ showed that, in some cases, a tablet could yield greater drug absorption than a powder-filled capsule. The release of aspirin from hard gelatin capsules was shown by Wood⁹² to be irregular and to have an average delay time of about 15 min.

Glazko, *et al*,⁹³ reported different absorption rates from capsules containing identical amounts of chloramphenicol manufactured by different pharmaceutical houses (Fig 5-23b). Poole⁹⁴ observed measurable differences in the dissolution rates of capsule formulations of ampicillin produced by several manufacturers.

Brice and Hammer⁹⁵ also noted significant bioavailability problems with oxytetracycline capsules when the antibiotic serum levels of about 16 commercially available brands were measured (Fig 5-24). These alarming findings have prompted several investigators to study the dissolution characteristics of capsules and the effects of the formulation design and processing techniques on their bioavailability. Certain factors were identified readily as the main contributors to the differences between the dissolution characteristics and physiologic availability of the same drug that is available in several market formulations. Factors such as particle size, density

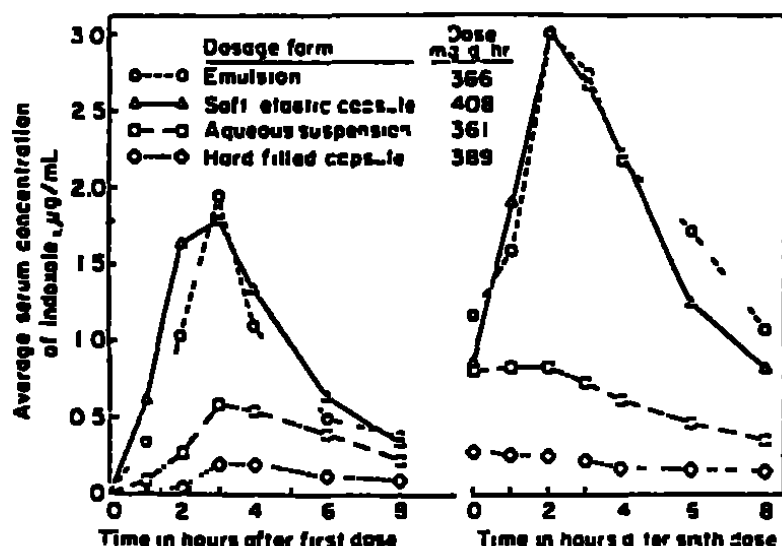


Fig 5-23a Average serum concentrations of indoxole observed in eight volunteers following oral administration of the indicated doses every 8 hr [Reproduced from Wagner *et al*, *Clin Pharmacol Ther* 7, 810 (1968).]

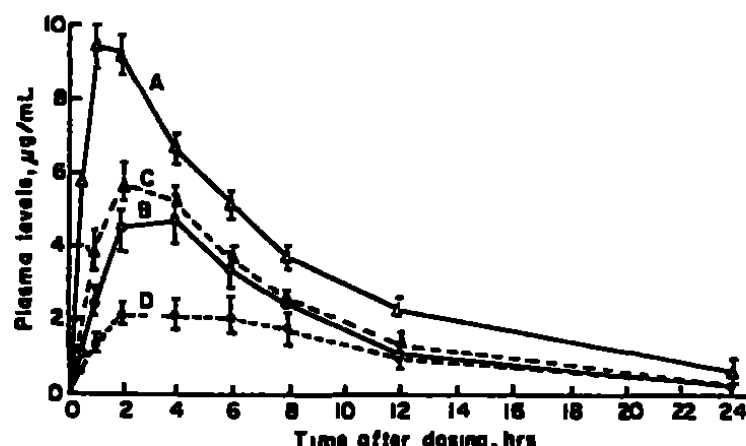


Fig 5-23b. Mean plasma levels for groups of ten human subjects receiving single 0.5 gm oral doses of chloramphenicol preparations A, B, C or D [Reproduced from Glazko *et al*, *Clin Pharmacol Ther* 9, 472 (1967)]

and crystalline form of the active ingredient, forced packing, addition of lubricants and their retarding effect on the wettability and penetration characteristics of the powder bed, particle deaggregation and rate of dispersion of the wet bed, all have been shown to be of prime importance. The problems related to drug particle size and crystalline form have been discussed previously under the effects related to the physicochemical properties of the drug material. Therefore, the following discussion will be concerned mainly with the influence of the several additives that usually are incorporated in capsule formulations, as well as the processing factors such as weight/volume filling ratio and the packing pressure employed.

Effects of Additives on the Dissolution Rate of Capsules

It is known that several adjuncts have to be added to the pure drug in capsule formulations to simplify weight adjustments and/or to allow mechanized filling of the capsules. Typically, capsule formulations contain a relatively high proportion of the drug moiety as compared to the amount of the diluent and fillers present. Therefore, if the drug has a dominant hydrophobic character, the wettability and dispersion of the powder bed will be very poor, even if the capsule shell dissolves very rapidly. McGee, *et al*⁹⁶ investigated the *in vitro* dissolution of acetylsalicylic acid packed in hard gelatin capsules and reported that the capsules

Comparative blood studies in micrograms of oxytetracycline per milliliter. Zero level = two squares above baseline. Squares vertically = 0.25 µg/ml each. Top line = 1.5 µg/ml.

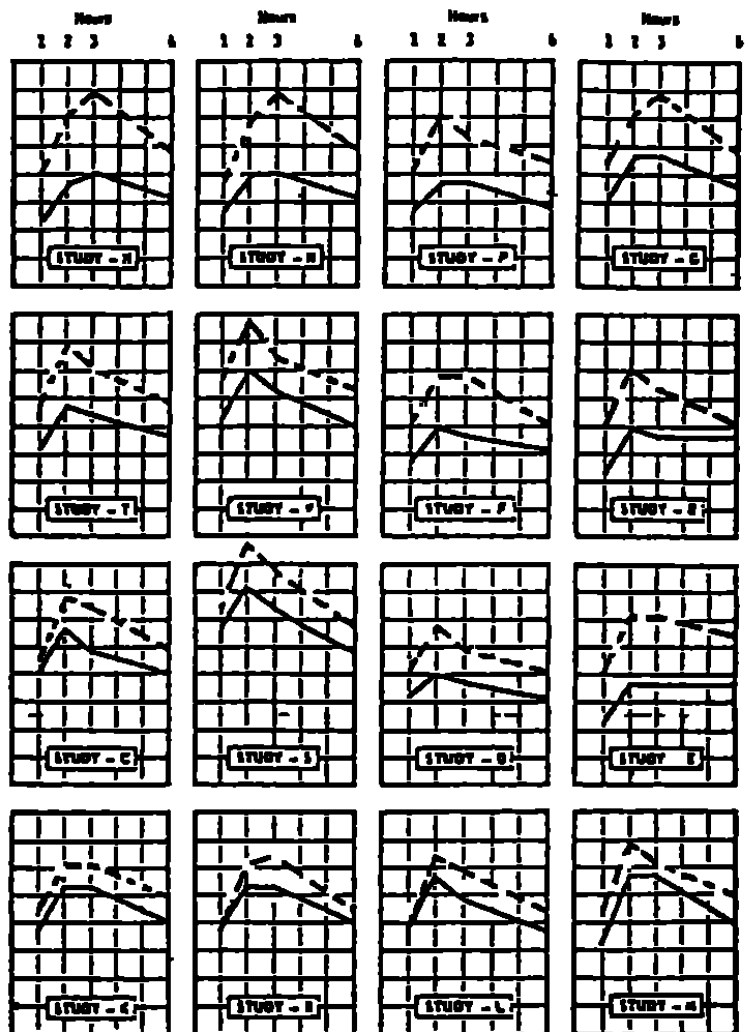


Fig 5-24. A cross-over serum level study with 20 subjects on 16 lots of oxytetracycline capsules. The Innovators batch was used as a control. [Reproduced from Brice and Hammer J Am Med Assoc, 208, No 7 1190 (1969).]

Key: Innovators Batch, —; Other Suppliers, - - -

showed distortion and did not appear to break down readily even in the presence of the digestive enzyme used and the relatively high agitation intensities of the oscillating tube method. Figure 5-25 presents sketches of the appearance of the capsule at various dissolution stages. The authors also studied the effects of two excipients, lactose and dibasic calcium phosphate, on the dissolution and absorption rate of acetylsalicylic acid from hard gelatin capsules. Their results showed that the use of dibasic calcium phosphate as a diluent provided a faster dissolution rate than did the use of lactose. Plasma level data confirmed the *in vitro* findings. The authors also noted that the acetylsalicylic acid became moist and after

awhile, the gelatin stretched and broke down only after striking against the 100 mesh screen. It was suggested that this was caused by some modification in the gelatin properties probably because of the acidity of the acetylsalicylic acid. This erratic dissolution behavior of aspirin from hard gelatin capsules confirmed the early finding of Wood.⁹² Calesnick, *et al*,⁹⁷ reported that in their study of the dissolution behavior of capsules, the contents of the hard gelatin capsule remained as a pasty mass for some time after the gelatin capsule had dissolved. Aguiar *et al*^{98,99} emphasized the importance of particle dispersion from tablets and capsules. It may be remembered that the granulation step, in the case of tablets,

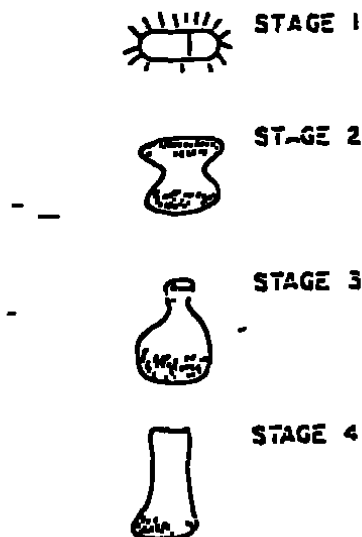


Fig 5-25 Appearance of capsule at various stages using the Levy and Hayes beaker method Stage 1 whiskers or needles 3 min, Stage 2 mushroom, 8-10 min; Stage 3 pyrenidium, 25-120 min Stage 4 cylinder over 120 min [Reproduced from McGee *et al J Pharm Sci*, 59 1433 (1970)]

imparts better hydrophilicity to the drug particles and thus minimizes the effects of the wet bed dispersion characteristics as compared to capsule formulations where no granulation step exists. Presence of hydrophilic diluents in capsule formulations however, may improve the wettability and dispersion properties of poorly soluble drugs as reported by Paikoff and Drumm¹⁰⁰ (Fig 5-26)

Aguar, *et al*,⁹⁹ investigated the deaggregation (or dispersion) rate of four commercial lots of chloramphenicol capsules by monitoring the percent transmittance of the dissolution media after the capsule shell has dissolved. The authors reported that while one brand was found to have a very fast deaggregation rate and reached the steady state in 10 min, another had a very poor deaggregation rate to the point that, after 3 hr, the product maintained its capsular appearance (Fig 5-27a) Quantification of the deaggregation rate was based on the premises that the deaggregation rate followed a first order process and that the species present in the media were either the large aggregates and/or small aggregates

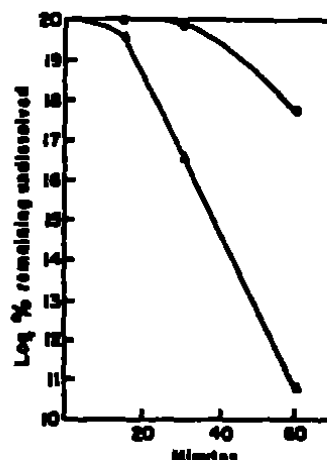


Fig 5-26. Effect of diluents on dissolution rate of drugs from capsules [Reproduced from Paikoff and Drumm, *J Pharm Sci*, 54, 1693 (1965).]

Key: ● drug alone; ▲ drug plus diluent.

The following equation was developed to describe the deaggregation process

$$\log \frac{A_s}{A_s - A_t} = \frac{Kt}{2.303} \quad (5-3)$$

where A_s is the absorbance at the final state, and A_t is the absorbance at time t , i.e., a plot of $A_s/A_s - A_t$ vs t should be linear. From the slopes, the relative aggregation rates can be evaluated. Dissolution studies correlated well with the deaggregation profile (Fig 5-27b) In addition, a qualitative correlation was found between the deaggregation rates of the four commercial lots of chloramphenicol capsules and the plasma levels shown in Fig 5-27c. The same brand that exhibited fast deaggregation rate also provided the highest plasma level after administration to adult humans. Capsules that had a very slow deaggregation rate, also gave significantly lower plasma levels. In order to study the effects of the diluents on the absorption of chloramphenicol the authors conducted permeation studies using the everted sac technique. Again a profile that correlated with the other parameters such as deaggregation and dissolution was obtained (Fig 5-27d) Samyn and Jung^{100a} examined the influence of commonly used pharmaceutical adjuvants on the disintegration and disso

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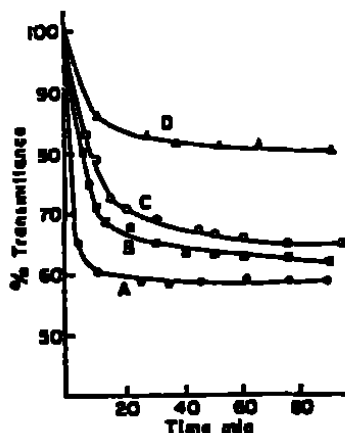


Fig 5-27a. Plot of percent transmittance of chloramphenicol vs time showing the relative desaggregation rates of the four capsules in simulated gastric fluid TS [Reproduced from Aguilar *et al*, *J Pharm Sci*, 57 1844 (1968).]

Key: ● Capsule A, □ Capsule B, ○ Capsule C, ▲ Capsule D.

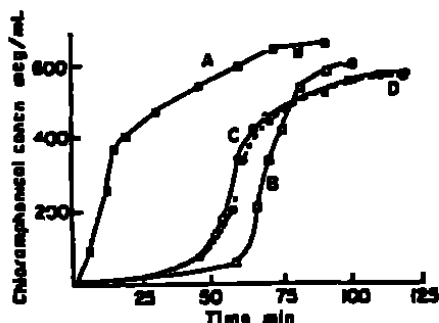


Fig 5-27b. Dissolution rates of chloramphenicol capsules in simulated gastric fluid TS [Reproduced from Aguilar *et al*, *J Pharm Sci*, 57 1844 (1968).]

Key: ● Capsule A, □ Capsule B, ○ Capsule C, ▲ Capsule D.

lution from experimental capsule formulations. The study clearly indicated that the filler (lactose or dibasic calcium phosphate dihydrate) and the capsule lubricant (magnesium stearate) had the greatest influence on the disintegration and dissolution properties of the capsules. Without magnesium stearate, the dissolution was rapid from capsules containing either lactose or calcium phosphate both in water and simulated gastric fluid. The slowest dissolution was observed for the formulation containing dibasic calcium phosphate and 2% magnesium stearate tested in water. This was due

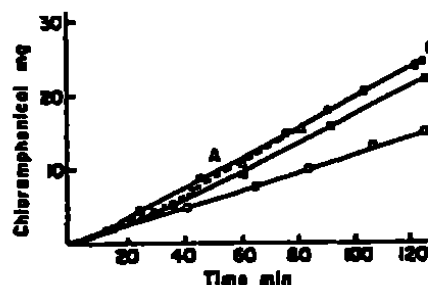


Fig 5-27c. Mean plasma levels in human volunteers of nitro compounds (chloramphenicol equivalents) following single oral doses of chloramphenicol capsules [Dose 0.5 g (92 capsules), 10 subjects] [Reproduced from Aguilar *et al*, *J Pharm Sci*, 57 1844 (1968).]

Key: ● Capsule A, ▲ Capsule B, ○ Capsule C, ■ Capsule D.

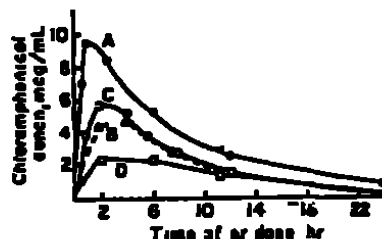


Fig 5-27d. Permeation rates of chloramphenicol from capsules through the everted sac. Solutions not filtered. [Reproduced from Aguilar *et al*, *J Pharm Sci*, 57 1844 (1968).]

Key: ● Capsule A, ■ Capsule B, ▲ Capsule C, ○ Capsule D.

to the hydrophobic nature of the magnesium stearate and the insolubility of calcium phosphate in water (Fig 5-28a). However, in simulated gastric fluid, there was no significant difference between the two fillers. The concentration of magnesium stearate on the other hand, seemed to be the critical factor in controlling the dissolution rate (Fig 5-28b). In those cases where slow dissolution was observed, the capsule content remained as a "slug" of wet powder pack long after the gelatin wall had dissolved. At this stage the drug dissolution was limited by the rate of erosion, diffusion, and/or solution of the drug and/or filler from this wet powder mass. The liquid penetration rates of the various drug/lactose/magnesium stearate blends are shown in Fig 5-28c. The data were plotted as the square of the depth of liquid penetration vs

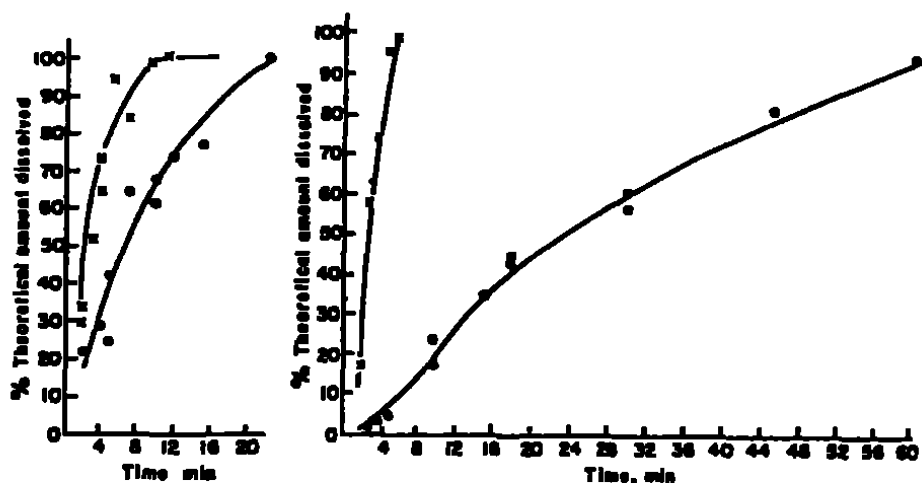


Fig 5-28a. Dissolution of drug from capsules. left, drug-lactose-2% magnesium stearate right, drug-CaHPO $2H_2O$ -2% magnesium stearate. [Reproduced from Samyn, and Jung *J Pharm Sci*, 59 169 (1970)]

Key X simulated gastric fluid; O water

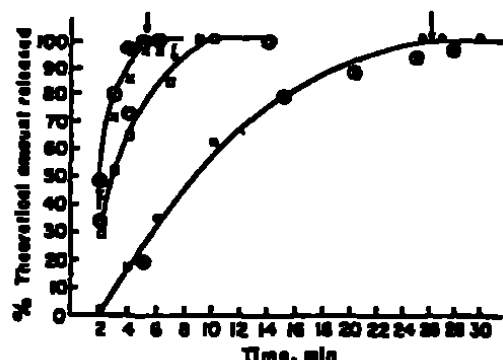


Fig 5-28b. Dissolution of drug from capsules in simulated gastric fluid (drug-lactose-magnesium stearate) [Reproduced from Samyn, and Jung, *J Pharm Sci*, 59, 169 (1970)]

Key X, ○ 0% magnesium stearate; □ ○ 2% magnesium stearate; ● 5% magnesium stearate.

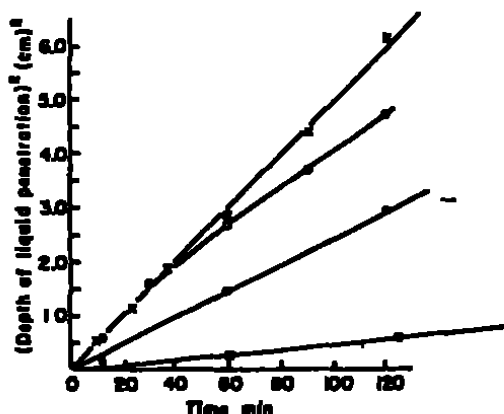


Fig 5-28c. Liquid penetration of packed powder beds (drug-lactose-magnesium stearate blends). [Reproduced from Samyn, and Jung, *J Pharm Sci*, 59 169 (1970).]

Key X, 0% magnesium stearate; ○ 1% magnesium stearate; ● 2% magnesium stearate; ■ 5% magnesium stearate.

time. Decreased penetration rates clearly were related to the increase in magnesium stearate level. Slow dissolution rates were obtained for powder blends that showed reduced liquid penetration rates. Additional measurements of the water content of the various powder beds and their viscosities suggested that the high viscosities of several of these powder packs were due to their restricted water content arising from the added hydrophobic lubricant. Newton, et al,¹⁰¹⁻¹⁰³ in a study of the effect of addi-

tives on the release of the hydrophobic drug ethinamate, reported that the additives have a greater effect on dissolution when finer particle size fractions are used due to the less permeable structure of the powder beds formed by the smaller particles. In order to modify the hydrophobic nature of the drug, Newton and Rowley¹⁰³ found that a large amount of the diluent is required (up to 50%). The authors reported that the presence of a lubricant at a 1% level reduced

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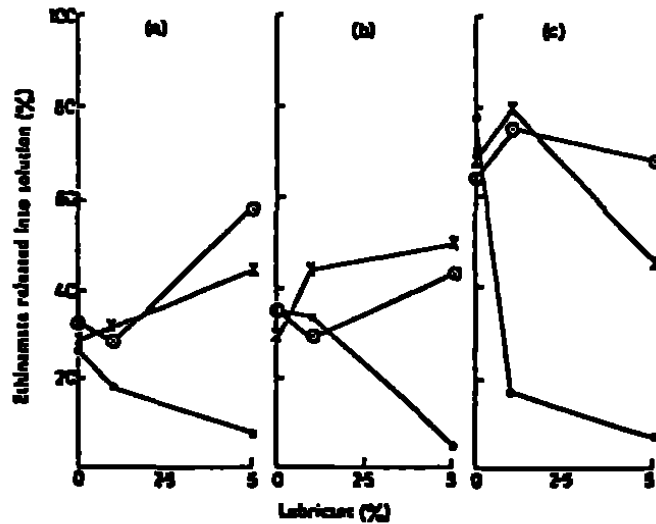


Fig 5-29 The effect of lubricant content on the release of ethinamate from high fill weight capsules after 40 min at zero wetting agent (●), low wetting agent (X) and high wetting agent (O) content for (a) zero diluent (b) low diluent, (c) high diluent. [Reproduced from Newton and Rowley *J Pharm Pharmacol* 22 Suppl 183S (1970).]

drug release, but apparently there was no further significant decrease until a concentration of 5% is reached. The adverse effect of lubricants on dissolution, however, was found to be alleviated, at least partially, by the addition of a wetting agent such as sodium lauryl sulfate (about 1%) to the capsule formulation (Fig 5-29). In addition, Newton and Rowley demonstrated that drug release and permeability decrease with the decrease in particle size and porosity of the powder bed. A moist granulation process was shown to transform a nonpermeable powder bed, which causes slow drug release, into one with high permeability and high drug release. The permeability of powder bed of different porosities, was measured by the pressure decline method of Dodd, Davis, and Pidgeon.¹⁰⁴ A final note on the effect of additives in capsule formulation is that care should be exercised that these additives do not have any tendency to react with the drug, such as in the case of dibasic calcium phosphate which reacts with tetracycline hydrochloride to form the poorly soluble calcium tetracycline complex. Also possible interaction between the drug (especially if acidic or alkaline in nature) and the gelatin shell has been reported.

Effects of Capsule Processing Factors

McGee, *et al*,⁹⁶ investigated the effects of two different pressures of fill on the rate of absorption of acetylsalicylic acid from hard gelatin capsules in rabbits, utilizing two diluents, lactose and dibasic calcium phosphate (Table 5-3). They found that more rapid *in vitro* dissolution and better plasma levels were obtained with the more tightly compacted capsules irrespective of the excipient used. This was explained by the assumption that the diffusion of the gastric juice through the tightly packed capsule, created higher pressure within, leading to faster dissolution.

Newton and Rowley¹⁰³ studied the effect of packing and its relation to the particle size on the *in vitro* release of the water insoluble drug ethinamate from hard gelatin capsules. They found that the rate of drug release and liquid permeability decreased with a decrease in particle size and porosity of the powder bed. If dissolution is compared with sample porosity, the rate of drug release is faster from capsules containing larger particle size fractions and packing has little effect. However, with finer particle size, compact packing

Table 5-3—Average Concentrations Obtained in Dissolution Determinations of No. 3 and No. 4 Capsules Containing Acetyl Salicylic Acid and Lactose^a

Time, min	Average Concentration, ^b mg/100 mL			
	No. 3 Capsule		No. 4 Capsule	
	SGF	SIF	SGF	SIF
10	5.3	1.0	15.3	8.5
20	10.6	10.0	16.1	16.3
30	13.3	12.0	17.5	19.9
45	14.3	15.5	18.1	
60	16.3	19.8	18.9	
90	18.5		19.1	
120	18.5		19.4	
180	19.8		19.5	

^a Oscillating tube method, 100-mesh screen.

^b Average of three determinations: SGF simulated gastric fluid; and SIF simulated intestinal fluid.

[Reproduced from McGee, *et al*, *J Pharm Sci*, 59, 1430 (1970)]

causes a marked decrease in the rate of drug release (Fig 5-30). Reducing the particle size also decreases the size of pores between the particles which in turn reduces the ease of access of the dissolution medium to the powder mass. In a later study, Newton, *et al*,¹⁰¹ while confirming the effect of particle size on the dissolution of capsules, observed that the range of fill weights used does not appear to influence greatly the effect which additives have on drug release. Samyn and Jung¹⁰⁰ studied the influence of packing density on the dissolution of drugs from capsules by measuring the liquid penetration, water content and viscosities of the powder beds. The authors utilized the method of Studebaker and Snow,¹⁰⁸ where various powder blends were packed into open-ended cylindrical tubes to provide large samples and controlled packing density for accurate measurements. The data showed wide variation in viscosity and water content of the powder beds. Some of the wet compacted powders were thick pastes while others were quite fluid. At any given water content the lactose based capsule blend appeared to be more fluid than with calcium phosphate blend probably due to the partial solution of lactose. Figure 5-31 shows that in the absence of hydrophobic lubricants the dissolution behavior was not

influenced by the packing density. However, in the presence of 5% magnesium stearate dense packing caused a marked decrease in the drug dissolution rate from capsules containing either diluent.

Dissolution Rate of Soft Elastic Capsules

Hom and Miskel¹⁰⁵ studied the dissolution characteristics of soft elastic capsules. Their comparative data showed that for several poorly soluble drugs the dissolution rate was much faster when the drug is filled into soft elastic capsules after being dissolved in polyethylene glycol in conjunction with nonionic surfactants, than when formulated into tablets. This agrees, in general with earlier findings of Wagner,⁹⁰ who studied the effects of dosage form variation on blood levels of indoxole and reported that a soft gelatin capsule was equivalent to the emulsion dosage form, followed by an aqueous suspension, and last was the powder-filled hard gelatin capsule.

Hom and Miskel investigated hydrocortisone, ethinyl estradiol, phenobarbital, digoxin, bishydroxycoumarin, sulfadiazine, phenylbutazone and propylthiouracil (Figs 5-32a and 5-32b). In every case, the dissolution rate from soft capsules was faster than a tablet formulation because suspensions or solutions of these drugs were encapsulated easily. Furthermore, surfactants or other solubilizers could be encapsulated conveniently along with the drug to improve its dissolution and bioavailability. They recommended the use of soft capsules for low dose medication of sparingly soluble drugs especially when an early high blood level of the drug is indicated.

Armstrong and James¹⁰⁷ reviewed several articles on drug release from lipid based dosage forms and pointed to the advantage of soft gelatin capsules as an excellent mechanism to seal the oil and mask the unpleasant taste associated with the drug or its oily base. Stella, *et al*,¹⁰⁸ showed that the bioavailability of a quinoline derivative (antimalarial drug) in the dog was better from soft gelatin capsules containing the drug base in oleic

Factors Affecting the Rate of Dissolution

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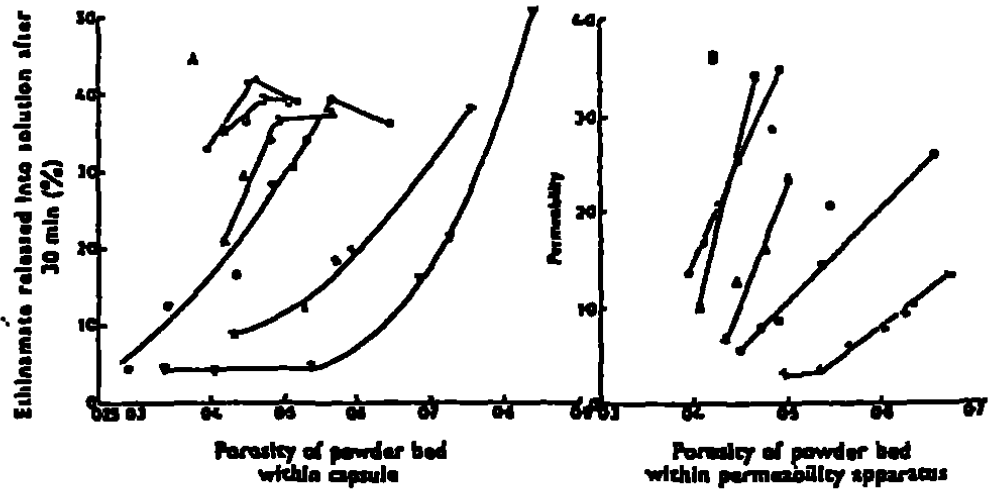


Fig 5-30. a The percentage of drug released after 30 min from capsules containing different particle size fractions of ethinamate packed to give different porosities b: The liquid permeability (m² × 10¹¹) of equivalent particle size fractions at known porosities [Reproduced from Newton and Rowley *J Pharm Pharmacol* 22 1653 (1970)]

Key: ●—● 251-420 μm □—□ 177-251 μm Δ—Δ 152-177 μm ○—○ 125-152 μm +—+ 66-76 μm ▽—▽ 8.3 μm.

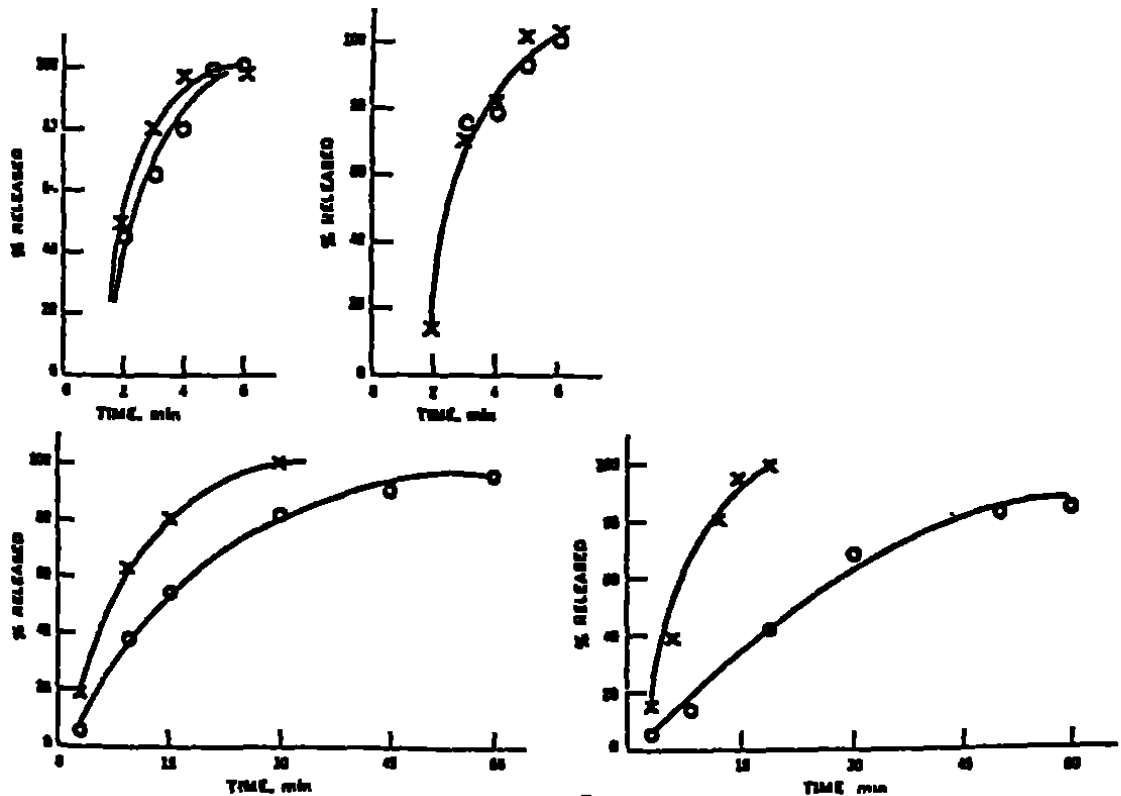


Fig 5-31 Influence of packing density on dissolution of drugs from capsules in simulated gastric fluid [Reproduced from Samyn and Jung, *J Pharm Sci*, 59 169 (1970)]

Key: X regular packing: 333 mg/No. 2 capsule; O dense packing: 400 mg/No. 2 capsule Upper left, drug: lactose lower left, drug: lactose 5% magnesium stearate upper right, drug: CaHPO₄ lower right, drug: CaHPO₄ 5% magnesium stearate

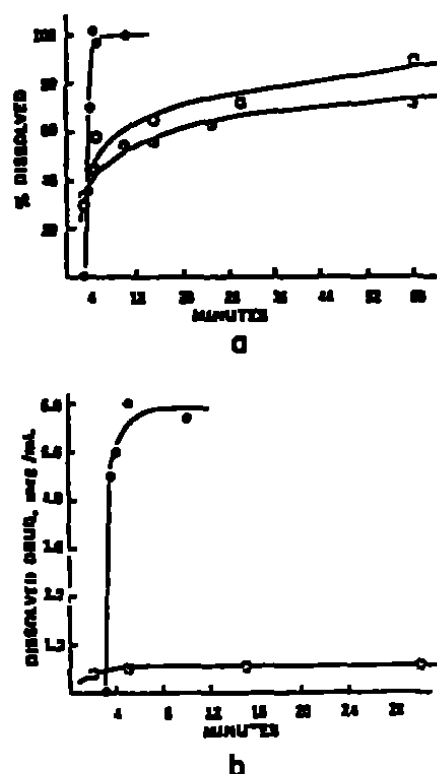


Fig 5-32. a: Dissolution rates of digitoxin capsule and tablets in simulated gastric fluid TS. b: Dissolution rates of bishydroxycoumarin capsule and tablet in simulated gastric fluid TS. [Reproduced from Horn and Mlakei *J Pharm Sci*, 59, 827 (1970)]

Key: ● soft elastic capsule; ○ Tablet A, □ Tablet B

from hard gelatin capsules containing the hydrochloride salt. Fischler, *et al*,¹⁰⁹ found that the peak plasma level in man was highest and attained quickest from a syrup containing chlormethiazole edisylate, followed by soft capsules containing the free base in arachis oil. Oral administration of the edisylate in tablet form gave the lowest bioavailability performance. Fuccella, *et al*,¹¹⁰ administered temazepam to healthy subjects as a single dose, both as a powder in hard gelatin capsules or as a solution in polyethylene glycol, in soft gelatin capsules. Absorption from the latter provided earlier and higher peak plasma levels although there was no significant difference between the overall total availabilities. Also, digoxin, when dissolved in a water soluble mixture containing polyethylene glycol and packed in soft gelatin capsules was found to

dissolve faster *in vitro* and *in vivo* than the tablet formulation.¹¹¹⁻¹¹⁴ Griseofulvin gave 88% absorption from soft gelatin capsules compared to 45% for commercial tablets and 33% for hard gelatin capsules containing the micronized drug.¹¹⁵

Armstrong and co-workers^{116,117} evaluated the British pharmacopoeia *in vitro* disintegration test for soft gelatin capsules using commercial lots of cod liver oil capsules. The majority of capsules swelled on being placed in water but after 3 min, a small drop of oil appeared, usually from a point on the capsule seam. The capsule then ruptured at this point releasing the contents, and the shell then dissolved. However, an appreciable number continued to swell until the shell dissolved without first releasing the oil by breakage, a behavior which caused prolonged disintegration time. It was suggested that this erratic behavior can be due to variations in the efficiency of the capsules sealing process by slight differences in machine adjustments during manufacturing. Weight and dimensions of the capsules showed no correlation with disintegration time but it was noted that as the water content of the shell increased the disintegration time decreased. The nature of the capsule contents did not appear to influence the disintegration time, but the addition of less than 1% of surfactants to the encapsulated oil significantly reduced the time of disintegration. The application of disks in the disintegration test seemed to affect dramatically the capsule behavior and therefore, their use was not recommended by the authors.

The *in vitro* disintegration and dispersion of soft gelatin capsules was also investigated by Armstrong, *et al*,¹¹⁷ using X radiography in rabbits and gamma scintigraphy in human volunteers. This procedure showed that *in vitro* disintegration usually began within 2-3 min and that the capsules swelled into isometric shapes. The presence of a surfactant in the oil and food in the stomach appeared to assist disintegration which was in agreement with the findings of Hunter, *et al*,¹¹⁸ and Casey, *et al*.¹¹⁹ Gamma

acid than scintigraphy data in humans indicated that the disintegration and dispersion times were shorter in humans than in rabbits probably because of the larger human stomach which permits more efficient agitation of the capsule. Also, it was found that the *in vitro* times were very close to those obtained *in vitro*. Serajuddin, *et al.*,¹²⁰ pointed out that the physicochemical characteristics of soft gelatin capsules are different from other conventional dosage forms, and hence, the properties of the drug, the solubilizing liquid, the gelatin shell and the compatibility of these three components after encapsulation must be evaluated carefully during formulation. The authors pointed out that due to the high initial water content of the soft gelatin capsule shell (>20%), water migrates from the shell to the fill material during the drying process and subsequent equilibration periods.^{121,122} Consequently, the objective of bioavailability enhancement through drug solubilization can be jeopardized if the drug crystallizes inside the capsule due to water migration from the soft gelatin capsule shell to the fill material. Such possibility however, can be avoided by selecting the proper vehicle for drug solubilization.

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Particle size, morphology, shape and surface area

The characteristics of a drug can be greatly affected by particle size, morphology, shape and surface area. This can affect such properties as formulation homogeneity, powder flow for respirables and surface area. It is therefore important to characterise each new drug candidate in order to facilitate the preparation and production of a viable formulation.

For instance, in the case of a drug to be administered in tablet form, the size and shape of the particles can influence the flow and mixing of powders and granules, both affecting the efficiency of tablet formulation.

Our laboratory staff have an in-depth knowledge of the characterisation of particulate matter with respect to size, shape, morphology, surface area, surface energies etc.

For more information on how we may be able to assist with your needs, please contact us.

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Particle-Size Distribution, Part I

Representations of Particle Shape, Size, and Distribution

Harry G. Brittain

Particle size determinations are undertaken to obtain information about the size characteristics of an ensemble of particles. Because the particles being studied are not usually the exact same size, information is required regarding the average particle size and the distribution of sizes about this average. However, the concept of particle size is irrevocably derived from aspects of particle shape and morphology because the idea of a particle diameter proceeds from preconceived shape factors.

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In the July 2001 *Pharmaceutical Technology* article about particle-size determination, the question of what constitutes a "correct" method for the determination of particle-size distributions was addressed (1). A correct method was defined as one whose sample was obtained by an appropriate sampling procedure, in which the sample was prepared properly and introduced into the instrument, and in which all instrumental parameters were used correctly for the analysis. It also was pointed out that all of the correct (but differing) particle size results obtained through various methodologies are equally accurate, but each method simply might be expressing its correct results in different terms. When viewed in this light, the decision about which particle-size methodology is most appropriate for a given situation can be seen as a simple matter of accuracy versus precision. If absolute accuracy is most important, then one must conduct rigorous research to verify that the method finally adopted does indeed yield particle-size results that are absolutely indicative of the characteristics of the bulk material. If, however, one is more interested in developing profiles of lot-to-lot variability, then the use of any of the available methods that yields correct results is appropriate.

The next several articles in the "Pharmaceutical Physics" column series will examine a variety of correct methodologies that can be used to deduce information about the shape and size distribution of particles. However, one cannot begin to address those topics without a prior exposition of what is meant by the shape and size of the particles that constitute a powdered solid.

Particle shape

It is not possible to discuss rationally the size of a particle or any distribution associated with the sizes of an ensemble of particles without first considering the three-dimensional characteristics of the particle itself. This is because the size of a particle is expressed either in terms of linear dimension characteristics derived from its shape or in terms of its projected surface or volume. As will be shown, some methods of expressing particle size discard any concept of particle shape and instead express the size in terms of some type of equivalent spherical size.

An appropriate starting place for a discussion of particle shape can be found in USP General Test (776) (see Figure 1) (2). In the shape performance aspect of this particular test procedure, USP

requires that "for irregularly shaped particles, characterization of particle size must also include information on particle shape."

The general method defines several descriptors of particle shape (see Figure 2). The USP definitions of these shape parameters are

- **acicular** slender needle-like particle of similar width and thickness
- **columnar** long, thin particle with a width and thickness that are greater than those of an acicular particle
- **flake** thin flat particle of similar length and width

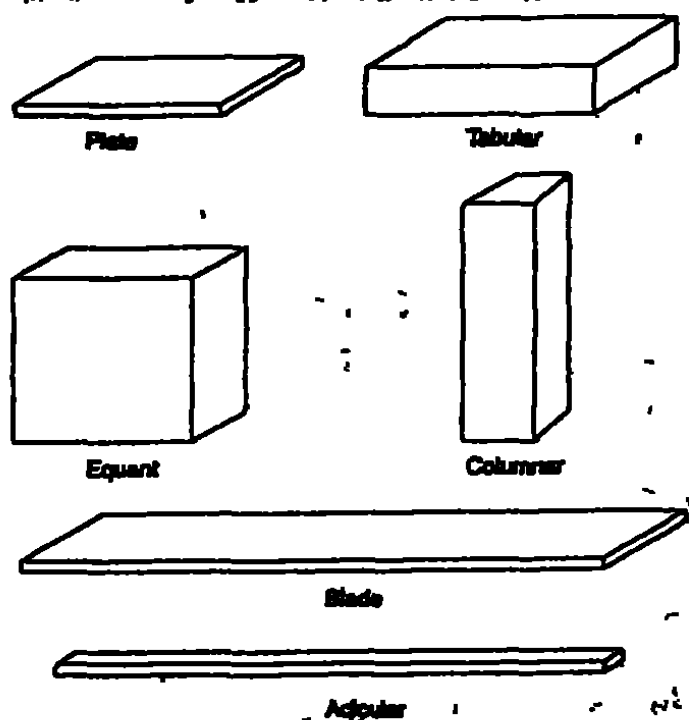


Figure 1 Description of particle shape as defined by USP

- **plate** flat particle of similar length and width but with greater thickness than flakes
- **lath** long, thin blade-like particle
- **equant** particles of similar length, width, and thickness; both cubical and spherical particles are included.

In ordinary practice, one rarely observes discrete particles but typically is confronted with particles that have aggregated or agglomerated into more-complex structures. USP provides several terms that describe any degree of association.

- **lamellar** stacked plates
- **aggregate** mass of adhered particles
- **agglomerate** fused or cemented particles
- **conglomerate** mixture of two or more types of particles
- **spherulite** radial cluster
- **drusy** particle covered with tiny particles (2)

The particle condition also can be described by another series of terms:

- **edges** angular rounded, smooth sharp, fractured
- **optical color** transparent translucent opaque
- **defects** occlusions, inclusions.

Furthermore surface characteristics can be described as

- **cracked** partial split break, or fissure
- **smooth** free of irregularities, roughness, or projections
- **porous** having openings or passageways
- **rough** bumpy, uneven, not smooth
- **pitted** small indentations.

The pharmaceutical descriptors of particle shape are derived from the general concept of crystallographic habit. The exact shape acquired by a crystal will depend on various factors such as the temperature, pressure and composition of the crystallizing solution. Nevertheless, precipitation of a given compound generally creates a characteristic shape or outline. Because the faces of a crystal must reflect the internal structure of the solid,

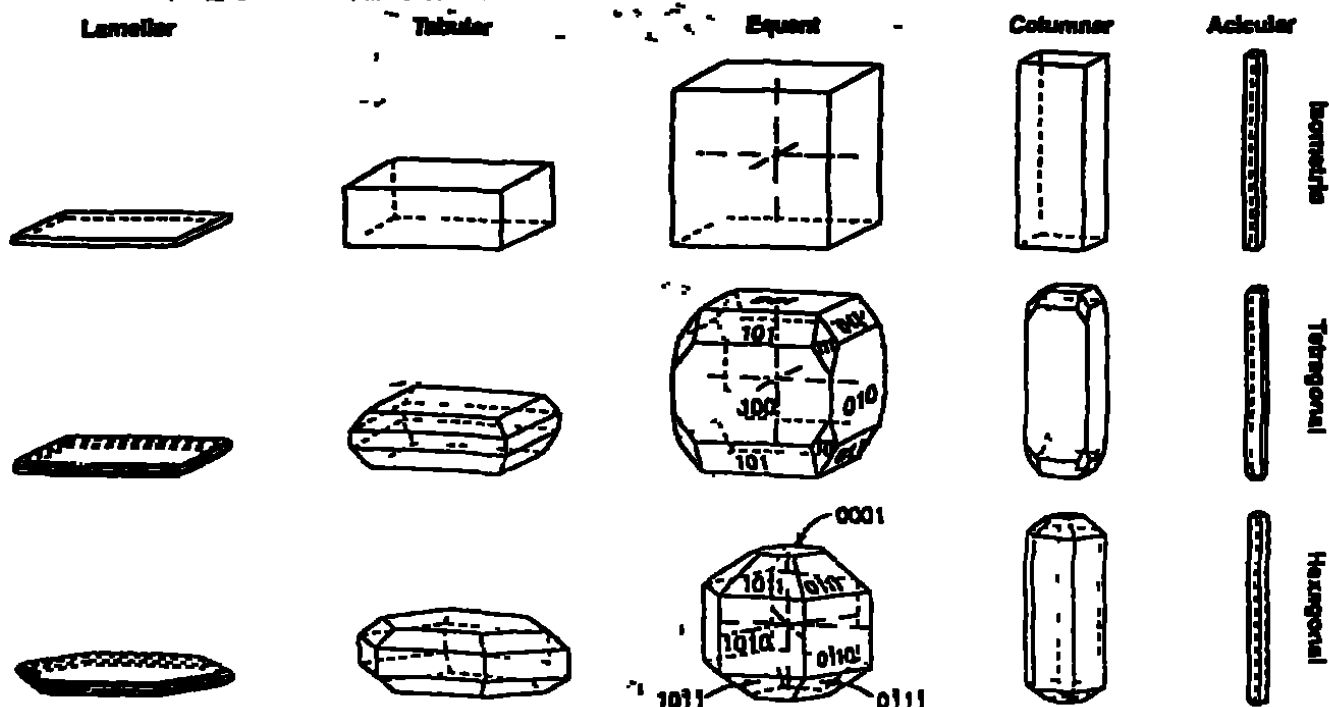


Figure 2: Growth along certain crystal directions can profoundly alter the characteristic habit of various crystals.

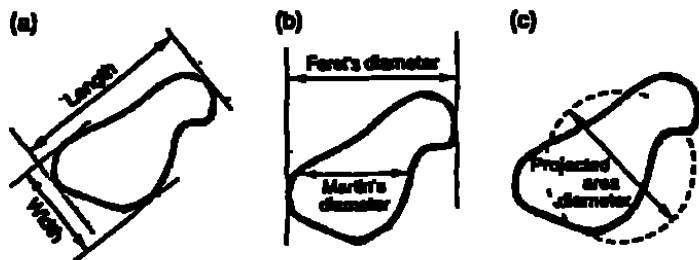


Figure 3: Some commonly used descriptors of particle size.

the angles between any two faces of a crystal will remain the same even if the crystal growth is accelerated or retarded in one direction or another (see Figure 2). Optical crystallographers usually will catalogue the various crystal faces and document the angles between them as they identify the crystal system to which the given particle belongs. When the particle is particularly well formed, a description of symmetry elements also is compiled.

For many individuals, however, the concept of qualitative shape descriptors has proven inadequate, and this deficiency has necessitated the definition of more quantitatively defined shape coefficients (3). For instance, Heywood describes the elongation ratio, n , as

$$n = \frac{L}{B} \tag{1}$$

and the flakiness ratio, m , as

$$m = \frac{B}{T} \tag{2}$$

in which T is the particle thickness (the minimum distance between two parallel planes that are tangential to opposite surfaces of the particle), B is the breadth of the particle (the minimum distance between two parallel planes that are perpendicular to the planes defining the thickness), and L is the particle length (the distance between two parallel planes that are perpendicular to the planes defining thickness and breadth) (4).

Particle size

It really is not possible to continue a discussion of particle shape or size without first developing definitions of particle diameter. This step is, of course, rather trivial for a spherical particle because its size is uniquely determined by its diameter. For irregular particles, however, the concept of size requires definition by one or more parameters. It often is most convenient to discuss particle size in terms of derived diameters such as a spherical diameter that is in some way equivalent to some size property of the particle. These latter properties are calculated by measuring a size-dependent property of the particle and relating it to a linear dimension.

Certainly the most commonly used measurements of particle sizes are the *length* (the longest dimension from edge to edge of a particle oriented parallel to the ocular scale) and the *width* (the longest dimension of the particle measured at right angles to the length). Intuitive as these properties may be, their definition still is best shown in Figure 3a. Closely related to these non-

which is the distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale, and *Martin's diameter*, which is the diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas (see Figure 3b).

The coordinate system associated with the measurement is implicit in the definitions of length, width, Feret's diameter, and Martin's diameter because the magnitude of these quantities requires some reference point. As such, these descriptors are most useful when discussing particle size as measured by microscopy because the particles are immobile. Defining spatial descriptors for freely tumbling particles is considerably more difficult and hence requires the definition of a series of derived particle descriptors. However, given the popularity of techniques such as electrozone sensing or laser light scattering, derived statements of particle diameter are extremely useful.

All of the derived descriptors for particle size begin with the homogenization of the length and width descriptors into either a circular or spherical equivalent and make use of the ordinary geometrical equations associated with the derived equivalent. For instance, the *perimeter diameter* is defined as the diameter of a circle having the same perimeter as the projected outline of the particle. The *surface diameter* is the diameter of a sphere having the same surface area as the particle, and the *volume diameter* is defined as the diameter of a sphere having the same volume as the particle. One of the most widely used derived descriptors is the *projected area diameter* which is the diameter of a circle having the same area as the projected area of the particle resting in a stable position. The concept of projected area diameter is illustrated in Figure 3c.

Several other derived descriptors of particle diameter have been used for various applications. For instance, the *sieve diameter* is the width of the minimum square aperture through which the particle will pass. Other descriptors that have been used are the *drag diameter* which is the diameter of a sphere having the same resistance to motion as the particle in a fluid of the same viscosity and at the same velocity; the *free-falling diameter* which is the diameter of a sphere having the same density and the same free-falling speed as the particle in a fluid of the same density and viscosity; and the *Stokes diameter* which is the free-falling diameter of a particle in the laminar-flow region.

Distribution of particle sizes

All analysts know that the particles that constitute real samples of powdered substances do not consist of any single type but instead will generally exhibit a range of shapes and sizes. Particle-size-determinations therefore are undertaken to obtain information about the size characteristics of an ensemble of particles. Furthermore, because the particles being studied are not the exact same size, information is required about the average particle size and the distribution of sizes about that average.

One could imagine the situation in which a bell-shaped curve is found to describe the distribution of particle sizes in a homogeneous material.

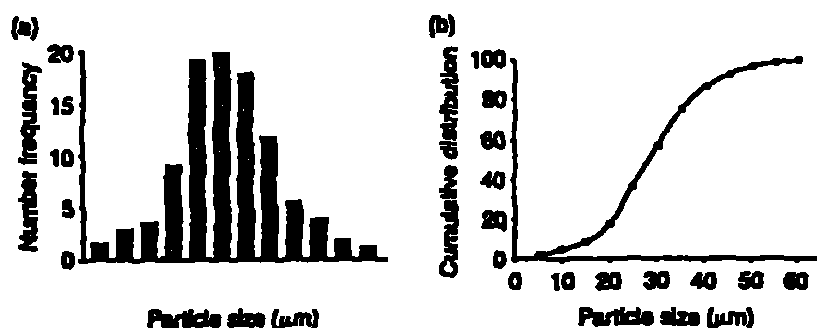


Figure 4. Particle-size representations for a hypothetical normal distribution. Shown are (a) the frequency distribution and (b) the cumulative distribution.

in each size fraction is identified, and then one calculates the percentage of particles in each size fraction. This calculation yields the particle size histogram (see Figure 4a). The number frequency ordinarily is used to construct a cumulative distribution, which can be ascending or descending depending on the nature of the study and what information is required (see Figure 4b).

The arithmetic mean of the ensemble of particle diameters is calculated using the relation

$$d_{ar} = \frac{\sum nd_i}{\sum n} \quad (3)$$

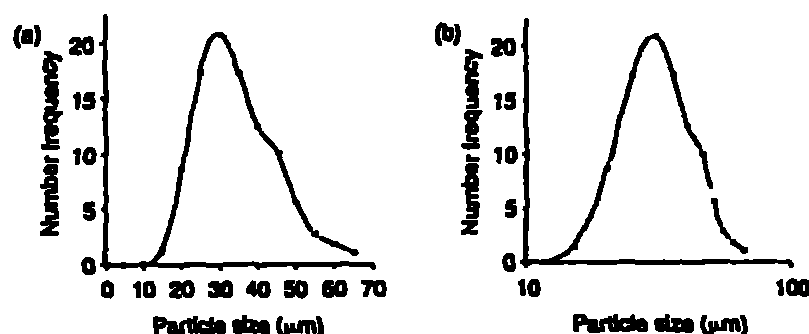


Figure 5. Particle-size representations for a hypothetical log-normal distribution, plotted on a (a) linear scale and on a (b) logarithmic scale.

in which n is the number of particles having a diameter equal to d_i . The standard deviation in the distribution then is calculated using

$$\sigma = \left[\frac{(d_{ar} - d_i)^2}{n} \right]^{1/2} \quad (4)$$

In the example shown in Table I, one calculates that $d_{ar} = 30.2 \mu\text{m}$ and that $\sigma = 1.1$.

The most commonly occurring value in the distribution is the *mode*, which is the value at which the frequency representation is a maximum value. The *me-*

*di*an divides the frequency curve into two equal parts and equals the particle size at which the cumulative representation equals 50%. In a rigorous normal distribution, the mean, mode, and median have the same value. For a slightly skewed distribution, however, the following approximate relationship holds.

$$\text{mean} - \text{mode} = 3 \left[\text{mean} - \text{median} \right] \quad (5)$$

It would be highly advantageous if powder distributions could be described by the normal distribution function because all of the statistical procedures developed for Gaussian distributions could be used to describe the properties of the sample. However, unless the range of particle sizes is extremely narrow, most powder samples cannot be described adequately by the normal distribution function. The size distribution of the majority of real powder samples usually is skewed toward the larger end of the particle size scale. Such powders are better described by the log-normal distribution type. This terminology arose because when the particle distribution is plotted by means of the logarithm of the particle size, the skewed curve is transformed into one closely resembling a normal distribution (see Figure 5).

The distribution in a log-normal representation can be completely specified by two parameters: the geometric median particle size (d_g) and the standard deviation in the geometric mean

Size (μm)	Number in Size	Number Frequency	Percent Less Than	Percent Greater Than
5	50	1.67	1.67	98.33
10	90	3.00	4.67	95.33
15	110	3.67	8.33	91.67
20	280	9.33	17.67	82.33
25	580	19.33	37.00	63.00
30	600	20.00	57.00	43.00
35	540	18.00	75.00	25.00
40	380	12.00	87.00	13.00
45	170	5.67	92.67	7.33
50	120	4.00	96.67	3.33
55	60	2.00	98.67	1.33
60	40	1.33	100.00	0.00
Total	3000	100		

distribution. Samples that conform to the characteristics of a normal distribution are described fully by a mean particle size and the standard deviation. Table I shows an example of a sample exhibiting a normal distribution in which 3000 particles have been sorted according to an undefined determiner of their size. In the usual data representation, the number of particles

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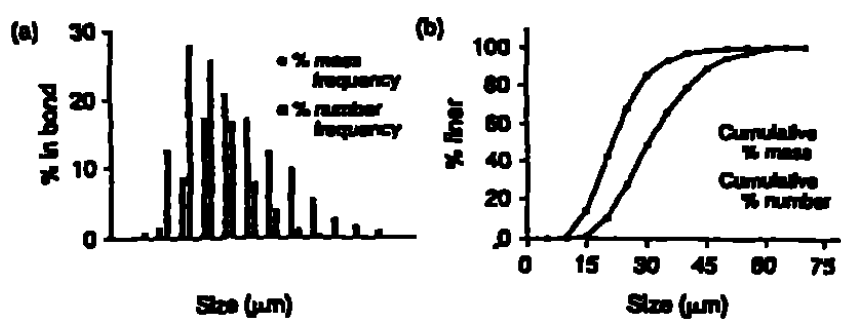


Figure 6: Particle-size representations for a hypothetical log-normal distribution. Shown are (a) the frequency distribution and (b) the cumulative distribution. Each contains the difference obtained when processing the data in terms of either particle number or particle mass.

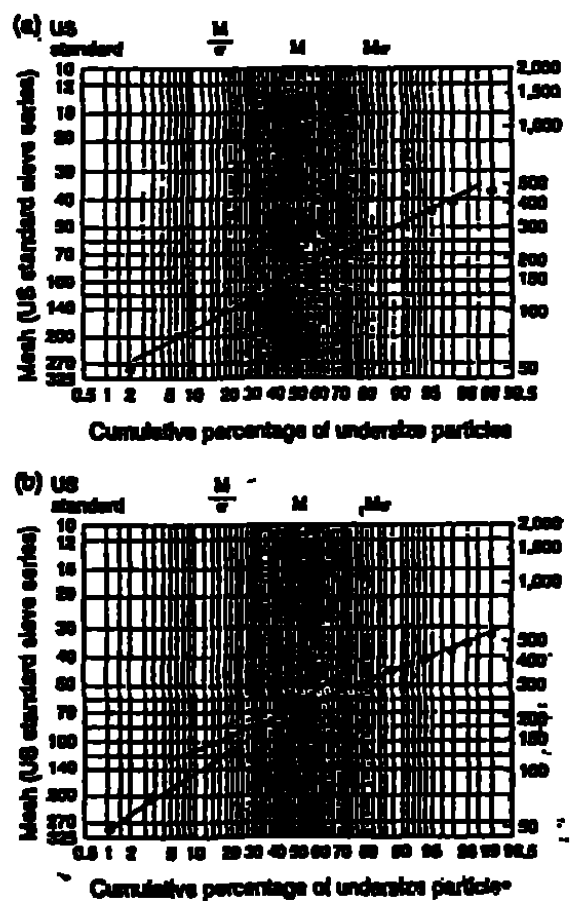


Figure 7: Particle-size representations plotted in a log-probability format for (a) a single hypothetical log-normal distribution and for (b) a hypothetical sample containing two log-normal distributions whose average particle sizes differ by ~50%.

(11) The geometric median is the particle size pertaining to the 50% value in the cumulative distribution and is calculated using

$$d_g = \text{antilog} \left[\frac{\sum n \log(d_i)}{\sum n} \right] \quad [6]$$

in which n is the number of particles having particle size equal to d_i . Two samples having identical d_g and σ_g values can be said to have been drawn from the same total population and exhibit properties of characteristics of the total population.

In many applications, particle-size results are processed by plotting the cumulative frequency data on a logarithmic scale. If a straight line is obtained, the particle-size distribution is said to obey the log-normal function. The value of d_g is equal to the 50% value of the cumulative distribution. The value of σ_g is obtained by dividing the 84.1% value of the distribution by the 50% value.

Although the distribution in the log-normal representation is specified completely by the geometric median particle size and the geometric mean standard deviation a number of other average values have been derived to define useful properties. These values are especially useful when the physical significance of the geometric median particle size is not clear. The arithmetic mean (d_a) particle size is defined as the sum of all particle diameters divided by the total number of particles and is calculated using Equation 3. The surface mean (d_s) particle size is defined as the diameter of a hypothetical particle having an average surface area and is calculated using

$$d_s = \left[\frac{\sum n d_i^2}{\sum n} \right]^{1/2} \quad [7]$$

The volume mean (d_v) particle size is the diameter of a hypothetical particle having an average volume and is obtained from

$$d_v = \left[\frac{\sum n d_i^3}{\sum n} \right]^{1/3} \quad [8]$$

The volume-surface mean (d_{vs}) particle size is the average size based on the specific surface per unit volume and is calculated using

$$d_{vs} = \frac{\sum n d_i^3}{\sum n d_i^2} \quad [9]$$

For the distribution plotted in Figure 5 one can calculate that $d_g = 32.91 \mu\text{m}$, $d_a = 34.42 \mu\text{m}$, $d_s = 35.93 \mu\text{m}$, $d_v = 37.43 \mu\text{m}$, and $d_{vs} = 40.62 \mu\text{m}$.

Various types of physical significance have been attached to the various expressions of particle size. For chemical reactions, the surface mean is important, although for pigments the volume mean value is the appropriate parameter. Deposition of particles in the respiratory tract is related to the weight mean diameter and the dissolution of particulate matter is related to the volume-surface mean.

Particle size distributions can be sorted according to the mass (or volume) of the particles contained within a given size band

or to the number of particles contained in the same size band. With substances having real density values, the distribution of the same ensemble of particles can look quite different depending on how the data are plotted. Figure 6 shows the frequency and cumulative distribution plots for the same sample, but the data have been separately processed in terms of the mass and particle numbers.

Unfortunately not every powdered sample is characterized by the existence of a single distribution, and the character of real samples can be quite complicated. Recognizing the existence of multimodal distributions is not always a straightforward process, but their existence often can be detected by plotting the data on log-probability paper. The existence of more than one particle population is indicated by a change in the slope of the line. Figure 7 shows a single log-normal distribution and a multimodal sample consisting of two populations whose means differed by approximately 50%. The break in the log plot is clearly evident, but if one were to simply plot the latter sample in either a frequency or cumulative view, one would not have been able to detect the existence of two particle-size populations in the sample.

Summary

This rather simplified discussion of particle shape, size, and distribution represents only an introduction to the topic. Interested readers should consult the primary sources in the list of

Recommended reading

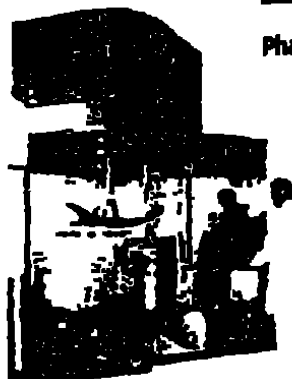
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recommended references to additional information (see "Recommended reading" sidebar). Most highly recommended are the various editions of *Particle Size Measurement* by Allen because they contain some of the most detailed and informative expositions available about these topics. However, the scope of the discussion in this opening article provides a sufficient basis for the expositions of the various methodologies that will follow in subsequent installments of this column.

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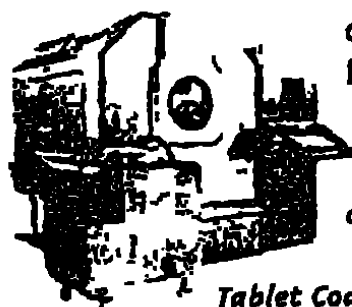
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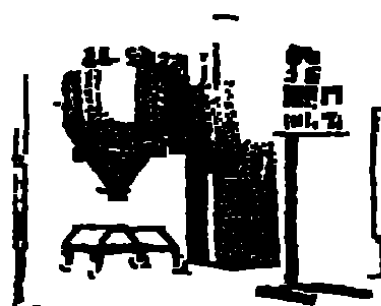
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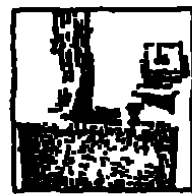
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Stationary Lifters



Mixers



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are needed to represent the bulk material and the size these will be. The analyst also must decide how the various samples are to be analyzed (e.g., pooled to yield a common sample or each to be characterized individually) and the required degree of accuracy in the results. The variability of the bulk material being sampled, the size of each individual sample, the number of samples taken, and the method in which these samples are prepared for analysis will determine the accuracy of the sampling program.

Probability sampling

Sampling procedures may be classified as either nonprobability sampling or probability sampling. Nonprobable methods typically are procedures of convenience and are chosen because the alternatives are deemed too difficult to implement. This type of sampling is also known as *judgment* or *authoritative* samplings. Samples often are chosen using the expertise of those who have a feel for the process and believe that they intuitively know when and where to obtain a representative sample. Nonprobability samples often contain hidden biases, and statistical methods for the estimation of precision cannot be applied.

On the other hand, probability sampling ensures that the sampling scheme is developed in such a manner that will yield samples that are highly indicative of the properties in the bulk ensemble. It goes without saying that although probability methods are more complicated than nonprobability methods, their use is infinitely more desirable.

Sampling methodologies

Although a considerable number of probability-sampling procedures can be used, this article describes the four most common approaches.

Random sampling. In random sampling, each of all possible sample units has an equal chance of being included in the sampling procedure. To obtain a random sample, a number is conceptually assigned to each potential candidate, and numbers then are selected at random to identify the units to be sampled. Alternatively, samples are selected during random time periods during a production run to obtain a pseudorandom sample. For instance, consider a process used to manufacture a material that is eventually packaged in 10,000 bottles containing 100 g of powdered solid in each. Each bottle in the run is assigned an identification number during the processing, and a random-number generator is used to select 10 bottles from the production run. The entire content of each bottle should be used to conduct the analysis, unless this is impractical for the type of measurement to be conducted. In that case, one must execute a further random procedure to select the sample for analysis.

Stratified sampling. In stratified sampling, the ensemble to be sampled is divided into subsets, and random samples are taken from each subset. This method is best applied when the subsets themselves are very different in their properties, but objects in individual subsets are equivalent. To apply the method, samples are taken in a random manner but only within specified time intervals. For example, consider a process used to manufacture a powdered solid at the rate of 5 kg/h that is scheduled to run for 10 h. To perform a stratified sampling procedure, one might sample 50 g of powder during each hour of operation. At the

end of the production run, the 10 50-g samples are combined into a single 500-g sample, and thus constitutes the sample that is subjected to analysis.

Systematic sampling. In systematic sampling, a definite sampling schedule is followed to obtain the units for testing. In other words, every n th sample is chosen during a production run to ensure regular sampling through the process. The time at which the sample is taken is not regulated, merely its position in the run. One should note, however, that systematic sampling only works when the ensemble is homogeneous. If the process happens to be cyclic or periodic in nature, then this procedure can lead to serious errors. As an example of systematic sampling, consider a process used to manufacture a powdered solid at the rate of 5 kg/h that is scheduled to run for 10 h. To perform systematic sampling, the operator pulls a 50-g sample exactly midway through each hour of operation. At the end of the production run, the 10 50-g samples are combined into one 500-g sample which constitutes the sample ultimately subjected to analysis.

Cluster sampling. In cluster sampling, the ensemble is divided into groups or clusters, each of which contains subsets. Clusters are chosen at random, and all the elements in a cluster are included in the sample. This method is used when there are many primary units, each of which can be sampled. The subsamples from the clusters make up the sample taken for analysis. For a cluster sampling example, consider a process used to manufacture a material that is eventually packaged in 10,000 bottles containing 100 g of powdered solid in each. The primary units are the bottles, and the subsample units will be subdivisions of the bottle contents. To perform cluster sampling, one randomly selects 10 bottles from the stock produced and then randomly selects a 25-g sample from each bottle. After all the subsamples are properly combined, the resulting 250-g powder mass constitutes the sample to be analyzed.

Static powder sampling methods

Various methods can be used to obtain samples that are purportedly representative of the bulk from which the samples were drawn. The most common of these are scooping off the top surface and pouring and quartering. More-sophisticated methods include the use of a grain thief, a sample splitter-reducer, or a rotatory sample divider. Unfortunately, a general rule of thumb that has emerged is that the simpler the sampling method, the less likely it is to yield an acceptable sample.

Scooping from the top. It is almost painful to mention the most widely used method of sampling, namely that of using a spatula to scoop off some powder from the top surface of its bulk. Although this is by far the easiest method for sampling a powdered solid, there is no doubt that scooping off the top is less effective than the least desirable method that could be imagined. Leaving aside questions of chemical degradation at the upper layer, it is well known that particle segregation will result in the top layer of a powdered solid becoming enriched in its coarse particle fraction (4). As a result, sampling this top layer would bias the particle size distribution toward larger particles. Shaking the powder may not solve the problem because one may induce even more segregation in this process. Because the composition of the upper surface

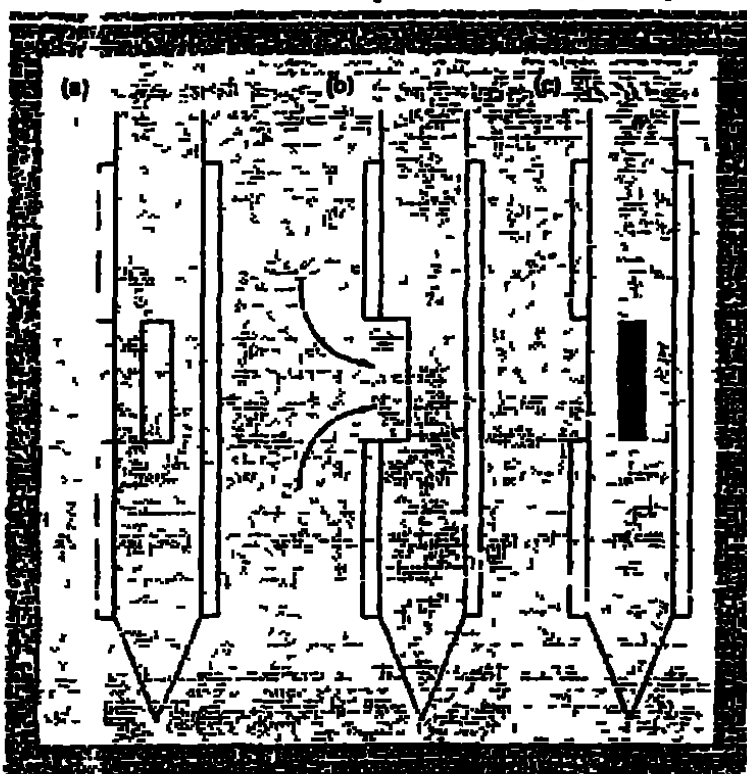


Figure 1 Operation of a sample thief. (a) The sleeve of the thief is rotated so that the interior compartment is isolated from the bulk powder. While in the closed position, the thief is plunged into the central mass of the powder. (b) Once the thief is at the desired position the unit is rotated so that the interior compartment is now exposed to the bulk powder. Powder flows into the thief compartment of its own accord. (c) Once the interior compartment of the thief is filled, the sleeve of the thief is rotated so that the interior compartment is again isolated from the bulk powder. The thief is then withdrawn from the powder, and the sample is analyzed.

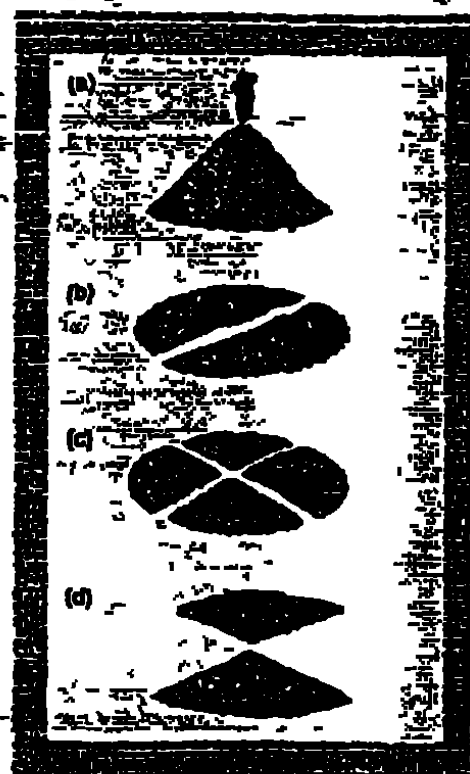


Figure 2 Performance of coning and quartering showing (a) pouring of the initial cone, (b) division of the flattened cone into halves, (c) further division of the flattened cone into quarters, and (d) removal of alternate quarters to define the subdivided sample.

of a bulk powder rarely is indicative of the bulk composition this method of sampling is the worst possible way to obtain a sample

Sample thief. A significant improvement in sampling can be achieved with the use of a sample thief, sometimes known as a grain thief for historical reasons. This device consists of two tubes, one fitting tightly inside the other, and with oblong holes cut through the tubes in corresponding positions. One end of the outer tube is fitted to a point to facilitate its insertion into a bulk powder. The sampling procedure, illustrated in Figure 1, consists of rotating the inner tube to close the holes, inserting the device into the powder, rotating the inner tube to open the holes, allowing the powder to enter the device, rotating the inner tube once more to close the holes, and finally removing the thief from the bulk powder.

Although thief sampling is a better method than merely scooping off the top of a bulk powder, it is still an inferior technique (5,6). Even though most thieves have relatively sharp ends, the very act of plunging the thief through the bulk powder must perturb the sample to some degree. A compressional force propagates ahead of the thief as it is pressed into the bulk, thus potentially changing the strata of the bulk and altering the wall of powder at the outer walls of the thief. Furthermore, because large particles will flow more easily than will small particles an

opened thief is liable to be filled preferentially with the coarse fraction of the particle distribution.

Coning and quartering. The main problem with scoop and thief sampling is that the samples are removed from a static powder bed and there is simply no effective way to sample a nonmoving powder and obtain a representative sample. One procedure that attempts to address this problem is that of coning and quartering. For this procedure, one begins by pouring a cone of material, which is then flattened as evenly as possible. The material is then divided into quarters, whereupon two opposite quarters are discarded. The remaining two quarters are recombined and poured into another conical pile, which is then flattened and divided. The quartering process is continued until one is left with an amount of material that is the desired sample size (see Figure 2).

Great care must be taken when obtaining a sample by coning and quartering. When the initial powder sample is poured, it will undergo the full range of processes that result in segregation of particles according to their relative size. Because their flowability is the poorest, the finer particles will collect at the center of the cone and the coarser particles will flow toward the edges of the cone. Hence, each wedge of a poured cone will become severely segregated by the act of pouring, making the process of subdivision and recombination critical. It is not unusual to ob-

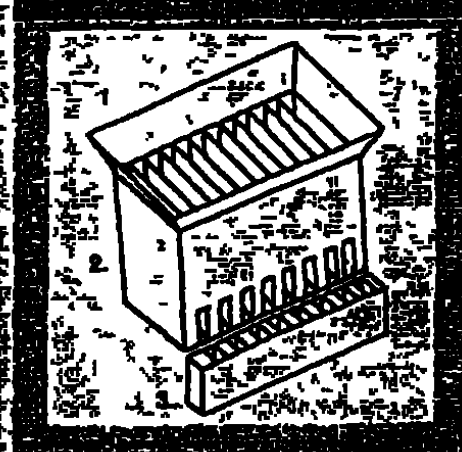


Figure 3: Schematic drawing of a chute sample splitter. Powder is fed through the upper baffles (1) and is discharged through the chutes (2) into the sample collection tray (3).

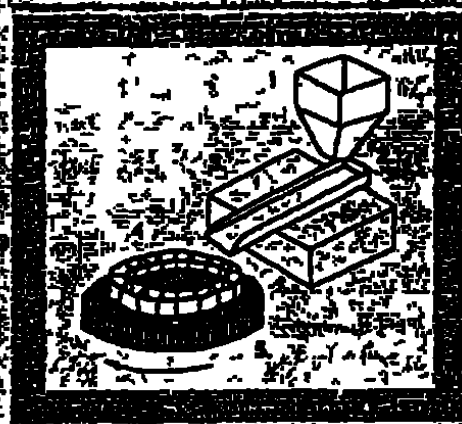


Figure 4: Schematic drawing of a rotary sample divider. Powder is fed through the hopper (1) into the delivery chute (2), expelled by the vibratory device (3).

The subdivided samples are assembled in the collection tray (4), which is mounted on the rotary stage (5)

tain large standard deviations in particle-size results when the coning and quartering method is used to obtain a sample.

Dynamic powder sampling methods

There is little doubt that the superior methods of powder sampling entail procedures whereby the sample is removed from a moving powder bulk. Allen has contributed the two Golden Rules of Sampling that should be followed whenever possible (7)

- Rule 1 A powder should be sampled when in motion.
- Rule 2 The whole of the stream of powder should be taken for many short increments of time, in preference to part of the stream being taken for the whole of the time.

One method that has been developed to obtain more representative samples from bulk powders involves the use of sample splitters or sample reducers. These devices work by systematically rejecting segments of material flowing down a preset incline (see Figure 3). The sample is diverted from the main bulk and fed into a collection vessel. If the powder being divided has strong segregation tendencies the powder flow must be rendered as homogeneous as possible to avoid bias. Only through homogenization of the powder stream will each subdivision of the bulk contain the same distribution of particle sizes as the mass from which it was taken.

The number of chutes necessary for a splitting device has been

investigated (8). Increasing the number of chutes in the device may increase the efficiency of the system, but there are constraints on how this is to be accomplished. The chutes must all be of equal size and their efficiency is improved when the size of the chute opening is reduced. However, when the system is appropriately designed and validated, its use can yield appropriately divided samples.

Arguably the best method for properly subdividing a powdered sample is through the use of a rotatory sample divider, commonly known as a *spinning riffler* and whose operation is illustrated in Figure 4. This device uses mechanical energy to provide a constant flow of material from its holder. The steady flow passes through a divider head operating at constant speed, thus minimizing segregation. Each sample from a rotatory sample divider can be analyzed separately or recombined to yield a representative sample. It almost goes without saying that the powder being tested must be free-flowing or it cannot be processed by the device.

A typical spinning riffler consists of three components. The powder hopper holds the bulk of powder that is to be subdivided, and its output is regulated by a feeding device. The most important part of the spinning riffler is the dividing head, which contains a number of sample collectors that are mounted on a rotating platform. During the rotation of the platform, the stream of powder emanating from the hopper is periodically cut into small portions. The riffler works best when the speed of rotation is relatively fast compared with the feed rate so that effects of flow segregation are minimal among each of the sample collectors. In other words, it is desirable that the powder accumulating in each sample collector is assembled from multiple samples of the powder in the hopper. Common sense dictates that the combined volume of all sample collectors must exceed that of the bulk powder volume in the hopper.

Conclusions

Regardless of how the sample is obtained, its composition must be representative of the bulk from which it was removed for analytical results to have any significance. Obtaining a representative sample from a static powder bulk is difficult and may not be possible even with the most thoughtful experimental design. Although it is widely believed that the use of sample thieves is an adequate method for good sampling, the literature seems to indicate otherwise. The general consensus is that only sampling from a bulk powder while it is in motion can yield the desired representative sample. These procedures present their own range of difficulties, but equipment exists that permits one to sample from moving powder beds on a variety of suitable scales. One can conclude that the use of a rotatory sampling device or spinning riffler is probably the best instrument available for the subdivision of powders having heterogeneous particle size distributions.

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Gent, continued from page 66

deliverables with storage location of the validation documents. In other words, the validation testing report is a place to document what happened and how it happened for each validation test. In addition, the report captures all deviations and out-of-specification results.

Procedures and policies manual. A computer system can have all the bells and whistles that will help it comply with applicable regulations. However, built-in functionality and validation documentation does not make a computer system compliant. Policies and procedures are an enforcement tool that companies use to protect their computer systems from fraudulent use. These written guidelines provide a framework for specifying how the system will be used and managed, how data will be recovered, and what disciplinary actions can be taken for violations. Procedures should be written and implemented and should include security and data integrity system operation, and system maintenance.

Team development

The activities of team development are an integral part of any development activity — validated or nonvalidated. The planning process helps the validation team implement a validated system. Standard documents are required to prove that a system is validated, and policies and procedures are necessary to implement and maintain a computer system in a validated state.

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Particle-Size Distribution, Part III Determination by Analytical Sieving

Harry G. Brittain

Analytical sieving is one of the fundamental methods for the classification of powders, and it is probably the method of choice for granular or coarse powders. The method is fairly simple to perform, its validation is relatively straightforward, and the interpretation and presentation of results are fairly standard. Well-established procedures for analytical sieving are found in the *United States Pharmacopeia*, and appropriate apparatus for its use are relatively available.

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Now that some of the general precepts of particle size and shape have been outlined (1) and the all-important topic of powder sampling has been addressed (2) it is appropriate to move into a discussion of the experimental methods used to deduce information about particle size. Analytical sieving is one of the most conceptually simple methods for deducing the particle-size distribution of a powdered solid. In sieving analysis, one simply passes the sample through wire meshes that have openings of various sizes and then measures how much of the sample is retained on each sieve.

Sieving is one of the fundamental methods for the classification of powders, and it is the method of choice for determining the size distribution of coarse powders. Although sieving is most suitable for powders whose average particle size exceeds 25–50 μm it can be used for finer grades of powders if the method is properly validated and executed. Sieving analysis is difficult to perform for oily or cohesive powders because they tend to clog sieve openings.

Sieve construction

Sieves are constructed from wire mesh that is sealed into the base of an open cylindrical container. The ideal sieve openings are apertures that are nearly square. Figure 1 shows examples of the two most commonly used types of mesh screen. Analytical sieving using wire-mesh sieves provides a two-dimensional estimate of size because the smallest lateral dimension of each particle dictates its ability to pass through a given sieve opening.

The Tyler Standard Scale is a widely used classification scheme for sieve sizes. In this system the standard is based on a wire cloth with 200 openings per linear inch, which is known as a 200-mesh sieve. The diameter of the wire used for a 200-mesh screen is 53 μm and the size of the opening is 74 μm . The ratio between the adjacent sizes of the screen scale is the square root of two. Thus, the areas of the openings of each sieve are twice those of the next finer sieve. In addition the ratio between the widths of openings of alternate sieves in the series is two. Closer sizing can be attained using screens that have a fixed opening width ratio equal to the fourth root of two.

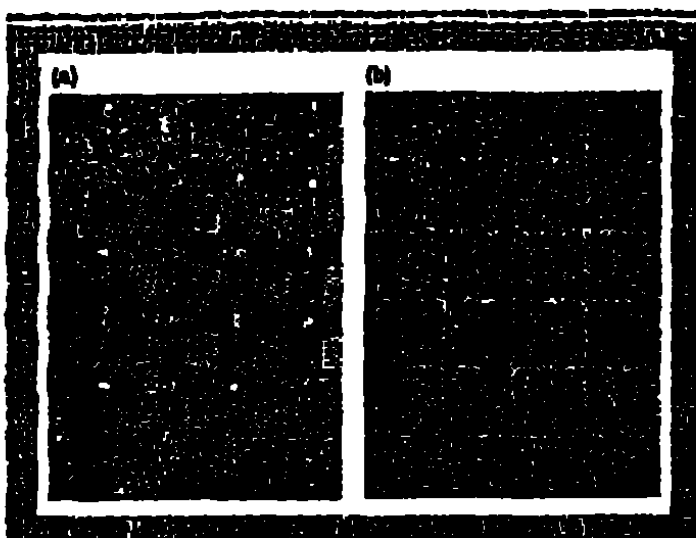


Figure 1. Photomicrographs of (a) woven-wire screen and (b) micromesh screen.

Another system was defined by the National Bureau of Standards using the same ratio as the Tyler Standard Scale, but it is based on an opening of 1 μm . This system is known as the US Sieve Series. The differences between Tyler and US sieves are small, and the sieves are often used interchangeably. However, USP General Test (786) specifies the use of sieves that meet the US Series definition (3).

A summary of Tyler and US Standard sieve classifications and the corresponding sieve openings has been documented (4) and Table I compares the systems. For fine sieves, the difference between the two systems is very small. However, for coarser sieves the difference between the Tyler and US Standard sieves is more pronounced.

Conducting sieving analysis

Conducting analytical sieving for the classification of pharmaceutical materials has been fully described in USP General Test (786) (3). The general method describes the use of both dry-sieving (Method I) and wet-sieving (Method II) procedures. In either method, sieves are stacked on top of each other in ascending degrees of coarseness, and the powder to be tested is placed on the top sieve. The nest of sieves is completed by a well-fitting pan at the base and a lid at the top. The literature provides additional sources of information about the performance of sieving analysis (5-8).

The nest of sieves is subjected to a standardized period of agitation, which causes the powder sample to distribute between the sieves. Agitation can be conducted using vibration, rotation-tapping, or ultrasound. The horizontal sieve motion loosens the powder packing and permits subsieve particles to pass through. Vertical motion mixes the particles and brings more of the subsieve particles to the screen surface. Although USP General Test (786) allows agitation by hand, it does not favor the use of this method.

In a properly designed sieve test, the sample is partitioned in approximately equal weights on each of five or six sieves and on the bottom pan. The sieving analysis is complete when the weight on any of the test sieves does not change by more than 5% of the previous weight on that sieve. Performance of a siev-

ing test yields the weight percentage of powder retained in each sieve size range.

Summary of USP General Test (786) Method I. USP General Test (786) Method I gives the procedure to be followed when conducting the sieving analysis of dry powdered solids. The steps are as follows:

- Tare each test sieve to the nearest 0.1 g.
- Place an accurately weighed quantity of test specimen on the top (coarsest) sieve and replace the lid.
- Agitate the nest of sieves for 5 min.
- Carefully remove each sieve from the nest without losing material.
- Reweigh each sieve and determine the weight of material on each sieve.
- Determine the weight of material in the collecting pan in a similar manner.
- Reassemble the nest of sieves and agitate it for 5 min.
- Remove and weigh each sieve as previously described.
- Repeat these steps until the end point criteria are met (the weight on any of the test sieves does not change by more than 5% of the previous weight on that sieve).

When the analysis is completed, the analyst reconciles the weights of material. The total losses must not exceed 5% of the weight of the original test specimen. If particles retained on any sieve are aggregates (rather than single particles), then the use of dry sieving is not likely to be an easily reproducible method. At that point, the analyst could consider the use of Method II as an alternate technique.

Summary of USP General Test (786) Method II. USP General Test (786) Method II gives the procedure to be followed when conducting the sieving analysis of wet or suspended solids. The steps are as follows:

20	840	833
30	880	880
45	350	351
60	250	248
80	177	175
120	125	124
170	88	88
230	62	61
325	44	43

205 301

TABLE II. Sieving results for a powdered sample.

50	300	13.55	8.4	14.7	85.3
70	212	32.57	22.9	52.4	47.6
140	106	22.47	15.8	36.9	3.1
Pan	—	1.24	0.9	100.0	0.0

- Modify the lid and collecting pan of the sieve nest to permit the addition of a liquid onto the surface of the top sieve and the collection of the liquid from the pan.
- Select a liquid in which the test specimen is insoluble and modify the sieving method as follows
- Thoroughly disperse the dried test material in the liquid by gentle agitation and pour this dispersion onto the top sieve
- Rinse the dispersion equipment with fresh liquid and add the rinsings to the top sieve.
- Feed the sieving liquid through a suitable pumping mechanism to the nozzle(s) in the lid and collect the sieving liquid from the pan in a suitable container
- Continue the wet-sieving process until the emerging liquid appears to be free of particles.
- Remove each sieve from the sieve nest and dry each sieve to constant weight at the same temperature as that previously described.
- Determine the weight of dried material on each sieve.

The results are analyzed in the same manner as those that are obtained using Method 1.

Validation of sieving methods. One of the most important experimental parameters to be determined in a sieving analysis is the time required to completely equilibrate the sample between all of the sieves. This time typically is determined by repeating the analysis with a fresh sample and continuing the mechanical agitation for successively longer periods of time. The proper sieving time is the smallest amount of time that leads to conformance with the requirements for end point determination. When this end point has been validated for a specific material then a single fixed time of sieving can be used for future analyses, providing the particle-size distribution does not change significantly. The determination of the proper sieving time is part of the robustness evaluation of the method.

The two most important analytical performance parameters to be determined during the validation of a sieving procedure are the precision and the accuracy associated with the analysis. To evaluate precision one repeats the particle size determination of a properly subdivided sample three to five times (2) and compares the percentages associated with each size fraction. The accuracy of a sieving analysis is usually evaluated using standard powders consisting of micron sized glass spheres of known particle size distribution. The size openings in a sieve can be verified according to the amount of passage of the reference ma-

terial or with a microscopic study of the screens themselves.

In sieving analysis, it is usually not possible to determine the analytical performance parameters of specificity, limits of detection and quantitation, linearity or range.

Data interpretation and presentation

In addition to including information about the weights on the individual sieves and in the pan, the raw data must include the weight of the test specimen, the total

sieving time, and the precise sieving methodology. The raw data are converted into a cumulative weight distribution and if one wishes to express the distribution in terms of a cumulative weight undersize then the range of sieves used should include a sieve through which all the material passes.

In many cases, the particle-size distribution of a real sample turns out to be adequately represented by a log-normal distribution. In such cases, the distribution can be specified by the geometric median particle size (d_g) and the geometric mean standard deviation (σ_g). One could conclude that two samples with identical d_g and σ_g values were drawn from the same total population. The value of d_g is equal to the 50% value of the cumulative distribution, and the value of σ_g is obtained by dividing the 84.1% value of the distribution by the 50% value.

Sieving results are most commonly plotted on 3-cycle log paper to compare the particle size with the cumulative percentage of undersize particles. If the plot is linear throughout the entire range, then the material is characterized by a log-normal distribution. If the line is curved or consists of two or more linear segments, then the distribution is polymodal. These concepts are described later in this article.

Table II shows the sieving results obtained from a powdered sample exhibiting a classic log normal distribution. The data are typically presented by listing them as a function of both the sieve mesh number and associated sieve size opening (typically described in microns). For each sieve in the nested series, one details the mass of sample retained on each sieve, the percentage of sample retained on each sieve, and usually the cumulative percentage of sample retained on each sieve. The cumulative percentage of sample passing through each sieve can also be summarized, although this quantity is not ordinarily used in an analysis.

To illustrate the sieving results, one can plot either the percentage of sample retained (from Table II) on each sieve in a histogram plot (see Figure 2a) or the cumulative distribution as a function of sieve size (see Figure 2b). A 3-cycle plot is the most illustrative means for representing these data (see Figure 3c) because any departure from linearity that would indicate the existence of a polymodal distribution is readily apparent.

For the particle size distribution shown in Figure 2, the value of the geometric median particle size (d_g) is 210 μm and the geometric mean standard deviation (σ_g) is 1.57. As discussed in Part 1 of this article series (1) several other mean particle values can

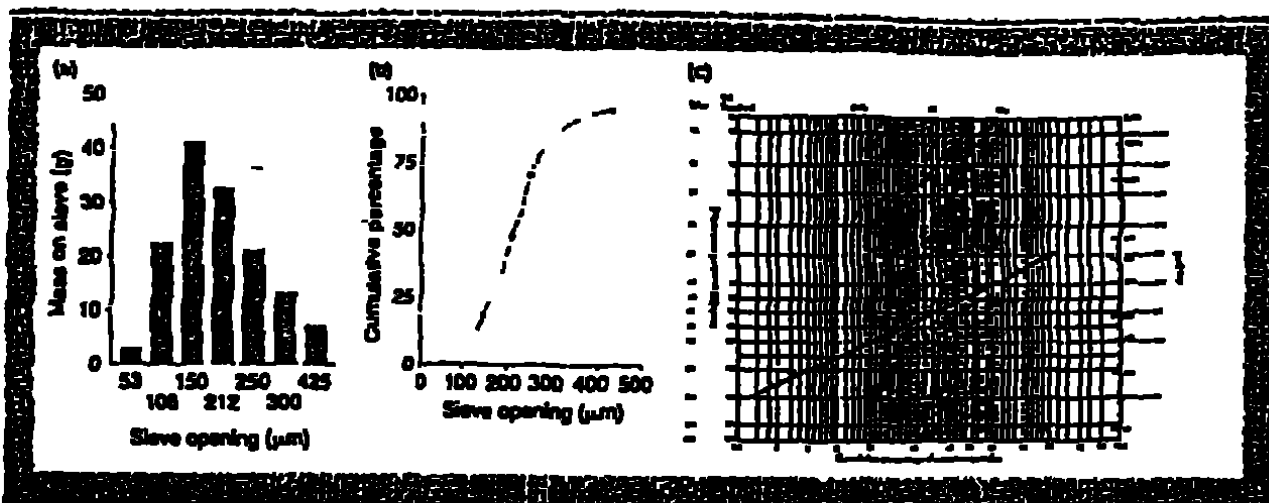


Figure 2: Representations of the particle-size distribution of a sample consisting of a unimodal distribution: (a) histogram plot, (b) cumulative distribution plot, (c) 3-cycle log plot.

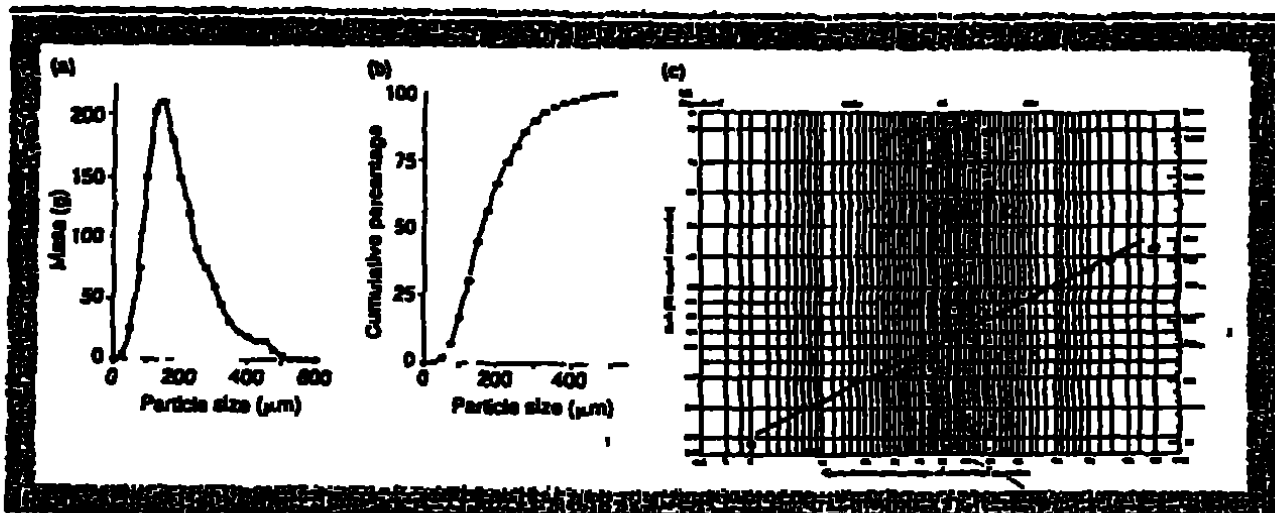


Figure 3: Log-normal representation of a sample consisting of a unimodal distribution.

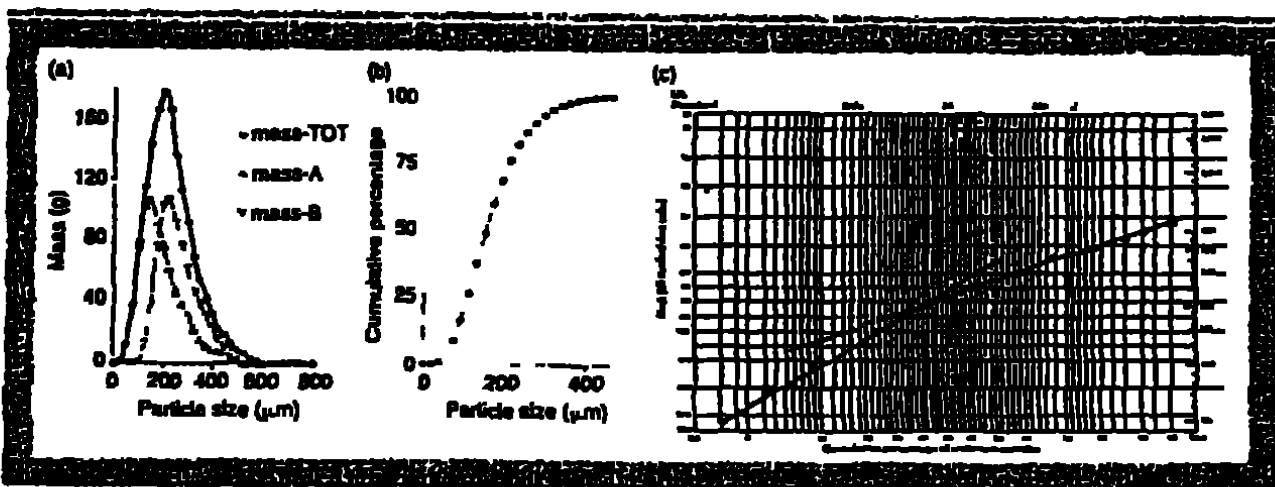


Figure 4: Representation of a sample consisting of a bimodal distribution, the modes of which differ by 100 μm.

be calculated. For this distribution the surface mean-particle size is 215 μm, the volume mean particle size is 231 μm, and the volume-surface mean particle size is 267 μm. Depending on the intended use for the information about particle size, one mean value can have more significance to the analyst than another.

Sieving analysis of samples characterized by polymodal distributions

When the particle size distribution of an analyzed sample is adequately characterized by a single (i.e., unimodal) distribution, then the method of data presentation described in the pre-

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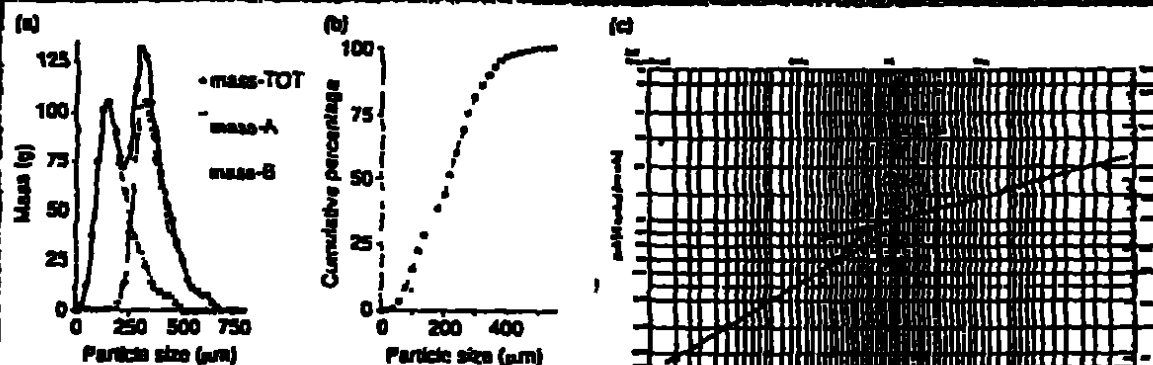


Figure 5. Representation of a sample consisting of a bimodal distribution, the modes of which differ by 200 μm .

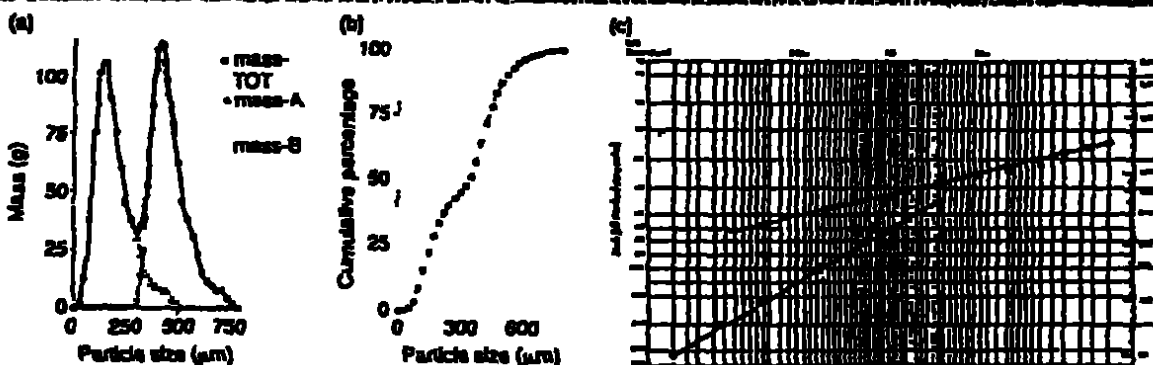


Figure 6. Representation of a sample consisting of a bimodal distribution, the modes of which differ by 300 μm .

ceding section works very well. However it is equally important to be able to recognize when the sample contains more than one population in its distribution.

To illustrate this situation, a series of model distributions consisting of two populations has been simulated and the distributions have been analyzed according to the usual technique. Figure 3 shows the representation of a unimodal distribution, and Figures 4–6 show the representations for samples consisting of bimodal distributions in which the modes differ by 100, 200, and 300 μm , respectively. The figures illustrate the power of the log plot in which the presence of the two particle-size populations is far more discernable than in either the histogram or cumulative-distribution plots.

Summary

Sieving is one of the fundamental methods for the classification of powders, and it is the method of choice for classifying coarse powders. The general consensus is that sieving is most suitable for granular solids or powders whose average particle size exceeds 25–50 μm . One must remember that the particle diameter information obtained using analytical sieving represents the minimum square aperture through which the particle can pass. Details of particulate shape will influence the separation of particles by sieving because particles will pass through openings on the basis of their cross sectional diameter.

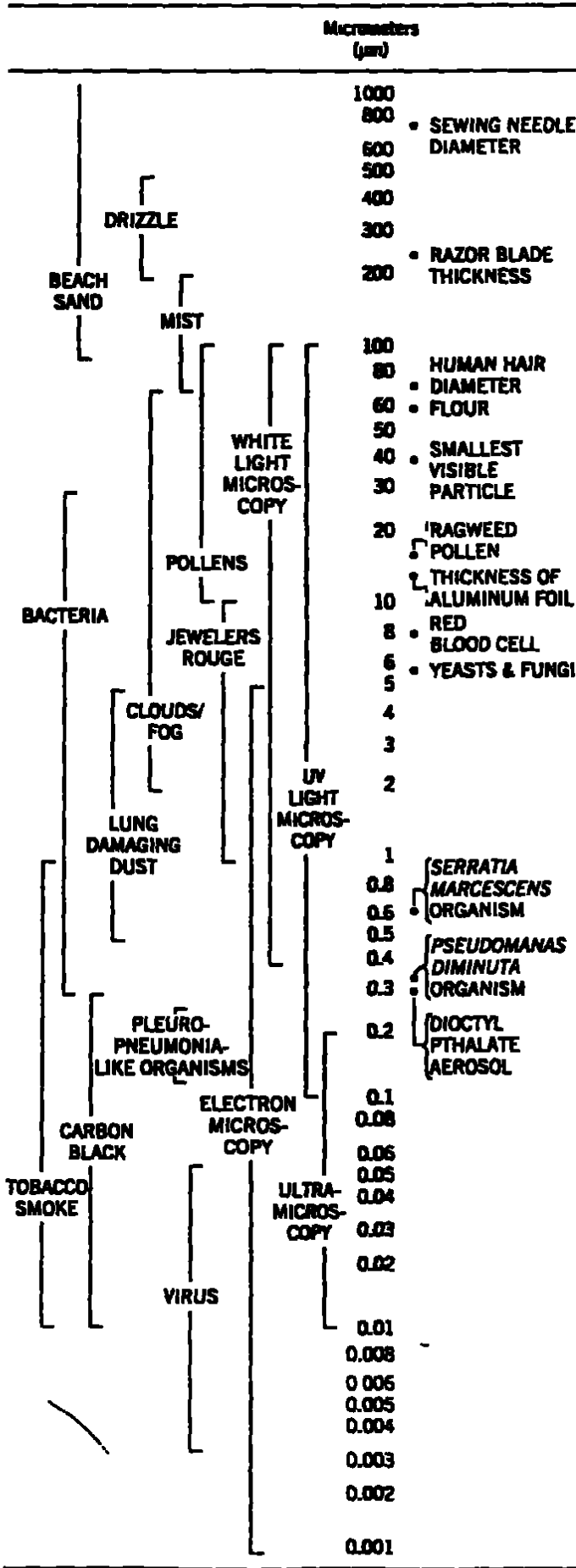
Nevertheless, analytical sieving, when it is properly performed, is a valuable method for determining the size distribution of granular and coarse powders.

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TABLE 16-1a. A scale of the Ranges of Various Small Particles, together with the Wavelength of Light and Other Electromagnetic Waves That Illuminate Materials Found in These Size Ranges. From Gehman Science, 1980, p. 4.

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Análisis por tamizado - El "patito feo" del laboratorio moderno

por Frank Best



análisis analítico con certificado

Con el equipo y el software adecuado, el análisis por tamizado es una técnica analítica que va más allá de proporcionar datos granulométricos rápidos, exactos y reproducibles.

La preparación de muestras no es una tarea exacta. Durante el submuestreo y la división de muestras pueden producirse errores debidos a la heterogeneidad del material en su composición o en la distribución granulométrica no aleatoria que normalmente ocurre como resultado de las fuerzas gravitacionales. Algunas muestras usadas para pruebas analíticas deben reflejar exactamente la composición del material a granel original. Si el material a granel tiene un tamaño de partícula inicial muy grande, es prácticamente imposible obtener una muestra representativa del mismo. En tal caso, el tamaño de partícula deberá ser reducido empleando métodos tales como la molienda o la trituración. El tamaño de partícula juega un papel principal en este proceso, por lo que el conocimiento adecuado de la distribución granulométrica es vital para asegurar que se cumplan los requisitos del muestreo, y con ello se alcance la calidad deseada en el producto. La técnica del tamizado resulta rentable con partículas cuyo tamaño es mayor de 75µ, aunque puede ser usada con algunos materiales de menor tamaño si el método puede ser validado. Asumiendo que se cumplen las normas relevantes para la aplicación y se disponga de un equipo limpio y bien mantenido en conformidad con las mismas, el tamizado brinda una medición exacta y reproducible de la distribución granulométrica de las muestras.

PROGRAMA PARA UN TAMIZADO DE CALIDAD

Los elementos mencionados a continuación son esenciales para garantizar un tamizado exacto:

Muestras parciales representativas
Las muestras parciales usadas para ensayos deben representar exactamente la masa total del material estudiado. La manera más efectiva de tomar una muestra representativa es instalar un muestreador completamente automático en el lugar apropiado. Si esto no es posible, deberá utilizarse un divisor o partidor de muestras para reducir una gran masa de material a muestras de tamaño analítico.

Tamices analíticos conformes con las normas importantes

Los tamices analíticos son una herramienta indispensable para la tecnología, por lo que se debe prestar especial atención a su correcto diseño y fabricación bajo condiciones controladas de limpieza, tal como estipula la norma ISO 3310, partes 1, 2 y 3. Cada tamiz que cumple con dicha norma se suministra con un certificado de conformidad y un rótulo mostrando los siguientes datos: abertura de malla nominal, referencia a la norma, material del tejido y del marco, identificación del fabricante con número de pieza y número de serie.

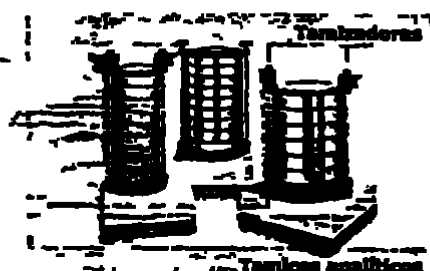
El marco portatamiz debe tener una superficie suave y apilarse fácilmente con otros tamices. La malla debe ser fijada al marco de tal manera que ninguna muestra de material quede atrapada en la misma.

Según las necesidades individuales, al comprar los tamices analíticos éstos pueden suministrarse con el certificado estándar de conformidad, o con un certificado de inspección detallado. Ambos certificados aseguran la conformidad de los tamices. Pero, ¿qué hacer cuando los tamices envejecen y siguen siendo utilizados y limpiados ininidad de veces? Un método para verificar el rendimiento

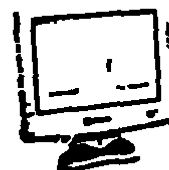
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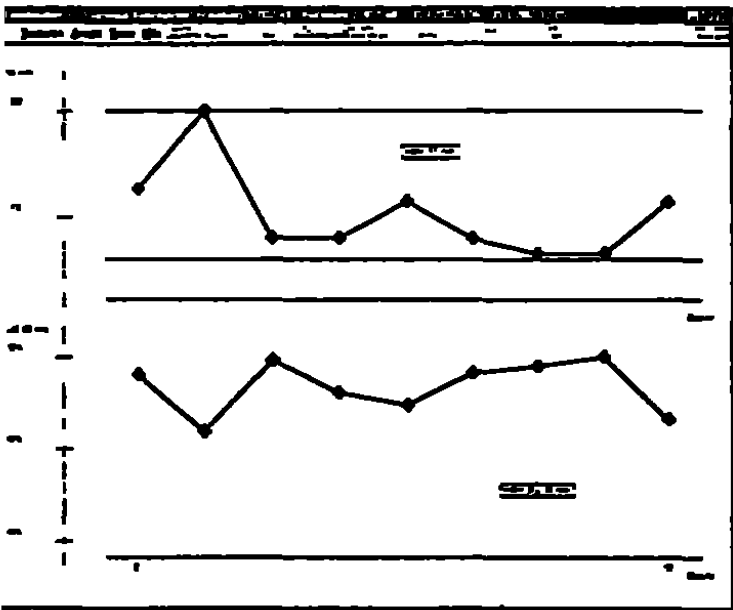
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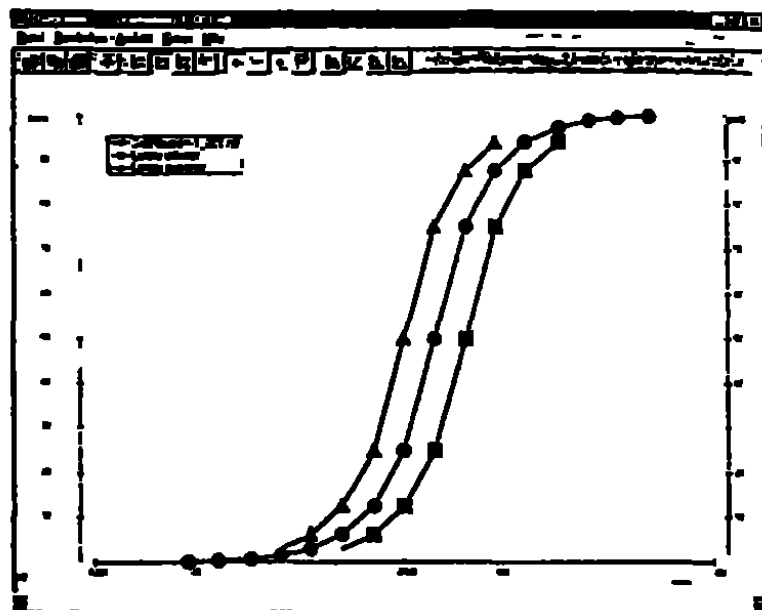
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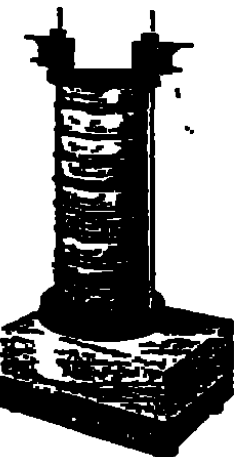


Tendencia de procedimientos de producción



Comparación con límites de especificación

le los tamices es realizar tamizados periódicos de una muestra conocida bajo exactamente las mismas condiciones y controlar los resultados comparándolos con los resultados de cuando los tamices estaban completamente nuevos. Si los resultados se salen de los márgenes aceptables, los tamices pueden recalibrarse. Sin embargo, si los tamices no cumplen con la norma requerida, la solución es reemplazarlos.



Tamizadora AS 200 Control

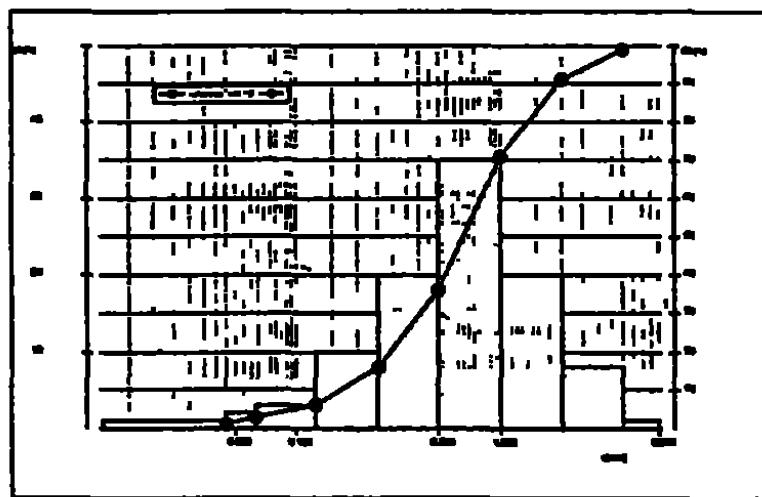
Tamizadoras fiables y balanzas analíticas
Las tamizadoras se han visto sujetas a grandes cambios en su diseño para reducir el ruido excesivo. Los modelos de accionamiento electromagnético libres de mantenimiento son muy silenciosos y pueden usarse sin atenuadores de ruido. La farmacopea estadounidense recomienda estos modelos como alternativa a las tamizadoras tradicionales

tales con movimiento vibratorio y de golpeteo. Algunas tamizadoras electromagnéticas funcionan mejor con la corriente eléctrica de los Estados Unidos por su frecuencia precisa y constante (60 Hz) pudiendo alcanzar amplitudes de hasta 3mm a pesar de la autoamplificación de la resonancia. Sin embargo, la USP recomienda mantener la amplitud entre 1 y 2mm. Una ventaja del diseño electromagnético es que a las partículas se les aplica por un período de tiempo dado una fuerza constante independientemente del número de tamices que puede afectar la frecuencia de otras tamizadoras electromagnéticas. Esto proporciona una reproducibilidad precisa, la cual es fundamental si se comparan resultados de diferentes tamizadoras analíticas, ya sea en un solo lugar de planta o a país.

La sincronización exacta es esencial para garantizar un análisis por tamizado preciso, particularmente si los tiempos de tamizado son cortos, por lo que la tamizadora debe incorporar un temporizador digital. Para mantener la conformidad, las tamizadoras deben ser enviadas periódicamente al fabricante para su calibración. Pregunte a posibles proveedores para asegurarse de que ofrecen este servicio.

Otro punto a considerar antes de seleccionar una tamizadora es la balanza, la cual debería tener un rango hasta los 5000g, una exactitud entre 0,01 y 0,1g, y una capacidad para tamices de 200mm u ocho pulgadas.

Evaluación y documentación libre de errores
Después del tamizado y pesada, la distribución granulométrica puede calcularse y presentarse en forma gráfica o de tabla. Esto puede hacerse manualmente, tarea que requiere mucho tiempo y en la que la posibilidad de cometer errores es mayor o utilizando un paquete de software comercial. Para tener a disposición todas las prestaciones que ofrece el software, se recomienda conectar la balanza y la tamizadora directamente al ordenador. En muchos laboratorios los equipos, y particularmente los tamices analíticos como instrumentos de precisión, son tratados en cuanto a la limpieza y cuidado como utensilios de cocina de segunda categoría. La limpieza y mantenimiento rigurosos de los tamices ayuda a mantener la calidad de los resultados y les da una vida más larga.



Evaluación gráfica de un ensayo granulométrico: Histograma de distribución y curva de control de masa total.

Sumergir brevemente los tamices nuevos en un baño con solvente suave para eliminar residuos de aceite. Durante la limpieza de rutina, tener cuidado de no dañar el material del tamiz ni aquellos tamices con aberturas de malla menores de 500µ. Limpiarlos en un baño ultrasónico con agua y un detergente suave por 3 a 5 minutos. Los tamices con aberturas de malla mayor de 500µ pueden limpiarse primero con un cepillo suave y luego con un baño ultrasónico. Después de la limpieza los tamices deberán ser enjuagados a fondo y puestos en posición vertical para el secado.

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POWDER PROPERTIES LABORATORY

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round Rules

You will work as a team of no more than 6 students. At the end of this laboratory session each team will turn in a single report. The report will be reviewed, and all members of the team will be given the same grade for completing the assignment if it is acceptable. It is therefore essential that you cooperate with each other. Your team report is to be turned in before you leave the laboratory. All the data should be reported, calculations shown, graphs drawn and questions answered. The final report should have a coversheet with the printed name of each team member and their signature. If a signature is missing no credit will be awarded to that person.

As a pharmacist you are expected to be able to communicate in writing. Accordingly, an organized, legible and thorough report will receive a higher grade than a disorganized, scruffy or cursory one. Similarly, pharmacies are expected to be neat, tidy and have a professional appearance. The same is true of your bench and shared areas, particularly after the laboratory session is over. Do not ignore this hint!

Part I: SIEVE ANALYSIS

INTRODUCTION

Dry sieving allows the fractionation of relatively coarse powders and granules. Sieves are stacked ("nested") with the largest apertures at the top and the smallest at the bottom (Figure 1). A sample of powder is placed on the top sieve and shaken for a fixed period of time at a given amplitude and pulse frequency. The weight of powder on each sieve can then be calculated and the particle size distribution obtained.

Particles must have a two dimensional profile smaller than the sieve aperture in order to pass through a particular sieve. A mean sieved diameter is calculated. Since the weight of particles on each sieve is determined the mean sieved diameter represents a mass distribution.

The size of the apertures in each sieve are denoted by a mesh number. The mesh number is the number of wire strands (of constant diameter) per inch used to weave the square mesh pattern. The side length of the aperture in microns is inversely related to the mesh number.

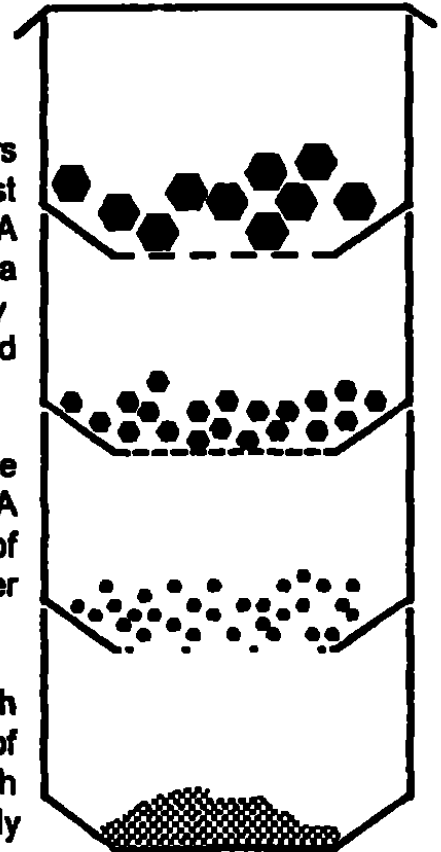


Figure 1

EXPERIMENTAL METHOD

You will determine the particle size distribution of a sample of coarse powder using a nest of sieves shaken in a Sonic Sifter. A TA will instruct your group when it is your turn to use the equipment.

- 1 Using at least a three decimal place electronic balance, record the weight of each empty sieve and the collection pan. Also record the sieve size.
- 2 Arrange the sieves in a sequential nest, smallest mesh number (largest aperture) at the top, largest mesh number (smallest aperture) at the bottom. Add the collection pan to the bottom of the nest.
- 3 Add approximately 5 g of accurately weighed coarse powder to the top sieve, and cover with the rubber cap.
- 4 A TA will insert the nest of sieves into the Sonic Sifter. The sample will be shaken for 5 minutes with a sieve "Amplitude" greater than 3.
- 5 Reweigh each sieve and the collection pan. Calculate the weight and percentage of powder on each sieve and in the collection pan. Then calculate the cumulative weight percentage of powder that is finer than the aperture, see tables below.
- 6 Obtain the sieve data from the TA on the fine powder samples.
- 7 Use the probability paper, last page, to calculate the mean diameter and standard deviation (If the TA suggest it you may want to calculate the geometric mean and standard deviation) for the coarse and fine powder particles.

RESULTS TABLES

Mesh Number	Aperture Size (um)	Sieve Weight (g)	
		Empty (Initially)	With Sieved Powder
Pan	—		

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Aperture Size (um)	Amount of Powder in Range		TA's Data % Finer
	Mass retained (g)	% Finer than d	
—	Total =	Total =	Total =

QUESTION N SIEVING

- Determine the mean sieved diameter and standard deviation (normal or log normal, see TA for directions) of your powder sample and with the data supplied by the TA, using the probability paper given on the last page
- Would you expect to get the same mean sieved diameter if you performed the expernment described above, but made the following changes? Justify your answer
 - Increased the sieving time to 10 minutes
 - Decreased the sieve amplitude to setting 1
- Dry sieving is a useful technique for particles down to around ~25 μm Why is it usually impossible to get a reliable particles size estimate with smaller particles by this method?
- Describe as many limitations as you can think of for particle size determination by sieving What types of particles could not be sized by sieving
- If a large percentage of powder were deposited on the top sieve or the bottom pan, is the particle size you determined representative of the powder sample? Justify your answer

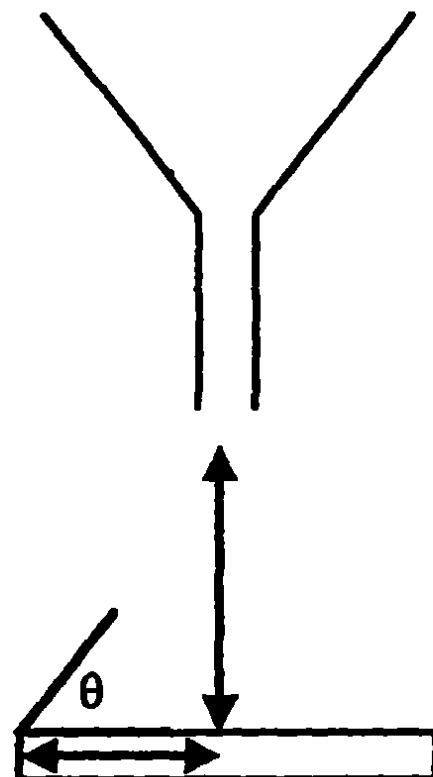
Part II: POWDER FLOW PROPERTIES

During many pharmaceutical production processes it is necessary to transfer large quantities of powder from one location to another in a controlled manner. For example

Figure 2

- 1 Powder blending
- 2 Powder filling into containers (e.g. dusting powders)
- 3 Powder flow into capsules
- 4 Powder filling into the dies of a tablet press

One method of assessing flow properties is the Angle of Repose. Powder is allowed to flow freely through a funnel onto the center of an upturned petri dish of known radius (Figure 2). When the powder reaches the side of the petri dish, the height of the cylindrical cone is determined. From the petri dish radius (r , cm) and cone height (h , cm), the angle of repose (between the petri dish and base of the powder cone) can be calculated. Flow rate can also be determined by measuring how fast a powder flows through an aperture. Free flowing powders exhibit a high flow rate and a smaller angle of repose. Angle of repose and flow rate depend on particle size, shape and surface roughness. Flow properties are frequently enhanced by the use of glidants.



EXPERIMENTAL METHOD

- 1 Measure the external diameter of the petri dish supplied to you. Position the bottom of a funnel or paper cone about 5 to 15 cm above the center of the upturned petri dish using a ring stand.
- 2 Make sure there is a piece of paper under the petri dish so you can pick up the powder and reuse the powder for all your replicates.
- 3 Slowly pour the coarse powder sample into the funnel, tapping the funnel as necessary to ensure that powder flows through the hole. Continue this process until the bottom of the powder pile just begins to fall over the edge of the petri dish. Measure the height of the pile using a ruler. If the powder is lumpy, sieve it prior to beginning the experiment.
- 4 Repeat Step 2 until you consistently obtain the same answer. Calculate the mean height of the coarse powder pile and the mean angle of repose (θ). Remember $\tan \theta = \text{Opposite} / \text{Adjacent}$, therefore $\tan \theta = h / r$.
- 5 Repeat Steps 2 and 3 using both fine powder and fine powder with glident.

RESULTS TABLES

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Sample	Run #	Height of Conical Powder Pile (cm)
Coarse Powder	1	
	2	
	3	
	Mean	
Fine Powder	1	
	2	
	3	
	Mean	
Fine Powder with Glident	1	
	2	
	3	
	Mean	

Petri Dish Radius = _____ cm

Sample	Mean Angle of Repose (°) (From Your Experiment)	Carr Index ^a
Coarse Powder		
Fine Powder		
Fine Powder and Glident		

^a see below for definition

QUESTIONS ON FLOW AND ANGLE OF REPOSE

- 1 Plot angle of repose (X-axis) against Carr Index (Y-axis), see below Is there any correlation between these two measures of powder flow? How about particle size
- 2 Name a typical glident used in tableting What properties would you expect this material to have?

- 3 Why is granulation (the process of producing larger aggregated particles from smaller individual particles) important in tableting?
- 4 If a batch of granules for compression showed unusually poor flow properties, how would you expect this to affect the uniformity of tablet weight?

Part III: REAL, TAPPED and BULK DENSITY

The true density (ρ_t) of a powder sample is the weight per unit volume of the material with no air spaces between particles. Therefore, if a material has a true density of 1 g cm^{-3} , 100 g of material will occupy 100 mL assuming individual particles fit together exactly. In practice most powders do not fit together very well. Therefore, if one fills a graduated cylinder to 100 mL with a powder, the weight of powder required may only be 70 g. This apparent density is known as the bulk or expanded density (ρ_b , 0.7 g cm^{-3}). If the 100 mL cylinder is then tapped, the particles slide past each other and become consolidated. The 70 g of particles which once occupied 100 mL may now only occupy 80 mL. They have an apparent packed or tapped density (ρ_p) of 0.875 g cm^{-3} .

Carr's index is a measure of interparticulate forces. If the interparticulate forces are high, powders will have a low bulk density because bridging will occur between particles. This results in a large Carr's index and a large change in volume caused by tapping. If the interparticulate forces are low, particles will have little affinity for one another, and will compact spontaneously. Under these circumstances, Carr's index is small and little change in apparent density is induced by tapping.

$$\text{Carr's Index} = \frac{\rho_p - \rho_b}{\rho_p}$$

Porosity is the volume ratio occupied by air spaces (voids) between particles of a powder sample.

$$\text{Porosity} = 1 - \frac{\rho_p}{\rho_t} \quad (\text{Packed}) \quad \text{and} \quad 1 - \frac{\rho_b}{\rho_t} \quad (\text{Expanded})$$

EXPERIMENTAL METHOD

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- 1 The true density of powder is 1.6 g cm⁻³.
- 2 Determine the weight of a 100 mL graduated cylinder (supplied by the TA's) Without tapping use a powder funnel to fill the cylinder to 100 mL with coarse powder. Record the weight of the cylinder and powder.
- 3 Give your filled cylinder to a TA for tapping using an automated tap density apparatus. Record the volume occupied by the sample after 100 taps.
- 4 Repeat Steps 1 and 2 using the fine powder sample.

RESULTS TABLE

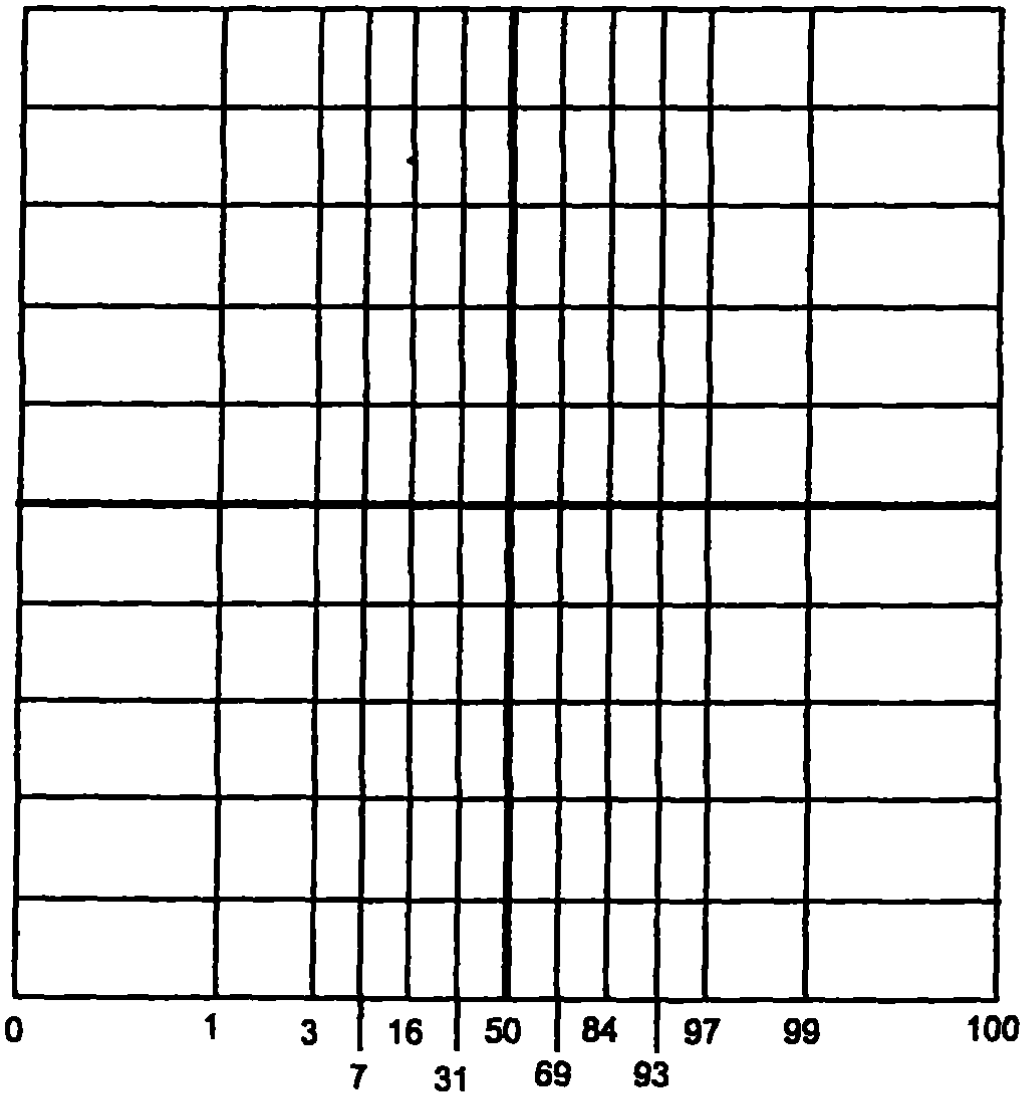
Sample	Weight of 100 mL Graduated Cylinder (g)		Volume occupied by powder after 100 taps (mL)
	Empty	Filled to 100 mL	
Coarse Powder			
Mean			
Fine Powder			
Mean			

Sample	Bulk Density (g cm ⁻³)	Packed Density (g cm ⁻³)	Carr's Index	Porosity	
				Bulk	Packed
Coarse Powder					
Fine Powder					

Questions on REAL, TAPPED and BULK DENSITY

- 1 A granulation has been prepared with a bulk density of 0.73 g cm⁻³. If the granulation is tableted with 10 mm diameter, flat faced tooling (circular), and the lower punch drops to a depth of 8 mm in the die cavity, what will be the theoretical weight of the resulting tablet?
- 2 Give reasons why the actual tablet weight might deviate from the theoretical weight.

Probability Paper



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Pharmaceutics- 2002

Selected Practice Problems on Powder Properties

- 1 Given a cube whose edge is 2 μm , what is the surface shape factor calculated from its projected area diameter?
- 2 A drug has a 5 mg dose and constitutes less than 1% of a formulation. The formulation pharmacist decided that each tablet should contain 1600 drug particles to help ensure acceptable content uniformity. To what particle size (ideally) should the drug be milled to achieve the above goal if its true density = 1.5 g cm^{-3} and assuming spherical shape?
- 3 What is the volume equivalent spherical diameter in μm of a rectangular prism (length = 3 μm , width = 2 μm , thickness = 1 μm)?
- 4 The total surface area in a powder is a function of particle size and is a measure of its "covering power", an important attribute of both therapeutic dusting powders as well as such excipients as glidants and lubricants. Given that the mean volume-surface diameter (d_{vs}) of a powder is 2 μm . What is the total surface area in m^2 in a 100 mg sample? (assume spherical shape and a true density of 1.5 g cm^{-3})
- 5 Given the following particle sizes (d_p) measured (in μm) using a microscope 1, 3, 5. What is d_{nl} and d_g ?
- 6 Given a Normal distribution of particles with a mean of 10 μm and a standard deviation of 5, estimate the percent of particles between 10 μm and 15 μm ?
You may wish to consult the table below

Standard Deviations around the mean	Correspond to this % Area Around the Mean Under the Normal Curve
3.00	99.70
2.68	99.25
2.60	99
2.33	98
1.96	95
1.65	90
1.30	82
1.00	68

- 7 In a plot of Cumulative % Undersize (Probability Scale) vs Particle size (Log Scale) for a particular powder for inhalation, 84% of the particles is less than what particle size? The geometric mean is 5 μm and the geometric standard deviation is 2

SOLUTIONS

- 1 S of particle = 6 faces $\times$ $4\mu\text{m}^2/\text{face}$ = $24\mu\text{m}^2$
 Proj Area of Particle = area of one face = $4\mu\text{m}^2$
 Projected Area of a sphere = $\pi d^2/4$
 Therefore, $\pi d^2/4 = 4$ and $d^2 = d_p^2$ (by definition) = $16/\pi$
 $S = \alpha_p d_p^2 = 24\mu\text{m}^2 = \alpha_p (16/\pi)$
 and, $\alpha_p = 3\pi/2$

$$2 \quad N_p = \frac{N}{\text{Dose}(g)} = \frac{1600}{0.005g} = 3.2 \times 10^5 \text{ particles / g required}$$

$$d_m = \left(\frac{6}{N_p \pi \rho} \right)^{1/3} = (0.398 \times 10^{-9})^{1/3} = 1.58 \times 10^{-2} \text{ cm} = 158 \times 10^{-4} \text{ cm} = 158 \mu\text{m}$$

$$3 \quad V = 3 \times 2 \times 1 = 6 \mu\text{m}^3$$

$$V_{\text{sphere}} = \frac{\pi d^3}{6} = 6 \mu\text{m}^3$$

$$d = d_p = 2.25 \mu$$

$$4 \quad S_p = \frac{6}{d_m \rho} = \frac{6}{(2 \times 10^{-4} \text{ cm})(1.5 \text{ g cm}^3)} = 2 \times 10^4 \text{ cm}^2 \text{ g}^{-1}$$

$$S = S_p \cdot g = (2 \times 10^4 \text{ cm}^2 \text{ g}^{-1})(0.1 \text{ g}) = 0.2 \times 10^4 \text{ cm}^2 = 0.2 \text{ M}^2$$

$$5 \quad d_m = \frac{1+3+5}{3} = 3 \mu\text{m}$$

$$d_g = (1 \times 3 \times 5)^{1/3} = 2.47 \mu\text{m}$$

- 6 Find how many SD's up from the mean $15 \oplus \text{m}$ is

$$\text{No. SD's} = \frac{15-10}{5} = 1$$

3/11/2015

Then consult table to see that 1 SD includes 68% area around the mean. Thus, one SD up from mean is 34% of the area. Therefore, 34% fall in the interval from the mean (10 μm) to the mean + one SD (15 μm).

- 7 Recall that in a log-Normal distribution, the geometric standard deviation is estimated from the ratio of d_{94} and d_{50} because is it a distribution of the logarithms of the diameters. Thus.

$$\sigma_g = \frac{d_{94}}{d_{50}} = 2 = \frac{d_{94}}{5m\mu}$$

$$d_{94} = 10m\mu$$

Particle Characterization

The Institute of Materials Processing uses many different methods and types of equipment to determine the size and shape of a particle. Listed below are some of the methods used and a description of the mechanism for determining either particle size or shape.

Sieve Analysis

Definition One of the most fundamental methods for determining particle size is a sieve analysis. This method involves passing the material being sized through openings of a particular standard size in a screen. The particle-size distribution is then reported as the weight percentage retained on each of a series of standard sieves of decreasing size and the percentage passed of the finest size.

Ro-Tap

Equipment Large assortment of screens available for sieving. Have Ro-tap for doing large (up to 100 kg) sample size as well as Sonic Sifter for small (2g) samples.

Particle Size Analysis

Definition The lineal dimension of a particle as determined by various analytical methods.

Equipment Leeds & Northrup Microtrac - laser based method for determining particle size. Sample is put into solution in an aqueous fluid. Laser intensity through the turbidity is used to determine material and particle size. The range of particle size is from 700 to 1 μm .
Microtrac instrument

Micromeretics Sedigraph 5000ET - x-ray based method for determining particle size. Sample is mixed with a viscosity specific fluid which allows the particles to go into solution while being stirred with a magnetic stirrer. X-ray intensity is used to determine the settling rate and to calculate the particle size distribution. Normally used for characterization of spherical particles between 100 and 0.3 μm in size.
Sedigraph instrument

Surface Area Analysis

Definition Measurement of the exposed external area of a particle

Equipment Micromeretics FlowSorbII 2300 - the measurement of surface area of a material is made by detecting the amount of nitrogen given off after absorption, considering one atomic layer of nitrogen adsorbed. Normally used for characterization of non-spherical and porous particles

Morphology

Definition Particle shape

Equipment SEM and image analysis can be used to define particle shape. Particle shape can be documented with a microphotograph. Particle shape can be quantified by using image analysis in conjunction with SEM. The image analysis unit has the capability to generate an array of chords across the particle to arithmetically define the shape of the particle.

To Scanning Electron Microscope Specs

[Back to the Material Characterization Page](#)

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STANDARD SIEVES - 8" DIAMETER		
Nominal Sieve Opening		
STD ISO	STD US	STD TYLER
5 6mm	No 3-1/2	3-1/2 mesh
4 75mm	No 4	4 mesh
4 00mm	No 5	5 mesh
3 35mm	No 6	6 mesh
2 80mm	No 7	7 mesh
2 36mm	No 8	8 mesh
2 00mm	No 10	9 mesh
1 70mm	No 12	10 mesh
1 40mm	No 14	12 mesh
1 18mm	No 16	14 mesh
1 00mm	No 18	16 mesh
850µm	No 20	20 mesh
710µm	No 25	24 mesh
600µm	No 30	28 mesh
500µm	No 35	32 mesh
425µm	No 40	35 mesh
355µm	No 45	42 mesh
300µm	No 50	48 mesh
250µm	No 60	60 mesh
212µm	No 70	65 mesh
180µm	No 80	80 mesh
STD ISO	STD US	STD TYLER
150µm	No 100	100 mesh
125µm	No 120	115 mesh
106µm	No 140	150 mesh
90µm	No 170	170 mesh
75µm	No 200	200 mesh
63µm	No 230	250 mesh
53µm	No 270	270 mesh
45µm	No 325	325 mesh
38µm	No 400	400 mesh
32µm	No 450	450 mesh
25µm	No 500	500 mesh
20µm	No 635	635 mesh

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Volume Fraction, %				
Size μ	A1 Ultrafine	A2 Fine	A3 Medium	A4 Coarse
1	1.0 to 3.0	2.5 to 3.5	1.0 to 2.0	0.6 to 1.0
2	9.0 to 13.0	10.5 to 12.5	4.0 to 5.5	2.2 to 3.7
3	21.0 to 27.0	18.5 to 22.0	7.5 to 8.5	4.2 to 6.0
4	38.0 to 44.0	25.5 to 28.5	10.5 to 13.0	6.2 to 8.2
5	58.0 to 64.0	31.0 to 36.0	15.0 to 19.0	8.0 to 10.5
7	83.0 to 88.0	41.0 to 46.0	28.0 to 33.0	12.0 to 14.5
10	97.0 to 100	50.0 to 54.0	40.0 to 45.0	17.0 to 22.0
20	100	70.0 to 74.0	65.0 to 69.0	32.0 to 36.0
40	—	88.0 to 91.0	84.0 to 88.0	57.0 to 61.0
80	—	99.5 to 100	99.0 to 100	87.5 to 90.5
120	—	100	100	97.0 to 98.0
180	—	—	—	99.5 to 100
200	—	—	—	100

**Graphical Comparison of ISO 12013-1 Test Dust Grades
Based on ISO 12103-1 Specified Limits Median
(Cumulative Volume)**

CAPITULO 2

CONTENIDO .

- 1 Visión crítica de los métodos propuestos para determinar tamaño de partícula**
- 2 Determinación de la distribución del tamaño de partícula por tamización analítica, microscopía óptica (USP 26)**
- 3 ISO 13320 Análisis del tamaño de partícula por difracción Laser**
- 4. Caracterización de sólidos farmacéuticos utilizando varias técnicas de medida del tamaño.**
- 5. Beneficios de la difracción Laser en el análisis de tamaño De partícula.**
- 6. Analizador de tamaño de partícula SUBMICRON**
- 7 Partículas certificadas para calibración de equipos**
- 8. Avances en la caracterización de micropartículas para inhalación.**

Critical Overview of the Proposed Particle Size Analysis Tests

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Center for Pharmaceutical Physics and Pharmacia Corporation

The determination of particle size distribution is an essential aspect of the characterization of drug substances and pharmaceutical excipients. The field is somewhat confusing in that a large number of methods exist for such determinations, and each has its own particular requirements for reduction and display of the results. In this article, the current state associated with the two most important methods of particle size determination (analytical sieving and laser light scattering) will be discussed.

Particle size determinations are undertaken to obtain information about the size characteristics of an ensemble of particles. A non-critical, and entirely unsatisfactory, view of this process can be represented as

Powdered Sample - Some Type of Machine - Particle Size Information

However, the nature of the sample under study, and the type of particle size information required, places a far higher degree of specificity on the procedure to be followed. Since the particles under study are not usually of the same exact size, information is required regarding the average particle size and the distribution of sizes about this average.

It is well known that if one performs particle size distribution studies on a given sample using microscopy, sieving, or light scattering, one will usually obtain different values for the mean particle size and the overall distribution. There simply is no single standard definition in current use for "particle size." The various statistical diameters that have been defined yield measures that have meaning, but only have value when averaged over a large ensemble of measurements. All measurements require an assumption that the particles making up the sample have not been biased in any sense and that the methods used for their sampling and measurement are entirely random.

Most workers would be happiest if the United States Pharmacopeia (USP) contained detailed methods for all methods of particle sizing. Unfortunately this ideal situation has not yet arrived, but the Expert Committees of USP are actively working to reach nirvana. In this article, the current state of the compendial methodology will be summarized.

Brief History of USP Particle Sizing Chapters

In the 10th edition of the United States Pharmacopeia, a general chapter entitled, "Powders - Fineness" was published [1]. This chapter provided a series of standards for categorizing the fineness of powdered solids, and introduced the definitions of Coarse (100% passes through a 20-mesh sieve, and not more than 40% passes through a 60-mesh sieve), Moderately Coarse (100% passes through a 40-mesh sieve, and not more than 40% passes through a 80-mesh sieve), Fine (100% passes through a 60-mesh sieve, and not more than 40% passes through a 100-mesh sieve), and Very Fine (100% passes through a 80-mesh sieve). In addition, the chapter also contained a brief description as how to conduct powder fineness testing using standard testing sieves.

In the 12th edition of USP, the "Fineness of Powders" chapter was the first to provide a table of the nominal dimensions of standard testing sieves [2]. The monograph differentiated between the fineness of powdered vegetable or animal drugs and the fineness of powdered chemicals. An additional size classification of powders, Very Coarse (100% passes through a 8-mesh sieve, and not more than 20% passes through a 60-mesh sieve) was also provided. The monograph also discussed standards for particle fineness, and provided a more detailed discussion of the method for determining the fineness of powders.

With the publication of USP 20, the "Powder Fineness" test had become identified as General Test <811>, but the content had actually changed very little over the years [3]. The monograph contained the same discussion of sieves for pharmacopoeial testing, and discussion of methods for determining the uniformity of fineness. The classification of powders by fineness was presented in Table 1, while Table 2 contained the openings of standard sieves.

Although the Powder Fineness chapter continued to be published as General Test <811>, a significant contribution to the compendial methodology was published in USP 24 in the form of General Test <786>, "Particle Size Estimation by Analytical Sieving" [4]. This monograph represents the first inclusion in the pharmacopoeia of methodology designed for the measurement of actual particle size distributions. The chapter contained a strong discussion of sieves and sieving principles, including sample size, agitation methods, and endpoint determination. Two methods of analysis were outlined and identified as Method I (dry sieving) and Method II (wet sieving). With the publication of USP 24, the Powder Fineness chapter began referring to General Test <786> and classified powder fineness based on commonly accepted definitions of d₁₀, d₅₀ and d₉₀ as determined by sieving. Unfortunately, neither chapter included as much discussion regarding

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data interpretation or its presentation as would have been useful

Particle Size Distribution by Analytical Sieving

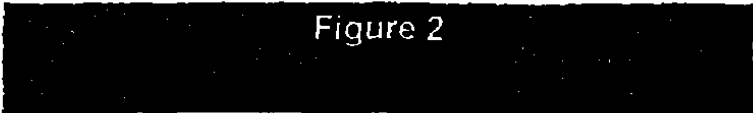
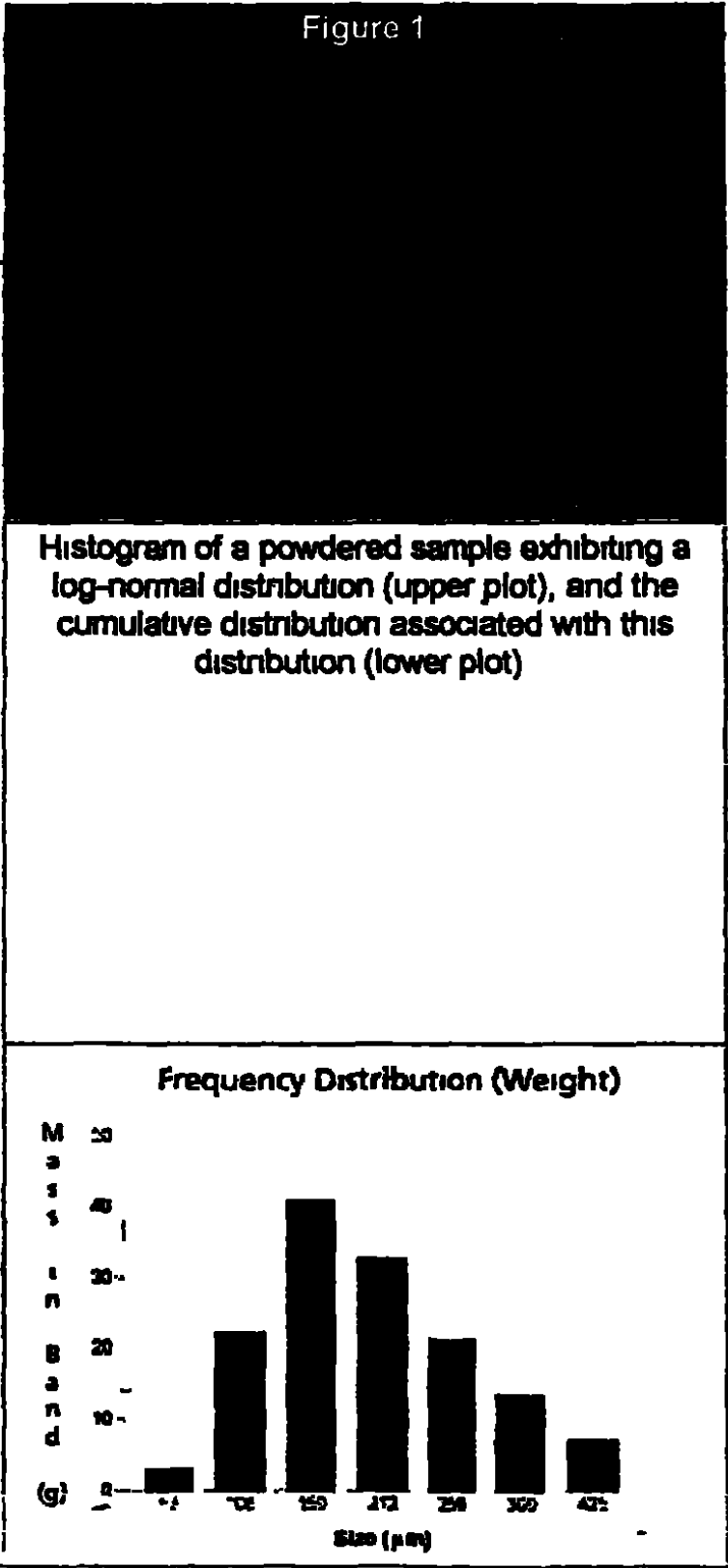
In its current incarnation in USP 26, General Test <786> "Particle Size Estimation by Analytical Sieving" [5] does not differ greatly from the version set forth in USP 24. The general chapter still contains a good discussion of sieves and sieving principles, including sample size, agitation methods, and endpoint determination. The use of dry sieving (Method I) and wet sieving (Method II) is still included, but the monograph now includes a discussion of air jet and sonic sifter sieving. Unfortunately, there is still not enough discussion on data interpretation or its presentation.

Sieving remains one of the most popular methods for the classification of powders and is probably the method of choice for coarse powders. Although sieving is most suitable for powders whose average particle size exceeds 25-50 μ m, it can be used for smaller sized powders if the method can be validated. Sieving analysis is difficult to perform for oily or cohesive powders, since they will tend to clog the sieve openings.

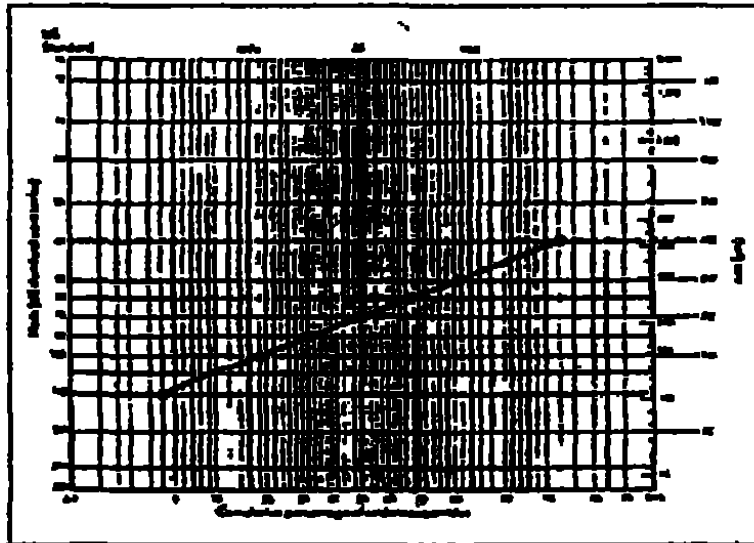
Sieves are constructed from wire mesh that is sealed into the base of an open cylindrical container, and ideally the sieve openings are nearly square apertures. As a result, the method provides essentially a two-dimensional estimate of size because passage of particles through a sieve is dictated by the smallest lateral dimension of each particle (i.e., sieve diameter). Sieving results are typically plotted on 3-cycle log paper to compare the particle size with the cumulative percentage of undersize particles. If the plot is linear over the entire range, then the material is characterized by a log normal distribution. If the line is curved, or consists of two or more linear segments, the distribution is polymodal.

To illustrate the type of results obtained upon performance of a typical sieving analysis, consider the particle distribution of a powdered sample. The histogram and cumulative distribution illustrated in Figure 1 are characteristic of a log-normal distribution. When the results are plotted in the usual manner on 3-cycle log paper, the straight line behavior noted confirms the existence of a single size population in the sample. To meet the need for additional guidance on analysis of particle size data, a draft document has been prepared for USP by the Expert Committee that provides additional information on common methods of measurement of particle size, types of weighting (e.g., number, length, surface area, volume), graphical presentation, and common descriptive terms (e.g., median diameter, width, use of percentiles). Such an informational chapter when published in USP will provide additional guidance.

regarding interpretation of both sieving and laser light scattering data



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Particle Size Distribution by Laser Light Scattering

At the time when this article was written, no official general chapter describing the determination of particle size distribution by means of laser light scattering had been published in the pharmacopoeia. However, a proposed chapter has been published in Pharmacopoeial Forum [6], which forms the basis for what will eventually become the official compendial method. General Test <429> contains a good discussion of general principles, and typical instrumentation for laser diffraction measurements, as well as procedures for wet and dry sample preparation. The chapter contains a strong module on validation, discussing replicates, system suitability, accuracy, and repeatability. At present, the discussion of result reporting is brief and hopefully will be expanded in the final version.

It is worthwhile to briefly discuss how laser light scattering can be used to deduce particle size information, since the method is not as direct as generally believed. When laser light is passed through an ensemble of particles, the angle of scattering will depend on the size of the diffracting particles. Experimentally, this angular dependence is typically measured using detectors consisting of photosensitive rings separated by insulating gaps. Distances in the detector plane are measured from the central optical axis, and the intensity measured at each ring represents the observable signal.

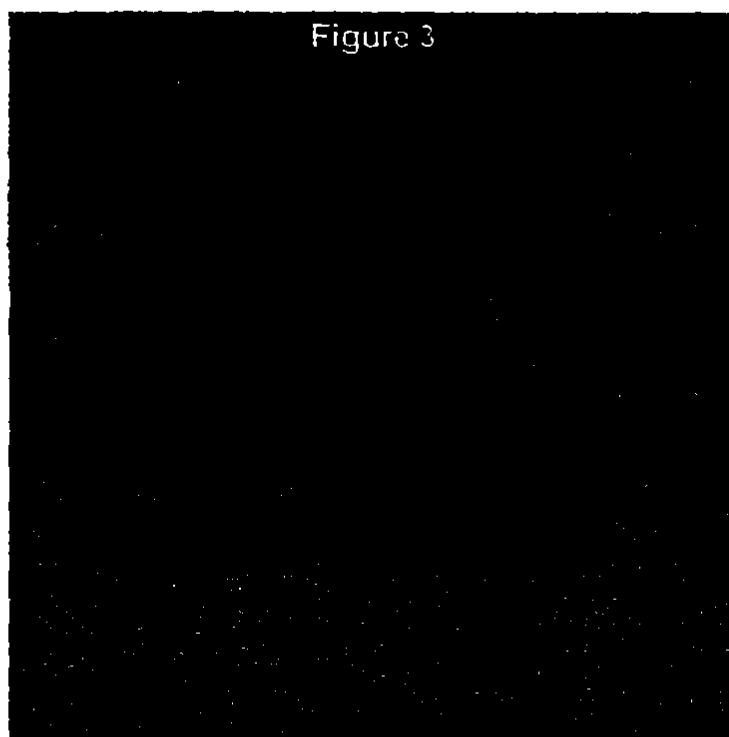
The intensity results must be processed in order to obtain particle size information, and the most commonly used approach uses least-squares criteria for deconvolution. There are a number of models in use, each of which begins with basic assumptions and then works toward a minimalization of the differences between the ideal and the measured.

The size distribution is ultimately derived from the modifications required by the least-squares minimalization

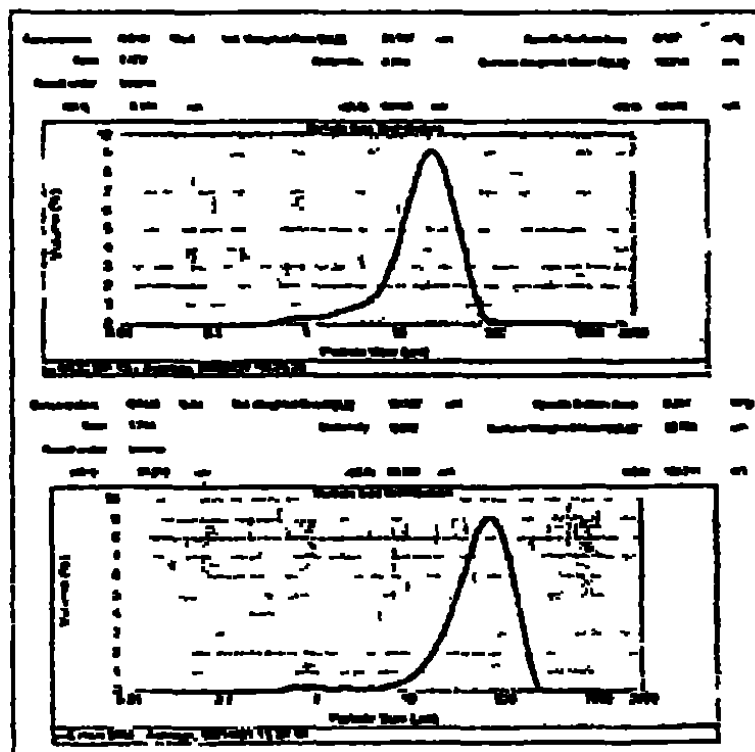
For instance, in the unimodal model-dependent method, one begins by assuming a model (such as log-normal) for the size distribution and the detector response expected for this distribution is then simulated. The model parameters are then optimized by minimizing the sum of squared deviations from the measured detector response, and this minimized set is then used to deduce how the original model distribution is to be modified to fit the empirical results. This fitted distribution is ultimately displayed as the "particle size distribution."

Another popular approach uses the unimodal model-independent method. Here, one assumes that the size distribution consists of a finite number of fixed size classes, and the detector response expected for this distribution is then simulated. One then optimizes the weight fractions in each size class by minimizing the sum of squared deviations from the measured detector response. When the minimalization criterion is attained, the deduced distribution is ultimately displayed as the "particle size distribution."

When particle size measurements are made using the same laser light scattering system, following the same method of sample preparation, and obtained using the same system parameters, it is possible to obtain good information regarding the particle size differences between different lots of material. For instance, the particle size distributions of two different grades of microcrystalline cellulose are shown in Figure 3.



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Current pharmacopoeial activities in the area of light diffraction include recent publication of a Proposal Stage 3 draft harmonized chapter 2.9.31 Laser Diffraction Measurement of Particle Size [7].

What is the Particle Size Method of Choice to Use on a Routine Basis?

Assuming the instrument is properly working and has been calibrated (if necessary), the questions to address when determining how "correct" a particle size distribution are

- 1 Was the sample obtained using appropriate sampling procedures?
- 2 Was the sample properly prepared and introduced into the instrument?
- 3 Were all instrumental parameters correctly used for the analysis?

If all of the answers to the preceding questions are in the affirmative, then one may believe that the particle size distribution is "correct." The "correct" (but differing) particle size results obtained using different instruments are all equally "correct," but each may simply be expressing its "correct" results in different terms.

The decision as to which particle size methodology is most appropriate for a given situation becomes largely a matter of accuracy vs. precision. If absolute accuracy is most important, then rigorous research must be conducted to verify that the method finally adopted does indeed yield

particle size results that are absolutely indicative of the characteristics of the bulk lot from which the sample was drawn. If, however, one is more interested in developing profiles of lot-to-lot variability, then use of any of the available methods that yields "correct" results is appropriate.

References

1 "Powders - Fineness" Pharmacopeia of the United States of America Tenth Decennial Revision (USP X), J.B. Lippincott Co. Philadelphia PA (1926) pp 451-452

2 "Fineness of Powders" Pharmacopeia of the United States of America Twelfth Revision (USP XII) Mack Printing Co. Easton PA (1942) pp 553-555

3 "8" "Powders - Fineness" The United States Pharmacopeia Twelfth Revision (USP XII) United States Pharmacopeia Convention Inc. Rockville MD (1995) pp 1072-1073

4 "11" "Powders - Fineness" The United States Pharmacopeia Twelfth Revision (USP XII) United States Pharmacopeia Convention Inc. Rockville MD (1995) pp 1072-1073

5 "12" "Powders - Fineness" The United States Pharmacopeia Twelfth Revision (USP XII) United States Pharmacopeia Convention Inc. Rockville MD (1995) pp 1072-1073

6 "13" "Powders - Fineness" The United States Pharmacopeia Twelfth Revision (USP XII) United States Pharmacopeia Convention Inc. Rockville MD (1995) pp 1072-1073

7 "14" "Laser Diffraction Measurement of Particle Size" Pharmacopeial Forum 28 (3) 895-901 (2002)

Prior to forming the Center for Pharmaceutical Physics, Dr. Brittain held positions at Discovery Laboratories, Inc., Ohmeda, Inc., and Bristol-Myers Squibb Co. He serves as Chairman of the USP Expert Committee on Excipient Monograph Content, and is an elected member of the International Center for Diffraction Data. Dr. Brittain was elected as a Fellow of the American Association of Pharmaceutical Sciences (AAPS) in 1991, received the AAPS Research Achievement Award in Analysis and Pharmaceutical Quality in 1998.

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X-Ray Diffraction for Solid State Pharmaceutical Products.



Introduction

X-ray diffraction is a unique analytical tool for solid state pharmaceutical products. Many parameters required by the FDA, legal patent issues and drug performance are only accessible by utilizing x-ray diffraction. With the introduction of new systems specifically designed for the pharmaceutical industry, x-ray diffraction has now become cost effective and easy to use. Any pharmaceutical company striving to compete in the aggressive world of drug development with all the associated legal issues and FDA requirements, would be lost without x-ray diffraction to characterize unambiguously the solid state nature of pharmaceuticals.

Strategic Pharmaceutical Analysis

Characterization of Solid State Parameters

X-ray diffraction is a direct result of the crystal structures which are present in the pharmaceutical under study. As such, the parameters typically associated with crystal structure can be simply accessed. For example, once an active drug has been isolated, an indexed x-ray powder diffraction pattern is required to secure a patent and protect the company's investment. An analysis of the active drug under most environmental conditions reveals the formation of any polymorphs that could adversely affect performance and toxicity.

The detection and quantification of polymorphic contamination can also be used to improve production efficiency and cost. Once the active ingredient is in the final dosage form the morphology parameters measured by x-ray diffraction can be directly related to the final drug performance.

For multicomponent formulations, the actual percentages of the active ingredients in the final dosage form can be accurately analyzed in situ, along with the percentage of any amorphous packing ingredients used.

**X-ray diffraction is the key technique for solid state drug analysis
benefiting all stages of drug development, testing and production**

Dedicated X-Ray Diffraction Technology

**In the past, the biggest barriers to the wide use of x-ray diffraction have
been ease of use and cost of ownership.**

**The XRD-6000 system addresses both concerns. The system is fully
IQOQPQ certified according to FDA procedures making it ready for
immediate operation. Many of the special requirements for pharmaceutical
analysis have been pre-automated with dedicated measurement and
analytical methods for easy operation without specialized training. Many
attachments have been developed to facilitate the analysis of
pharmaceutical products, such as a non-ambient environment for high and
low temperatures, controlled humidity and gas flow. When other
specialized non-standard methods are required, these can be developed
in conjunction with our in-house team of specialists.**

**The pre-certification and ease of use have reduced the overall operating
cost of the XRD-6000, but real savings are also available in the initial
purchase price. The specialized production of the XRD-6000 provides a
price/performance ratio significantly better than any other comparable x-
ray diffraction system.**

ANALYTICAL METHODS

Formulation Analysis, Polymorph Identification and Percentage Crystallinity

**Phase analysis and polymorph identification are the study of different
polycrystal structures within a pharmaceutical product. One phase or
polymorph is distinguished from another by its unique powder diffraction
pattern which arises from its unique crystal structure. Phase analysis can
be restricted to identification only or can be extended to a full quantitative
analysis. The analysis is applicable to polymorphs or to multi-component
formulations. Phase analysis is usually considered to be a "1% technique"
except in special cases where this can be extended to 0.1% sensitivity. A**

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special case of this analysis is percentage crystallinity where the volume percentage of an amorphous filler to a crystalline active matrix is measured within the dosage form.

Some typical results of phase analysis are shown in Figure 1 (of the full Note) at the end of this summary. The first set of data shows a measured sample of Mannitol which is clearly made up of a 65/45 mix of the Alpha and Delta polymorphs of Mannitol. The same Mannitol sample is analyzed for percent crystallinity. After removing the amorphous component by profile fitting, the crystalline content of the sample was calculated at approximately 25% (Refer to Figure 2 in the full Note).

Crystal Structure Determination

Although it is possible to determine the crystal structure from a general powder diffraction pattern, in most cases it is sufficient simply to identify the unit cell symmetry and cell parameters. With this information it is possible to index the complete measured pattern. If additional peaks are observed which cannot be indexed then additional phases must be present in the sample or the unit cell chosen was not the correct one. Once all peaks are indexed from a pure active drug its crystal structure is understood and it can be uniquely fingerprinted.

In addition to fingerprinting active drug components, the unit cell can be used to predict morphology and hence physical properties. The unit cell index and fingerprint of the alpha polymorph of mannitol is displayed.

Non-Ambient Analysis

All the above methods can be performed under non-ambient conditions. High and low temperature and/or humidity and different gas environments. This helps to track possible changes in polymorphism and/or formulation changes under a wide range of conditions possibly encountered by the drug. As with the phases analysis itself this can be performed on either the final dosage form or the raw materials or any stage between the two. In Figure 3, a non-ambient study of Aspirin is shown, performed over a temperature range of 40° to 180°C in 20°C steps.

Morphology

There are many morphology components measured by x-ray diffraction that are directly related to drug performance in both its raw form and final dosage form.

Some of the more typically measured properties are crystal shape, size and orientation. All of these affect the activation rates and uptake speeds for the measured drug. The analysis (given in the full version of this report) using the full pattern Hall method on the alpha polymorph of mannitol indicates that the average crystal size is about 140 Angstroms. Due to the x-ray transparency of mannitol this value needs calibration to ensure absolute accuracy, but from sample to sample the method is very sensitive to any change in average crystal size. The characteristic spread in the data points indicates a distinct characteristic morphological shape for the alpha mannitol crystals. As the crystallite shape changes, the Hall plot spread will reflect this.

Reference

1 Kratos Analytical Applications Note "X-Ray Diffraction for Solid State Pharmaceutical Products", NY Office, August 1998

List of Figures

Figure 1 Phase analysis - 85/45 mix of alpha and delta polymorphs of mannitol

Figure 2: Percent crystallinity calculated by total pattern fitting

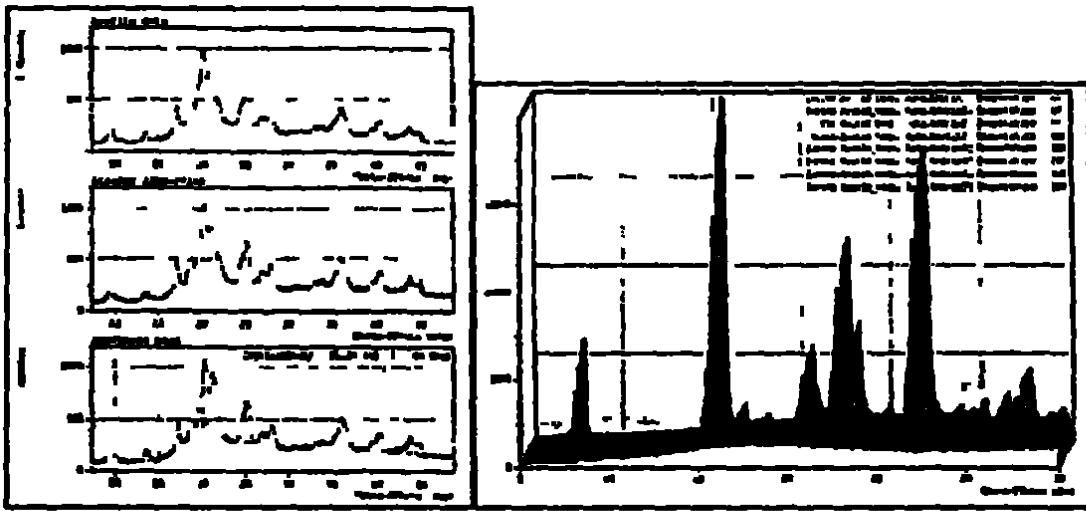
Figure 3 Non-ambient study of aspirin over a temperature range 40° to 1280° in 20° steps.

Figure 4 Full pattern hall method showing variation of crystal size

Table 1 Unit cell indexing and fingerprint of the alpha polymorph of mannitol

(31 lines. cf J. Appl. Cryst. 12 (1979) p60)

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Instrumentation | More X-Ray Applications | Percentage Crystallinity | Geological Applications |

(786) PARTICLE SIZE
DISTRIBUTION ESTIMATION BY
ANALYTICAL SIEVING

Sieving is one of the oldest methods of classifying powders by particle size distribution. Sieving is most suitable where the majority of the particles are larger than about 75 µm, although it can be used for some powders having smaller particle sizes where the method can be validated. In pharmaceutical terms, sieving is usually the method of choice for classification of the coarser grades of single powders. It is a particularly attractive method in that powders are classified only on the basis of particle size, and in most cases the analysis can be carried out in the dry state.

Among the limitations of the sieving method are the need for an appreciable amount of sample (normally at least 25 g) and difficulty in sieving oily or other cohesive powders that tend to clog the sieve openings. The method is essentially a two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length.

This method is intended for estimation of the total particle size distribution of a single material. It is not intended for determination of the proportion of particles passing or retained on one or two sieves.

Estimate the particle size distribution as described under *Method I* unless otherwise specified in the individual monograph. *Method I* is the dry sieving method. Where difficulty is experienced in reaching the endpoint (i.e., material does not readily pass through the sieves) or when it is necessary to use the finer end of the sieving range (below 75 µm), *Method II*, which is a wet sieving technique, may be used, however in the latter case serious consideration should be given to the use of an alternative particle-sizing method.

Principles of Analytical Sieving—Analytical test sieves are constructed from a woven-wire mesh, which is of simple weave that is assumed to give nearly square apertures and is sealed into the base of an open cylindrical container. The basic analytical method involves stacking the sieves on top of one another in ascending degrees of coarseness, and then placing the test powder on the top sieve.

The nest of sieves is subjected to a standardized period of agitation, and then the weight of material retained on each sieve is accurately determined. The test gives the weight percentage of powder in each sieve size range.

This sieving process for estimating the particle size distribution of a single pharmaceutical powder is generally intended for use where at least 80% of the particles are larger than 75 µm. The size parameter involved in determining particle size distribution by analytical sieving is the length of the side of the minimum square aperture through which the particle will pass.

TEST SIEVES

Test sieves suitable for pharmacopoeial tests conform to the most current edition of American Society for Testing and Materials (ASTM) Specification E 11 U.S. Standard Sieve Series (see Table 1). Unless otherwise specified in the monograph, use those ASTM sieves listed in Table 1 as recommended USP sieves.

Table 1 Sizes of Standard Sieve Series in Range of Interest.

Sieve Size	Sieve U.S. No.	ASTM E 11 ^a	Recommended USP Sieves ^b
4.00 mm	5	X	X
3.35 mm	6	X	
2.80 mm	7	X	X
2.36 mm	8	X	
2.00 mm	10	X	X
1.70 mm	12	X	
1.40 mm	14	X	X
1.18 mm	16	X	
1.00 mm	18	X	X
850 µm	20	X	
710 µm	25	X	X
600 µm	30	X	
500 µm	35	X	X
425 µm	40	X	

Sieve Size	Sieve U.S. No.	ASTM E 11	Recommended USP Sieves ^b
355 µm	45	X	X
300 µm	50	X	
250 µm	60	X	X
212 µm	70	X	
180 µm	80	X	X
150 µm	100	X	
125 µm	120	X	X
106 µm	140	X	
90 µm	170	X	X
75 µm	200	X	
63 µm	230	X	X
53 µm	270	X	
45 µm	325	X	X

ASTM E 11 U.S. Standard Sieve Series. For further information, reference may be made to ASTM STP 447, "A Manual on Test Sieving Methods," available from the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19380-2900.

^b Note: The equivalent ISO Standard sieves may be substituted.

Sieves are selected to cover the entire range of particle sizes present in the test specimen and include all the recommended USP test sieves in this range; i.e., none should be omitted. This nest of sieves is completed by a well-fitting collecting pan at its base and lid at its top. Use micrometers or millimeters in denoting test sieve openings. [NOTE—Mesh numbers are provided in the table for conversion purposes only.] Test sieves are made from stainless steel or, less preferably, from brass or other suitable nonreactive wire.

Calibration and recalibration of test sieves is in accordance with the most current edition of ASTM Method E 11. Sieves should be carefully examined for gross distortions and fractures, especially at their screen frame joints, before use. Sieves may be calibrated optically to estimate the average opening size and opening variability of the sieve mesh. Alternatively, for the evaluation of the effective opening of test sieves in the size range of 212 to 850 µm, Standard Glass Spheres are available from the National Institute of Standards and Technology as Standard Reference Material 1018. Unless otherwise specified in the individual monograph, perform the sieve analysis at controlled room temperature and a relative humidity between 30% and 70%.

Cleaning Test Sieves—Ideally, test sieves should be cleaned using only an air jet or a liquid stream. If some apertures remain blocked by test particles, careful gentle brushing may be used as a last resort.

Test Specimen—If the test specimen weight is not given in the monograph for a particular material, use a test specimen having a weight between 25 and 100 g, depending on the bulk density of the material, and test sieves having an 8-inch diameter. Determine the most appropriate weight for a given material by test sieving accurately weighed specimens of different weights, such as 25, 50, and 100 g, for the same time period on a mechanical shaker. [NOTE—If the test results are similar for the 25-g and 50-g specimens, but the 100-g specimen shows a lower percentage through the finest sieve, the 100-g specimen size is too large.] Where only a specimen of 10 to 25 g is available, smaller diameter test sieves conforming to the same ASTM specifications may be substituted, but the endpoint must be redetermined.

If the test material is prone to picking up or losing significant amounts of water with varying humidity, the test must be carried out in an appropriately controlled environment. Similarly, if the test material is known to develop an electrostatic charge, careful observation must be made to ensure that such charging is not influencing the analysis. If both of the above effects cannot be eliminated, an alternative particle-sizing technique must be selected.

Agitation Methods—Use a mechanical device that imparts either a rotating-tap (200 to 300 horizontal revolutions and 140 to 300 taps per minute) or vibrator (1 to 2 mm amplitude) motion to the sieves as the reference method of agitating test sieves, unless otherwise stated in the individual monograph. Methods utilizing entrainment of the particles in an air stream may also be used. The results must indicate that an air entrainment sieving method was used.

Alternatively but less desirable because of difficulties in reproducibility and validation, agitation by hand may be used, but the methodology must be such as to impart a rotary motion to the material on

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sieves by tilting the sieve nest. In addition the sieves are tapped on a hard surface at approximate 10- to 15-second intervals. The results so indicate that a *hand sieving method* was used.

Endpoint Determination—The test sieving analysis is complete when the weight on any of the test sieves does not change by more than 5% (10% in the case of 3-inch sieves) of the previous weight on that sieve. If less than 5% of the total specimen weight is present on a given sieve, the endpoint for that sieve is increased to a weight change not more than 20% of the previous weight on that sieve.

If more than 50% of the total specimen weight is found on any one sieve, the test should be repeated, but with the addition to the sieve of the next coarsest sieve to that carrying the excessive weight, addition of the ASTM series sieve omitted from the USP series in Table 1. For example, if more than 50% of the total specimen weight found on the 180- μ m sieve, the ASTM 212- μ m sieve should be added between the 180- μ m and 250- μ m sieves in the sieve nest.

SIEVING METHODS

Method I (Dry Sieving Method)—Tare each test sieve to the nearest 0.1 g. Place an accurately weighed quantity of test specimen on the top (coarsest) sieve, and replace the lid. Agitate the nest of sieves for 5 minutes. Then carefully remove each from the nest without loss of material. Reweigh each sieve and determine the weight of material on each sieve. Determine the weight of material in the collecting pan in a similar manner. Reassemble the nest of sieves, and agitate for 5 minutes. Remove and weigh each sieve as previously described. Repeat these steps until the endpoint criteria are met (see *Endpoint Determination* under *Test Sieves*). Upon completion of the analysis, reconcile the weights of material. Total losses must not exceed 5% of the weight of the original test specimen.

Repeat the analysis with a fresh specimen, but using a single sieving time equal to that of the combined times used above. Confirm that the sieving time conforms to the requirements for endpoint determination. When this endpoint has been validated for a specific material, a single fixed time of sieving may be used for future analyses, providing the particle size distribution does not change significantly.

If there is evidence that the particles retained on any sieve are aggregates rather than single particles, the use of dry sieving is unlikely to give good reproducibility, and *Method II* should be considered as the preferred technique.

Method II (Wet Sieving Method)—Modify the lid and collecting pan of the sieve nest to permit addition of a liquid onto the surface of the top sieve and collection of the liquid from the pan. Dry a sufficient quantity of the test material to constant weight at a temperature that will not have a detrimental effect on the material, e.g., if it is a solvate select a liquid in which the test specimen is insoluble and modify the sieving method as indicated below. Thoroughly disperse the dried test material in the liquid by gentle agitation, and pour this dispersion into the top sieve. Rinse the dispersion equipment with fresh liquid, and add the rinsings to the top sieve. Feed the sieving liquid through a suitable pumping mechanism to the nozzle(s) in the lid, and collect the sieving liquid from the pan in a suitable container. Continue the wet sieving process until the emerging liquid appears free of particles.

Remove each sieve from the sieve nest, and dry each sieve to constant weight at the same temperature as that used above. Determine the weight of dried material on each sieve.

Air Jet and Sonic Sifter Sieving—Different types of commercial equipment that use a moving air current are available for sieving. A system that uses a single sieve at a time is referred to as *air jet sieving*. It uses the same general sieving methodology as that described under *Method I* but with a standardized air jet replacing the normal agitation mechanism. It requires sequential analyses on individual sieves to provide a particle size distribution. This technique is more suitable where only oversize or undersize fractions are needed.

In the *sonic sifting* method a nest of sieves is used, and the test specimen is carried in a vertically oscillating column of air that lifts the specimen and then carries it back against the mesh openings at a given number of pulses per minute. The air jet sieving and sonic sieving methods may be useful when the standard dry and wet sieving techniques are incapable of giving a meaningful analysis.

These methods are highly dependent upon proper dispersion of the powder in the air current. This requirement may be hard to achieve if the method is used at the lower end of the sieving range (i.e., below 75 μ m) when the particles tend to be more cohesive, and especially if there is any tendency for the material to develop an electrostatic

charge. In the latter case an antistatic agent, such as silicon dioxide or aluminum oxide, may be added at the 0.5% (w/w) level to minimize this effect. For the above reasons endpoint determination is particularly critical, and it is very important to confirm that the oversize material is in fact single particles and is not composed of aggregates.

INTERPRETATION

The raw data must include the weight of test specimen, the total sieving time, and the precise sieving methodology in addition to the weights on the individual sieves and in the pan. It may be convenient to convert the raw data into a cumulative weight distribution, and if it is desired to express the distribution in terms of a cumulative weight undersize, the range of sieves used should include a sieve through which all the material passes. If there is evidence on any of the test sieves that the material remaining on it is composed of aggregates formed during the sieving process, the analysis is invalid.

(788) PARTICULATE MATTER IN INJECTIONS

Particulate matter consists of mobile, randomly-sourced, extraneous substances, other than gas bubbles, that cannot be quantified by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, should be essentially free from particles that can be observed on visual inspection. The tests described herein are physical tests performed for the purpose of enumerating subvisible extraneous particles within specific size ranges.

Microscopic and light obscuration procedures for the determination of particulate matter are given herein. This chapter provides a test approach in two stages. The injection is first tested by the light obscuration procedure (stage 1). If it fails to meet the prescribed limits, it must pass the microscopic procedure (stage 2) with its own set of test limits. Where for technical reasons the injection cannot be tested by light obscuration, microscopic testing may be used exclusively. Documentation demonstrating that the light obscuration procedure is incapable of testing the injection or produces invalid results is required in each case. It is expected that most articles will meet the requirements on the basis of the light obscuration test alone; however, it may be necessary to test some articles by the light obscuration test followed by the microscopic test to reach a conclusion on conformance to requirements.

All large-volume injections for single-dose infusion and those small-volume injections for which the monographs specify such requirements are subject to the particulate matter limits set forth for the test being applied, unless otherwise specified in the individual monograph. Excluded from the requirements of this chapter are injections intended solely for intramuscular and subcutaneous administration.

Not all injection formulations can be examined for particles by one or both of these tests. Any product that is not a pure solution having a clarity and a viscosity approximating those of water may provide erroneous data when analyzed by the light obscuration counting method. Such materials may be analyzed by the microscopic method. Emulsions, colloids, and liposomal preparations are examples. Similarly, products that produce air or gas bubbles when drawn into the sensor such as bicarbonate buffered formulations may also require microscopic testing. Refer to the specific monographs when a question of test applicability occurs. Higher limits are appropriate for certain articles and will be specified in the individual monographs.

In some instances, the viscosity of a material to be tested may be sufficiently high so as to preclude its analysis by either test method. In this event, a quantitative dilution with an appropriate diluent may be made to decrease viscosity as necessary to allow the analysis to be performed.

In the tests described below for large-volume and small volume injections, the results obtained in examining a discrete unit or group of units for particulate matter cannot be extrapolated with certainty to other units that remain untested. Thus statistically sound sampling

stances under General Notices, and Sterilization and Sterility Assurance of Compendial Articles (1211)). Ophthalmic ointments that are packaged in single-use containers are not required to contain antibacterial agents; however, they meet the requirements for Sterility Tests (71)

Containers—Containers, including the closures, for ophthalmic ointments do not interact physically or chemically with the preparation in any manner to alter the strength, quality or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use

Metal Particles—Follow the Procedure set forth under Metal Particles in Ophthalmic Ointments (751)

Leakage—Select 10 tubes of the Ointment, with seals applied when specified. Thoroughly clean and dry the exterior surfaces of each tube with an absorbent cloth. Place the tubes in a horizontal position on a sheet of absorbent blotting paper in an oven maintained at a temperature of $60 \pm 3^\circ$ for 8 hours. No significant leakage occurs during or at the completion of the test (disregard traces of ointment presumed to originate externally from within the crimp of the tube or from the thread of the cap). If leakage is observed from one, but not more than one, of the tubes, repeat the test with 20 additional tubes of the Ointment. The requirement is met if no leakage is observed from the first 10 tubes tested, or if leakage is observed from not more than one of 30 tubes tested.

(776) OPTICAL MICROSCOPY

Optical microscopy for particle characterization can generally be applied to particles in the size range between 0.5 and 100 μm . The lower limit is imposed by the resolving power of the microscope. The characterization of smaller particles can often be accomplished by means of electron optical imaging techniques such as those described under Scanning Electron Microscopy (1181) where practical image resolution approaches 0.01 μm . The upper limit is less definite and is determined by the increased difficulty associated with the characterization of larger particles compared with sieve analysis. For particles in excess of 75 μm , the preferred method of particle size analysis is by use of sieve analysis. Often stereo-microscopy can be a useful aid with larger particles, yet it is not as definitive. Optical microscopy is particularly useful for characterizing particles that are not spherical. This method may also serve as a base for the calibration of faster and more routine methods that may be developed.

Apparatus—Use a microscope that is stable and protected from vibration. The microscope magnification (product of the objective magnification, ocular magnification, and additional magnifying components) must be sufficient to allow adequate characterization of the smallest particles to be classified in the test specimen. The greatest numerical aperture of the objective should be sought for each magnification range. Polarized light may be used in conjunction with suitable analyzers and retardation plates. Color filters of relatively narrow spectral transmission should be used with achromatic objectives and are preferable with apochromats and are required for appropriate color rendition in photomicrography. Condensers corrected for at least spherical aberration should be used in the microscope substage and with the lamp. The numerical aperture of the substage condenser should match that of the objective under the conditions of use; this is affected by the actual aperture of the condenser diaphragm and the presence of immersion oils.

Adjustment—The precise alignment of all elements of the optical system and proper focusing are essential. The focusing of the elements should be done in accordance with the recommendations of the microscope manufacturer. Critical axial alignment is recommended.

Illumination—A requirement for good illumination is a uniform and adjustable intensity of light over the entire field of view. Kohler illumination is preferred. With colored particles, choose the color of the filters used so as to control the contrast and detail of the image.

Visual Characterization—The magnification and numerical aperture should be sufficiently high to allow adequate resolution of the edges of the images of the particles to be characterized. Determine

the actual magnification using a calibrated stage micrometer to calibrate an ocular micrometer. Errors can be minimized if the magnification is sufficient that the image of the particle is at least 10 ocular divisions. Each objective must be calibrated separately. To calibrate the ocular scale, the stage micrometer scale and the ocular scale should be aligned. In this way, a precise determination of the distance between ocular stage divisions can be made. Several different magnifications may be necessary to characterize materials having a wide particle size distribution.

Photographic Characterization—If particle size is to be determined by photographic methods, take care to ensure that the object is sharply focused at the plane of the photographic emulsion. Determine the actual magnification by photographing a calibrated stage micrometer using photographic film of sufficient speed, resolving power, and contrast. Exposure and processing should be identical for photographs of both the test specimen and the determination of magnification. The apparent size of a photographic image is influenced by the exposure, development, and printing processes as well as by the resolving power of the microscope.

Preparation of the Mount—The mounting medium will vary according to the physical properties of the test specimen. Sufficient, but not excessive, contrast between the specimen and the mounting medium is required to ensure adequate detail of the specimen edge. The particles should rest in one plane and be adequately dispersed to distinguish individual particles of interest. Furthermore, the particles must be representative of the distribution of sizes in the material and must not be altered during preparation of the mount. Care should be taken to ensure that this important requirement is met. Selection of the mounting medium must include a consideration of the analyte solubility.

Crystallinity Characterization—The crystallinity of a material may be characterized to determine compliance with the crystallinity requirement where stated in the individual monograph of a drug substance. Unless otherwise specified in the individual monograph, mount a few particles of the specimen in mineral oil on a clean glass slide. Examine the mixture using a polarizing microscope. The particles show birefringence (interference colors) and extinction positions when the microscope stage is revolved.

Number of Particles to Characterize—The number of particles characterized must be sufficient to ensure an acceptable level of uncertainty in the measured parameter. Successively higher magnification may be necessary to ensure proper dispersion of the specimen. An estimate of the number of particles, n , to be measured that will provide an acceptable level of uncertainty in the mean particle diameter can be obtained from the statistical theory of normal populations. For a sufficiently large population ($n > 30$), the uncertainty in the estimate for the mean particle diameter, d , is given in the formula.

$$d \pm z_c \left(\frac{s}{\sqrt{n}} \right)$$

in which z_c corresponds to the desired confidence coefficient and s is the standard deviation of the test specimen. For $n > 30$, z_c is about 1.96 at the 95% confidence level. Other confidence coefficients can be obtained from reference books on statistics, and, if necessary, small population statistics can be similarly applied. From this equation, it can be seen that the uncertainty in the measured diameter decreases as the number of particles increases. As an example, to obtain an uncertainty of $\pm 5 \mu\text{m}$ in a specimen that has a standard deviation of 20 μm would require that 61 particles be accurately measured.

An estimate of the uncertainty in the standard deviation of a specimen can be obtained in a similar fashion. The standard deviation of the population, σ , is estimated to lie in the interval

$$\sqrt{s^2 \left(\frac{n}{\chi^2_1} \right)} < \sigma < \sqrt{s^2 \left(\frac{n}{\chi^2_2} \right)}$$

where s is the standard deviation of the specimen, and $\chi_{.975}^2$ and $\chi_{.025}^2$ are the confidence coefficients obtained from the χ^2 distribution. $\chi_{.975}^2$ and $\chi_{.025}^2$ can be obtained from standard statistics references or approximated by the following expressions at the 95% confidence level where $\chi_{.975}^2$ and $\chi_{.025}^2$ represent the 97.5 and 2.5 percentile values, respectively

$$\chi_{.975}^2 \approx \frac{1}{2} \left(+1.96 + \sqrt{2n-3} \right)^2$$

and

$$\chi_{.025}^2 \approx \frac{1}{2} \left(-1.96 + \sqrt{2n-3} \right)^2$$

In general, a larger sample must be acquired to obtain a good estimate of the standard deviation or distribution of the population. For the example population described above, if the mean particle dia-

meter was 50 μm , only 61 particles would have to be measured to obtain an uncertainty of 10% in the diameter (e.g. $d = 50 \pm 5 \mu\text{m}$), but about 200 particles would have to be measured to obtain a similar confidence of $\pm 10\%$ in the standard deviation (e.g., $18.3 \leq s < 22.3$).

For a material that conforms more closely to a log normal distribution, the logarithm of the individual particle diameters can be computed, and the mean and the standard deviation of the log particle diameter directly substituted in the above equations. The anti logs correspond to the geometric mean and geometric standard deviation, respectively. Additional information on particle size measurement, sample size, and data analysis is available, for example, in ASTM E20-85.

Particle Size Characterization—The measurement of particle size varies in complexity depending on the shape of the particle. For spherical particles, size is defined by the diameter. For irregular particles, a variety of definitions of particle size exist. In general, for irregularly shaped particles, characterization of particle size must also include information on the type of diameter measured as well as information on particle shape. Several commonly used measurements of particle size are defined below (see Figure 1):

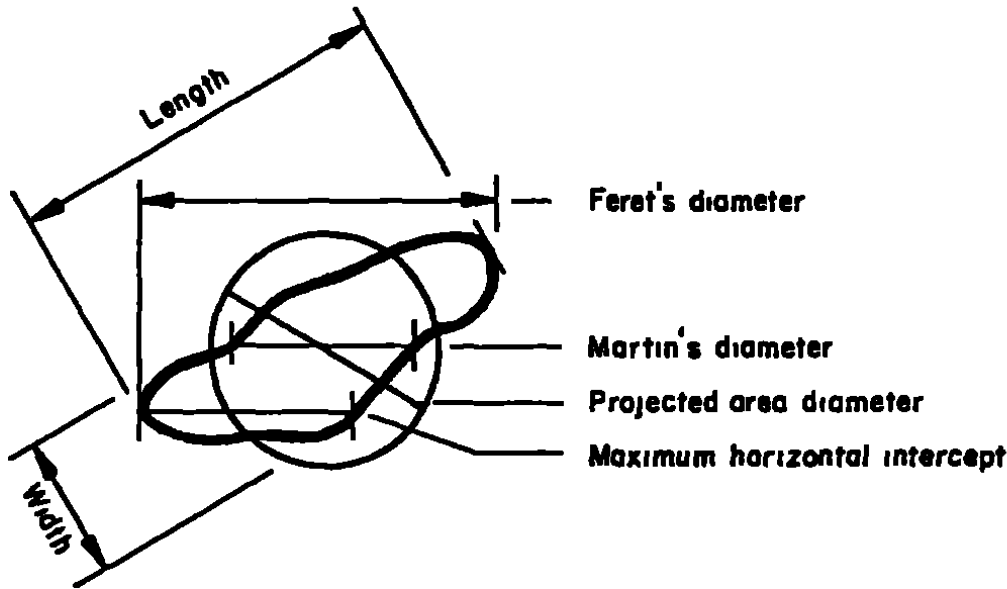


Fig. 1 Commonly used measurements of particle size.

Feret's Diameter—The distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale

Martin's Diameter—The diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas.

Projected area Diameter—The diameter of a circle that has the same projected area as the particle

Length—The longest dimension from edge to edge of a particle oriented parallel to the ocular scale

Width—The longest dimension of the particle measured at right angles to the length.

Particle Shape Characterization—For irregularly shaped particles, characterization of particle size must also include information on particle shape. The following defines some commonly used descriptors of particle shape (see Figure 2)

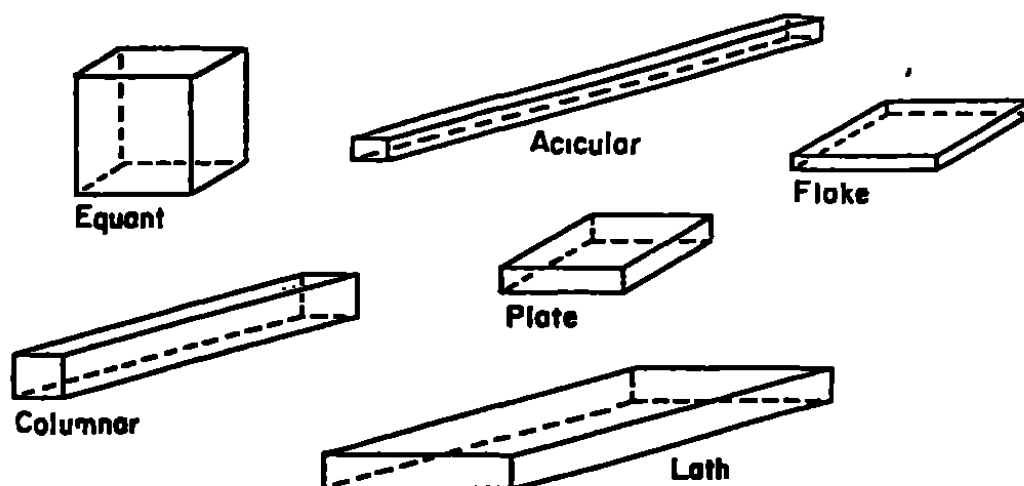


Fig. 2. Commonly used descriptions of particle shape.

Acicular—Slender needle-like particle of similar width and thickness.

Columnar—Long, thin particle with a width and thickness that are greater than those of an acicular particle.

Floke—Thin, flat particle of similar length and width.

Plate—Flat particles of similar length and width but with greater thickness than flakes.

Lath—Long, thin, and blade-like particle.

Equant—Particles of similar length, width, and thickness both cubical and spherical particles are included.

General Observations—A particle is generally considered to be the smallest discrete unit. A particle may be a liquid or semisolid droplet; a single crystal or polycrystalline; amorphous or an agglomerate. Particles may be associated. This degree of association may be described by the following terms:

Lamellar—Stacked plates.

Aggregate—Mass of adhered particles.

Agglomerate—Fused or cemented particles.

Conglomerate—Mixture of two or more types of particles.

Spherulite—Radial cluster.

Drusy—Particle covered with tiny particles.

Particle condition may be described by the following terms:

Edges—Angular, rounded, smooth, sharp, fractured.

Optical—Color (using proper color balancing filters), transparent, translucent, opaque.

Defects—Occlusions, inclusions.

Surface characteristics may be described as:

Cracked—Partial split, break, or fissure.

Smooth—Free of irregularities, roughness, or projections.

Porous—Having openings or passageways.

Rough—Bumpy, uneven not smooth.

Pitted—Small indentations.

light. This property is characteristic of some crystals and of many pharmaceutical liquids or solutions of solids. Where the property is possessed by a liquid or by a solute in solution it is generally the result of the presence of one or more asymmetric centers, usually a carbon atom with four different substituents. The number of optical isomers is 2^n , where n is the number of asymmetric centers. Polarimetry the measurement of optical rotation, of a pharmaceutical article may be the only convenient means for distinguishing optically active isomers from each other and thus is an important criterion of identity and purity.

Substances that may show optical rotatory power are *chiral*. Those that rotate light in a clockwise direction as viewed towards the light source are *dextrorotatory* or (+) *optical isomers*. Those that rotate light in the opposite direction are called *levorotatory* or (–) *optical isomers*. (The symbols *d*- and *l*-, formerly used to indicate dextro- and levorotatory isomers, are no longer sanctioned owing to confusion with D- and L-, which refer to configuration relative to D-glyceraldehyde. The symbols *R* and *S* and α and β are also used to indicate configuration, the arrangement of atoms or groups of atoms in space.)

The physicochemical properties of nonsuperimposable chiral substances rotating plane polarized light in opposite directions to the same extent, *enantiomers* are identical except for this property and in their reactions with other chiral substances. Enantiomers often exhibit profound differences in pharmacology and toxicology, owing to the fact that biological receptors and enzymes themselves are chiral. Many articles from natural sources, such as amino acids, proteins, alkaloids, antibiotics, glycosides, and sugars, exist as chiral compounds. Synthesis of such compounds from nonchiral materials results in equal numbers of the enantiomers *racemates*. Racemates have a net null optical rotation, and their physical properties may differ from those of the component enantiomers. Use of stereoselective or stereospecific synthetic methods or separation of racemic mixtures can be used to obtain individual optical isomers.

Measurement of optical rotation is performed using a polarimeter. The general equation used in polarimetry is

$$[\alpha]_D^{25} = \frac{100\alpha}{lc}$$

(781) OPTICAL ROTATION

Many pharmaceutical substances are optically active in the sense that they rotate an incident plane of polarized light so that the transmitted light emerges at a measurable angle to the plane of the incident

Standard calibration is available from the Office of Standard Reference Materials, National Institute of Standards and Technology (NIST), Gaithersburg, MD 20899 as current lots of Standard Reference Materials, Dextrose and Sucrose. Alternatively calibration may be checked using a Polarization Reference Standard, which consists of a plate of quartz mounted in a holder perpendicular to the light path. These standards are available traceable to NIST from Rudolph Research Analytical 35- Route 206 Flemington, NJ 07836 or from Rudolph Instruments Inc 40 Pier Lane Fairfield NJ 07004.

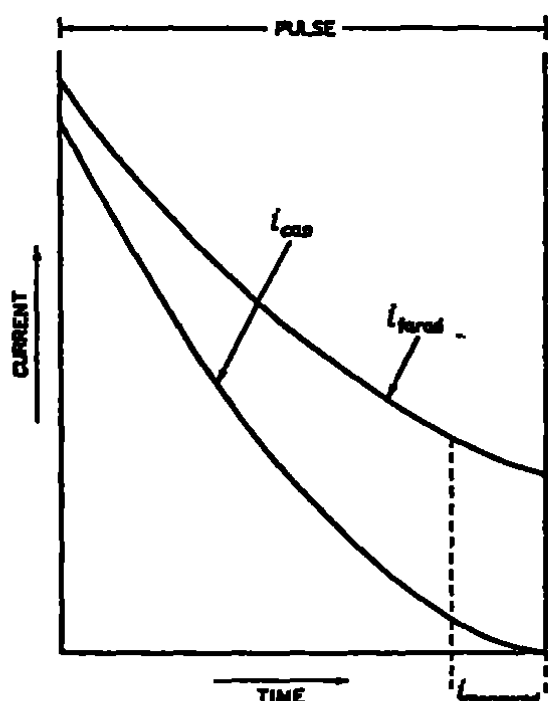


Fig. 4. Plot of Current Versus Time in Pulse Polarography

Differential pulse polarography is a technique whereby a fixed-height pulse applied at the end of the life of each drop is superimposed on a linear increasing dc ramp (see Figure 5). Current flow is measured just before application of the pulse and again at the end of the pulse. The difference between these two currents is measured and presented to the recorder. Such a differential signal provides a curve approximating the derivative of the polarographic wave, and gives a peak presentation. The peak potential is equivalent to

$$E_{1/2} - \Delta E/2,$$

where ΔE is the pulse height. The peak height is directly proportional to concentration at constant scan rates and constant pulse heights. This technique is especially sensitive (levels of 10^{-7} M may be determined) and affords improved resolution between closely spaced waves.

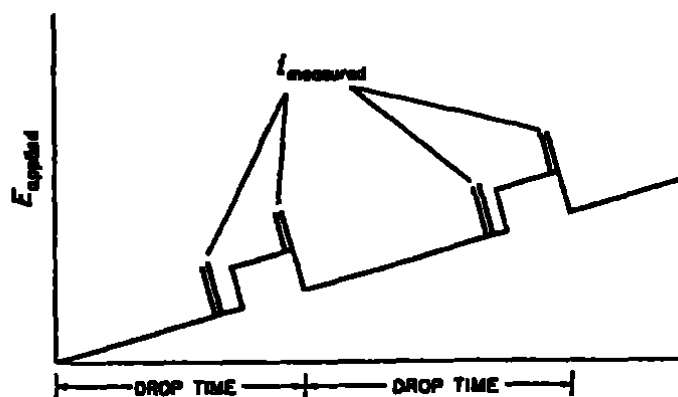


Fig. 5. Differential Pulse Polarography

Anodic Stripping Voltammetry—Anodic stripping voltammetry is an electrochemical technique whereby trace amounts of substances in solution are concentrated (reduced) onto an electrode and then stripped (oxidized) back into solution by scanning the applied voltage anodically. The measurement of the current flow as a function of this

voltage and scanning rate provides qualitative and quantitative information on such substances. The concentration step permits analyses at 10^{-7} M to 10^{-4} M levels.

Basic instrumentation includes a voltage ramp generator; current-measuring circuitry; a cell with working, reference, and counter electrodes; and a recorder or other read-out device. Instruments having dc or pulse-polarographic capabilities are generally quite adequate for stripping application. The working electrode commonly used is the hanging mercury drop electrode (HMDE) although the mercury thin-film electrode (MTFE) has acquired acceptance. For analysis of metals such as silver, platinum, and gold, whose oxidation potentials are more positive than mercury and mercury itself, the use of solid electrodes such as platinum, gold, or carbon is required. A saturated calomel electrode or a silver-silver chloride electrode serves as the reference except for the analysis of mercury or silver. A platinum wire is commonly employed as the counter electrode.

Test specimens containing suitable electrolyte are pipetted into the cell. Dissolved oxygen is removed by bubbling nitrogen through the cell for 5 to 10 minutes.

Generally, an electrolysis potential equivalent to 200 to 300 mV more negative than the half-wave potential of the material to be analyzed is applied (although this potential is to be determined experimentally) with stirring for 1 to 10 minutes. For reproducible results, maintain constant conditions (i.e., deposition time, stirring rate, temperature, specimen volume, and drop size if HMDE is used).

After deposition, the stirring is discontinued and the solution and electrode are allowed to equilibrate for a short period. The potential is then rapidly scanned anodically (10 mV/second or greater in dc polarography and 5 mV/second in differential pulse polarography). As in polarography the limiting current is proportional to concentration of the species (wave height in dc and pulse, peak height in differential pulse), while the half wave potential (dc, pulse) or peak potential (differential pulse) identifies the species. It is imperative that the choice of supporting electrolyte be made carefully in order to obtain satisfactory behavior. Quantitation is usually achieved by a standard addition or calibration method.

This technique is appropriate for trace-metal analysis, but has limited use in organic determinations, since many of these reactions are irreversible. In analyzing substances such as chloride, cathodic stripping voltammetry may be used. The technique is the same as anodic stripping voltammetry except that the substance is deposited anodically and then stripped by a cathodic voltage scan.

(811) POWDER FINENESS

Test procedures for sieving powder materials are described under *Particle Size Distribution Estimation by Analytical Sieving* (786) and, where practical, the particle size distribution should be estimated by this procedure. The classification of powder fineness in this Pharmacopeia, expressed in descriptive terms, is provided in the table. For practical reasons, sieves are the preferred means of measuring powder fineness for most pharmaceutical purposes. Sieving is most suitable where a majority of the particles are larger than about 75 μ m, although it can be used for some powders having smaller particle sizes where the method can be validated. Avoid processing conditions that would alter the true particle size distribution of the powder being tested.

Sieves for Pharmacopeial Testing—Sieves for Pharmacopeial testing are described under *Particle Size Distribution Estimation by Analytical Sieving* (786).

Powdered Vegetable and Animal Drugs—In determining the powder fineness of a vegetable or animal drug, no portion of the drug may be rejected during milling or sifting unless specifically permitted in the individual monograph.

Air Permeation Method for Determining Fineness of Sub-sieve Size Particles—The average particle size measured is in the range of 0.2 to 50 μ m. The test specimen is loaded into a precision bore tube and is compacted between two paper disks and porous plugs by a rack-and-pinion packing plunger. The determination of the particle size of the specimen in the uniformly packed column is based on its resistance to the flow of a closely regulated current of dried air.

The liquid level of a flowmeter-manometer corresponds directly to particle size. Special handling instructions and procedures are provided in the individual monographs.

Classification of Powder Fineness—Powder fineness may be classified by determining the smallest sieve opening through which a specified quantity of material passes. Results are typically reported as

- d_{90} = smallest sieve opening through which 90% or more of the material passes
- d_{50} = smallest sieve opening through which 50% or more of the material passes
- d_{10} = smallest sieve opening through which 10% or more of the material passes.

The upper and lower limit of the sieve opening values may be reported when results of two or more test lots are combined, e.g., "Lot A has a d_{50} value of 1000 μm with a range of 850–80 μm ."

An alternative but less informative method of classifying powder fineness is by use of the terms in the following table.

Classification of Powders by Fineness	
Classification of Powder	d_{50} Sieve Opening (μm)
Very Coarse	> 1000
Coarse	355–1000
Moderately Fine	180–355
Fine	125–180
Very Fine	90–125

(821) RADIOACTIVITY

Radioactive pharmaceuticals require specialized techniques in their handling and testing in order that correct results may be obtained and hazards to personnel be minimized. All operations should be carried out or supervised by personnel having had expert training in handling radioactive materials.

The facilities for the production, use, and storage of radioactive pharmaceuticals are generally subject to licensing by the federal Nuclear Regulatory Commission, although in certain cases this authority has been delegated to state agencies. The federal Department of Transportation regulates the conditions of shipment of radioactive materials. State and local agencies often have additional special regulations. Each producer or user must be thoroughly cognizant of the applicable regulations of the federal Food, Drug, and Cosmetic Act, and any additional requirements of the U S Public Health Service and of state and local agencies pertaining to the articles concerned.

Definitions, special considerations, and procedures with respect to the Pharmacopeial monographs on radioactive drugs are set forth in this chapter.

GENERAL CONSIDERATIONS

Fundamental Decay Law

The decay of a radioactive source is described by the equation.

$$N_t = N_0 e^{-\lambda t}$$

in which N_t is the number of atoms of a radioactive substance at elapsed time t , N_0 is the number of those atoms when $t = 0$, and λ is the transformation or decay constant, which has a characteristic value for each radionuclide. The half-life, $T_{1/2}$, is the time interval required for a given activity of a radionuclide to decay to one-half of its initial value, and is related to the decay constant by the equation.

$$T_{1/2} = \frac{0.69315}{\lambda}$$

The activity of a radioactive source (A) is related to the number of radioactive atoms present by the equation

$$A = \lambda N$$

from which the number of radioactive atoms at time t can be computed, and hence the mass of the radioactive material can be determined.

The activity of a pure radioactive substance as a function of time can be obtained from the exponential equation or from decay tables, or by graphical means based on the half life (see Normalized Decay Chart, Figure 1).

Particle size analysis by laser diffraction: ISO 13320, standard operating procedures, and Mie theory

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Red M. Jones

Published in late 1999, ISO 13320 was the first formal international standard to provide the basis for harmonization of particle size analyzers based on low angle laser light scattering (LALLS) techniques. This is an important development because of the wide variety of particle sizing methods available and the fundamental differences between them. Approaches may vary and harmonization is undoubtedly a vital issue.

ISO 13320 is a guidance document that clearly describes the principles of LALLS, defines terminology, and explains what one can expect from an instrument of this type. Sample handling and dispersion guidance, on the use of dry powder feeders, information on error diagnosis, and a discussion of Mie theory versus the Fraunhofer approximation are all included.

Consistent measurements

The purpose of the international standard is to provide a methodology for adequate control in particle size analysis. In practice, ensuring consistency and reliability of measurements is the real key to successful control, and one way to achieve this is through the development and application of standard operating procedures (SOPs).

The importance of SOPs in an industry such as pharmaceuticals manufacturing is well documented. However, it is the ease with which they can be developed and the subsequent adherence to these SOPs that make a difference when evaluating consistency and comparability of results. Product development and production are increasingly global operations, raising issues of

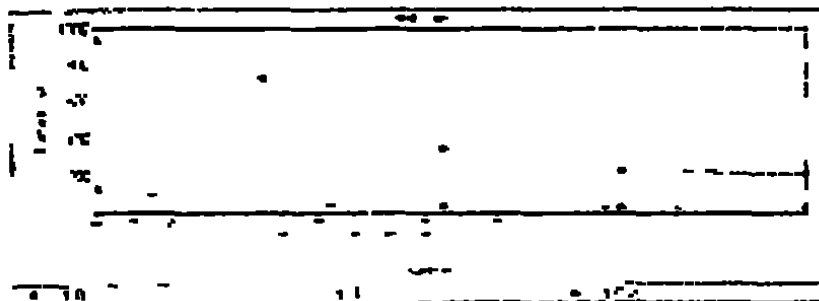


Figure 1 Effect of dispersive pressure on the particle size of milk powder granules. The three plotted lines show the sizes in microns of the 90% ($d(0.9)$), the median ($d(0.5)$), and the 10% ($d(0.1)$) of the milk powder. As can be seen, increasing the dispersive pressure from 0.1 to 3.9 bar causes the size of the material to be reduced until it reaches a primary particle size at a pressure of 3 bar.

method transfer and comparability of results.

Rugged hardware and robust software do not in themselves guarantee good performance. As more people are called upon to undertake the same measurements, the degree of variation can increase enormously. Therefore

Some milk powders are fragile agglomerates of granules of many different sizes; thus, it is critical to decide whether the intention is to measure the composite particles or the primary particles from which they are formed. If one is trying to preserve the agglomerates, the dispersive air pressure must be carefully

In the past, the need to input the refractive indices of the materials being measured may have deterred some from using the Mie theory

individual operator involvement must be kept to a minimum, and protocols and SOPs must be easily set up and protected.

Controlling parameters

The issue of sample handling and dispersion techniques is raised within the guidelines of the international standard. The importance of ensuring a consistent approach for specific sample types and incorporating this into SOPs can be illustrated using the dry analysis of milk powder as an example.

controlled in order to avoid excessive breakup. Generally, the granules are agglomerated loosely through the freeze-drying process, and application of more than a small amount of energy (0.25–0.5 bar) is sufficient to break this agglomeration. Beyond this, the milk is milled to a more fundamental size.

Figure 1 shows the effect of changes in dispersive air pressure on the particle size of milk powder. Control of the air pressure to ensure the same degree of dispersion is applied to the sample every time, and is crucial for producing particle size

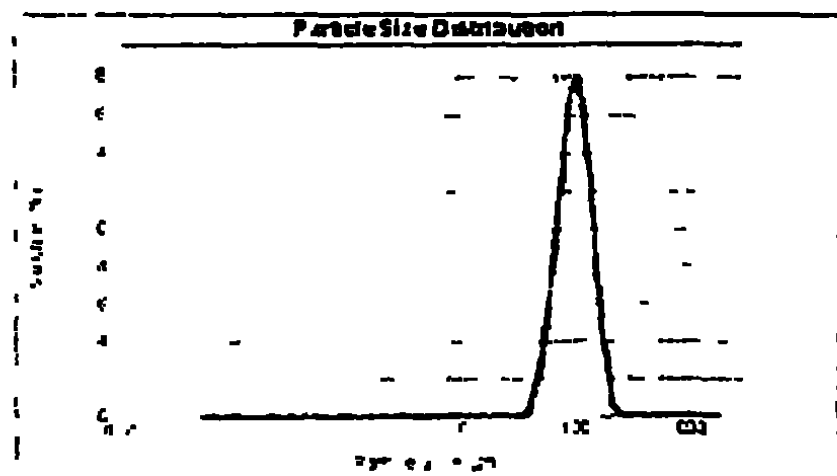


Figure 2 Overplot of results from five experienced and five novice analysts.

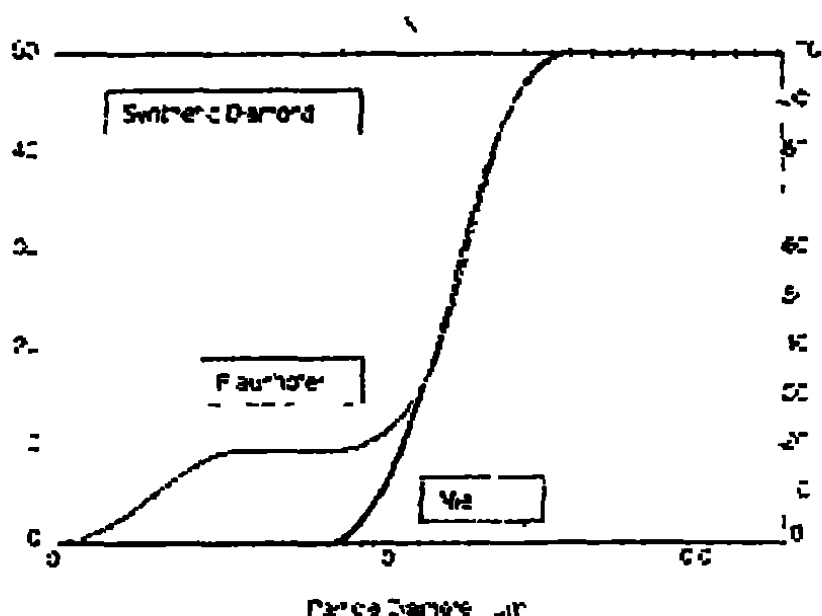


Figure 3 Comparison of results obtained for synthetic diamond using Mie theory and Fraunhofer approximation.

information that will enable valid assessment and control of the material being tested. ISO 13320 recommends dry analysis at a number of pressures to fully understand how the material under test is dispersed. Once the optimum conditions have been determined they can most easily be achieved routinely through the development and use of an SOP

Removing operator variability

The practical advantages of SOP driven operation were demonstrated in an exercise in which five novice and five experienced users made the same measure

ments of alumina side by side using the same SOP on the Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, U.K.) The results were overplotted (Figure 2) and show no significant difference for either group

Optical models

One of the key recommendations in the new standard is the choice of the correct optical model for the material being measured. Laser diffraction operates as a sizing technique by predicting the light scattering behavior of particles and the quality of this

prediction determines the accuracy of the size determination performed. The most rigorous and comprehensive prediction of the light scattering behavior of particles is provided by Mie theory. However, when laser diffraction instruments were introduced in the late 1970s, computer power was at a premium and the first PCs were limited to 8 K of random access memory (RAM). Since the use of Mie theory demanded a considerable amount of computing power, manufacturers used an approximation of Mie theory known as the Fraunhofer approximation. The computing power provided by modern PCs ensures that there is no longer a valid reason to continue its use.

The new ISO standard states that although Fraunhofer can still be used for the measurement of particles greater than 50 μm , Mie theory is recommended for those below 50 μm and it is applicable across the entire measurement range. Instruments designed to measure in the size range below 50 μm should therefore uniformly support Mie theory.

In the past, the need to input the refractive indices of the materials being measured may have deterred some from using the Mie theory. To simplify this procedure, the Mastersizer 2000, for example, has a database containing the refractive indices of the most common materials, making the implementation of Mie theory very straightforward. The advances in computer power referred to above make its adoption transparent to the user.

Practical applications

The following examples demonstrate the importance of the Mie theory.

1 **Synthetic diamond powder**
Synthetic diamond powder was fractionated in such a way that it had a limited size distribution and a tight specification of median size. This type of fraction is used in the grinding and polishing industries. The refractive index (RI) of synthetic diamond is well known

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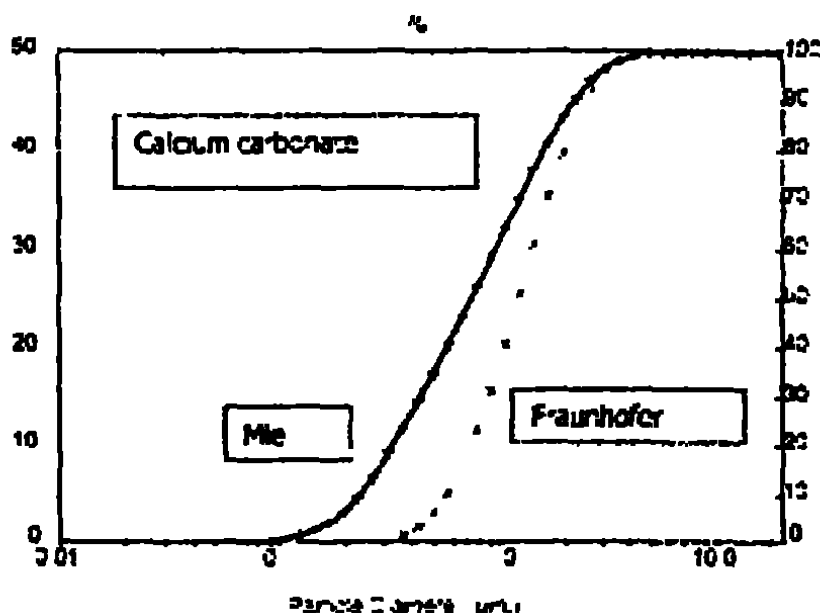


Figure 4 Comparison of results obtained for calcium carbonate using Mie theory and Fraunhofer approximation.

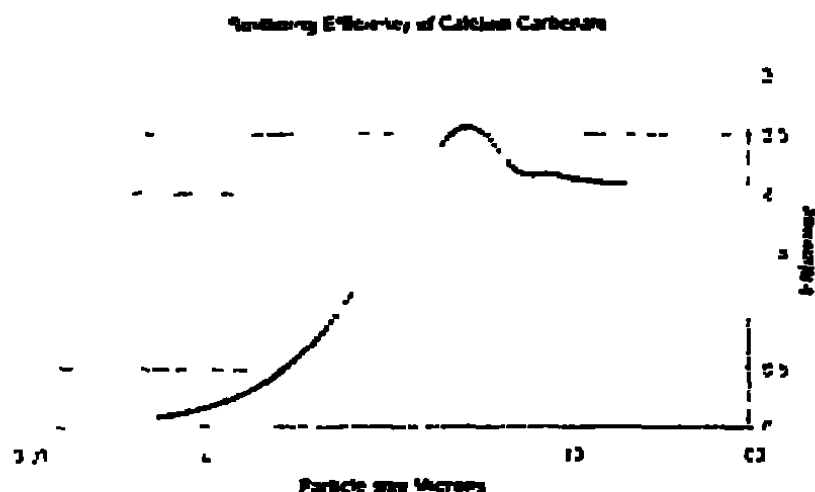


Figure 5 Extinction efficiency of calcium carbonate as a function of particle size as calculated using Mie theory.

and has a value of 2.41-0.0. The material was suspended in water (RI 1.33). Figure 3 shows the results of measuring this material applying both the Fraunhofer approximation and Mie theory.

Using the Fraunhofer approximation, the results indicate a bi-modal distribution, but it is known from extensive electron microscope evaluation that this is incorrect. The curve produced using the Mie theory in which the appropriate RI values were entered provides the correct result. Again, this was confirmed by detailed electron microscopy.

2 Calcium carbonate For the measurement of calcium carbonate the Fraunhofer approximation interpreted the size distribution as being too large (see Figure 4). This error stems from the approximation's inability to predict the true extinction behavior of the particles. The Fraunhofer approximation assumes that the extinction efficiency of all sizes of particle is 2. In practice for most commonly found materials this approximation is only correct for particles greater than about 10 μm . The extinction efficiency for

calcium carbonate is shown in Figure 5.

As can be seen, the scattering power actually falls off rapidly below 2 μm . The amount of light scattered from the 0.3- μm contribution for this example is very small. Therefore, the Fraunhofer approximation assumes that there must be very little of this size present. Mie theory, however, predicts this fall off and thus continues to weight the fine sizes correctly.

The above examples demonstrate how Mie theory correctly anticipated the effect on light scattering behavior caused by differences in refractive index, the relative transparencies of particles, and the extinction efficiencies of particles. The Fraunhofer approximation was unable to consider these variations and was in error in each case described.

Conclusion

The publication of ISO 13320 has been a welcome advance. Laser diffraction methods have been in existence for many years, but the development of this standard shows that laser diffraction is now a fully accepted and mature technology. Application of these best practice guidelines should ensure higher measurement reproducibility, especially between instruments from different manufacturers. The importance of SOP development and the use of appropriate and controlled sample dispersion techniques cannot be underestimated in ensuring greater comparability of results. The standard highlights the weaknesses of the Fraunhofer approximation and the need for full application of the Mie theory.

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Characterization of Pharmaceutical Solids Using Various Particle Sizing Techniques

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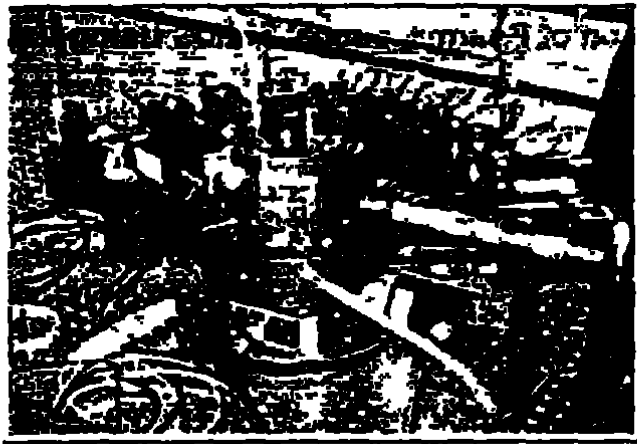
Particle sizing is an important aspect of pharmaceutical development and validation process as the particle size of active ingredients strongly affects their bio-availability. There are many methods available for particle size and size distribution determination. In general, these techniques can be divided into three basic categories: ensemble methods, counting methods, and separation methods.^{1,2} An ensemble method takes a snap shot of a sample and then elucidates the distribution of particles sizes based on the physical properties revealed by the measurement. A counting method characterizes the sample one particle at a time in a more direct manner. The accumulative account the particles provides the size distribution information. A separation method, on other hand, first physically separates the samples according to their particle size. Then various techniques are applied to determine the relative amount each fraction. In this article, the general working principle of each method will be reviewed using a representative technique. The key advantages and disadvantages of each technique will be given based on their performance in terms of sensitivity, dynamic range, and resolution. Finally some general comments and recommendations will be given in relationship to the characterization of pharmaceutical solid particles.

Ensemble Techniques

Common ensemble techniques include Low Angle Laser Light Scattering (LALLS), Photon Correlation Spectroscopy (PCS), and Back-Scattering Spectroscopy.¹ In a typical LALLS system, a laser beam passes through a sample of particles and the light intensity data at different low scattering angle away from the axis of the laser beam are collected. Mie theory light scattering calculations are applied to the intensity data to generate a distribution of particle size. LALLS method requires a relatively low particle concentration to avoid multiple scattering. The method has a broad dynamic range on particles ranging from 0.1 μm to millimeters. Yet, the resolving power is somewhat low and is difficult to deconvolute data generated from a mixture of particles with different optical properties.

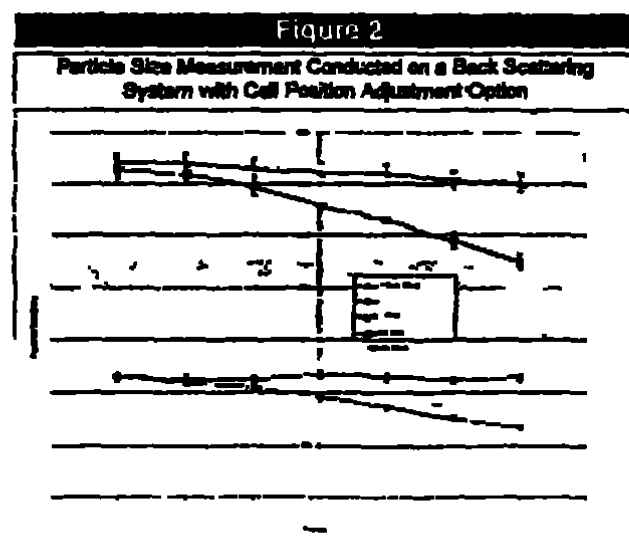
For smaller particles, a dynamic light scattering system is preferred.³ A PCS method uses laser light with well defined properties (wavelength, polarization, etc) to determine the velocity distribution of particles by measuring dynamic fluctuations of scattered light intensity. The particles suspended in a liquid medium undergo Brownian motion that causes the fluctuations of scattering light intensity. By extracting information from such dynamic behavior (auto correlation function obtained in the time domain), average particle size and size distribution can be calculated. The typical scattering angle is 90 degrees. To avoid multiple scattering, high dilution is needed. Rigorous dilution may introduce many variables such as pH shock, ionic strength change, and surfactant migration. An additional disadvantage is that small particles can get lost in the crowd of larger particles. One innovative set up includes an array of detectors at different scattering angles and simultaneously conducts measurement on the dynamic and static light scattering properties. Such a time-resolved simultaneous static and dynamic light scattering (SSDLS) technique (Figure 1) permits the investigation of early-stages of particle aggregation. With proper assumptions, the information on particle shape and particle-particle interaction can also be revealed.⁴

Figure 1
Time-Resolved Simultaneous Static and Dynamic Light Scattering (SSDLS) Set Up



To overcome the difficulties encountered in a conventional dynamic light scattering system, back scattering spectroscopy has been developed to utilize the information at high scattering angle. One such system involves the use of a single fiber optics that provides both the probing and scattering beam. The most important advantage of the technique is the ability to measure particle size and distribution for concentrated samples *without dilution*. When an effective photon correlator is used in a back scattering system, it offers very high sensitivity as well as high dynamic range. It has been claimed for one such instrument that, using Lysozyme ($M_w = 14400$ Dalton) as an example, the measurement can be conducted at mass concentrations as little as 0.1 mg/ml and sample volume as small as 150 μ l. This translates to an impressive detection limit of 15 μ g of the protein (Lysozyme). At the same time, it can also handle solid content as high as 20% wt for some particles.

Another very useful feature in such a setup is the ability to vary sampling volume by adjusting the sample cell position. When the sample cell is moved toward the detector (negative position), the sampling volume is decreased, which further lowers the amount of multiple scattering and allow even higher concentrated samples to be measured. Conversely, when the sample cell is moved away from the detector (positive position), the analytic volume is increased. The increased analytic volume allows for more dilute samples. Figure 2 shows two sets of silica particles that are surface modified for pharmaceutical applications. For smaller particles (115 nm diameter), the instrument can provide anticipated particle size at solid content as high as 2% wt without dilution. For a higher concentration sample (10% wt) the cell position has to be adjusted to a negative position (decreased sampling volume) to yield an anticipated particle size. For larger particles (300 nm), a similar trend is found even at lower solid concentration. From signal-to-noise point of view, an optimum cell position should be selected to balance the need for strong signal and weak multiple light scattering. In addition to back scattering systems, acoustic method has also attracted attention for high concentration sampling without dilution. The particle sizes can range from 10 nm to 1000 μ m. The method is particularly useful for highly concentrated samples.⁵



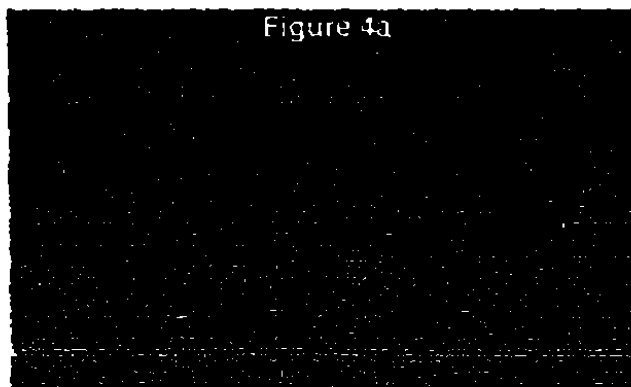
fractionation As sieves and gravitational sedimentation are relatively self-explanatory, they are not included in this article

A disc centrifuge method uses a rotating optically clear disc that is filled with slurry to be analyzed. At high speed (up to ~24,000 RPM), the liquid in the spinning disc chamber has a slight density gradient: the liquid at the outside edge of the ring is slightly denser than that near the inside edge. The particles suspended in the liquid move at rates that depend on particle size. Large particles move much faster than the small ones. A light beam detector is used to monitor the amount and the size of particles that pass through the edge of the disc. The time required to reach the detector versus the degree of light attenuation can be correlated to a size distribution. The disc centrifuge method should have extremely high resolution. It has been claimed that particles with <5% difference in diameter can be completely resolved. The method can handle particles from <0.02 to >40 microns, with dynamic range up to 1000. Most measurements require only 3 - 15 minutes. The method provides more accurate results for spherical particles than non-spherical ones.

In Capillary Hydrodynamic Fractionation (CHDF) system, a very dilute suspension of particles flows through a very thin capillary. Due to Brownian motion, over time, a parabolic velocity profile is developed for each particle size group. On average, large particles have a higher velocity than small particles, due to the fact that they would have less interaction with the capillary wall. As the particles pass through the detector at the end of the capillary, the relative particle concentration is determined according to the amount of light obstruction. The method, therefore, requires minimal information about the particles and is capable of measuring particles in the range of 0.01 - 2 microns. The resolution is usually poor. It has been estimated that narrow families must differ in diameter by 35% to be physically separated in capillary. In addition, the particles must be compatible with aqueous emulsifier environment. Large particles or strong aggregation of small particles may plug the capillary.

One method that combines the strength of a hydrodynamic fractionation and disc centrifugation is called Sedimentation Field Flow Fractionation. In an SF instrument, a rotating disc provides a flow chamber for the particle suspension to be analyzed. As the disc is spinning at up to several thousand RPM, the particles are driven by g-force toward the outside edge of the flow chamber (if higher in density than the fluid), or toward the inside edge of the chamber (if lower in density than the fluid). Similar to CHDF, liquid velocity profile inside the chamber is parabolic. Unlike CHDF, smaller particles spend more time in the higher velocity portions of the flow due to Brownian motion and exit the chamber sooner during the initial phase of high g-force. As the speed of rotation falls, the g-forces fall as well, allowing larger and larger particles to spend time away from the chamber wall and move faster than smaller particles. After this point, the flow velocity profile is similar to CHDF again. Extremely complicated algorithm is required to unravel the size separation and distribution profile. For particles that are less than 3-5 microns, the method can provide extremely good resolving power. It has been claimed that narrow peaks with 5% difference in size can be resolved. In addition to the highly convoluted separation mechanisms, the run time is typically long (1 hour or more).

A modified version of hydrodynamic fractionation is the packed column hydrodynamic chromatography. In essence, the capillary is packed with chromatographic materials that create many tiny channels for the suspended particles to flow through. The basics of hydrodynamic fractionation are still applicable here. An advantage of this technique is the increased resolution for particles with small size difference or particles that may have different surface chemistry. Figure 4a shows a silica sample that is contaminated with larger particles. The packed column chromatographic result shown in Figure 4b clearly revealed the extent and particle size of the contaminants.

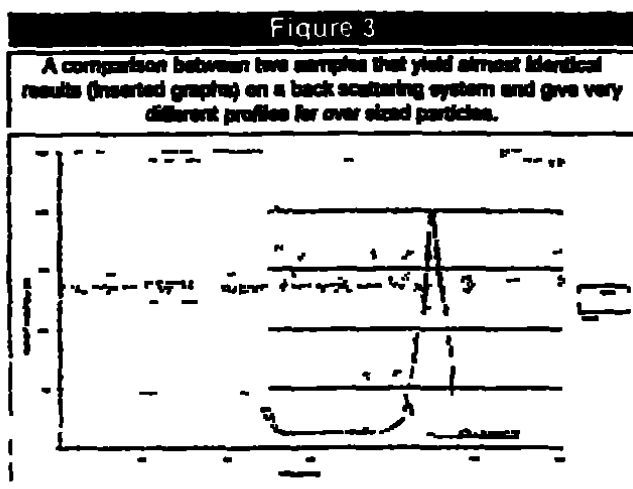


Counting Method

In a counting method each particle is identified and counted at a time. Among the popular counting methods are electrozone counter, optical counter, time of flight, and microscope. During an electrozone measurement, particles dispersed in an electrolyte are drawn through a fine aperture. A constant voltage is applied across the electrodes positioned at either side of the aperture. When a particle passes through the aperture, the resistance increases causing a change in voltage represents the number of aperture, whereas the voltage is related to the particle be used to measure a broad um) using corresponding provide limited dynamic range. In addition, the sample must be and the particle must be

A light counter is very much electrozone counter. Particles chamber, where a focused as the particle passes. The reaching a detector is related the particle and this is

The method provides the "true" particle size distribution (PSD) by quickly sizing and counting large numbers of particles, one at a time. The light counter has resolution and accuracy comparable to electrozone and LALLS methods. It does have a much wider size range (~0.5 micron to >2,000 microns), although resolution appears to suffer with smaller particles. As matter of fact, it is impossible for this method to measure particles below 0.5 micron. An advanced instrument should have a high counting rate (>20,000 particles/sec) and autodilution feature. One must take precaution when using autodilution, pH shock or ionic strength change may have a negative impact on the stability of the slurry. This method is particularly useful for counting number of oversized particles that other methods would have difficulty to quantify. Figure 3 shows a comparison that two samples yield almost identical results on a back scattering system described above, but they contain a very different number of particles above 1.0 micron. This is particularly important as oversized particles not only decrease the bioavailability of a pharmaceutical formulation, it could also be dangerous in a blood stream.



The frequency of this event particles traveling through the magnitude of the change in size. Although this method can range of sizes (0.5 um to 300 orifice, each orifice can only (ca. 2% to 80% of the orifice) placed in a conductive fluid insulators.

the optical equivalent of the are forced through a counting laser beam is partially blocked reduction in light intensity to the optical cross section of converted to a size distribution.

In a Time of Flight Counter a very dilute particulate suspensions in water is first "nebulized". After the evaporation of water particles are carried by airflow through two adjacent detectors. As small particles are accelerated more rapidly than larger particles, the time that is required to flight between the two detectors is shorter. The particle size and size distribution information are then elucidated from the recorded time of flight data. The advantages of this technique include high resolution and reasonable dynamic range. The disadvantage is that particle may aggregate during the evaporation of solvent.

In a microscope counting scheme, the sample could be either placed under a regular light microscope or an electron microscope. As we are mainly interested in particles that are smaller than a micron, the usefulness of a light microscope is limited. For SEM or TEM microscope the sample preparation is somewhat destructive. The evaporation of solvent can alter the environment of the sample and produce artificial larger particles. In addition, the counting process requires extensive imaging analysis and complicated deconvolution logarithms. Therefore it is not practical as a tool for routine analysis.

Separation Methods

A separation method exerts an external force to a sample and physically groups the particles according to size. Once the particles are separated the characterization of individual groups of particles can be conducted using either a counting method or an ensemble method. Common separation techniques include sieves, gravitational sedimentation, disc centrifuge, capillary hydrodynamic fractionation, packed column chromatography, and sedimentation field flow.

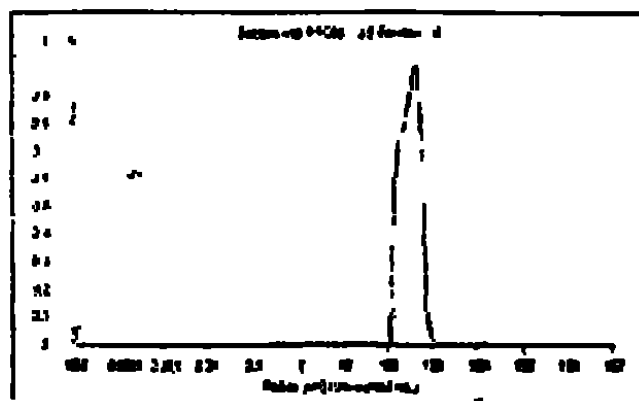
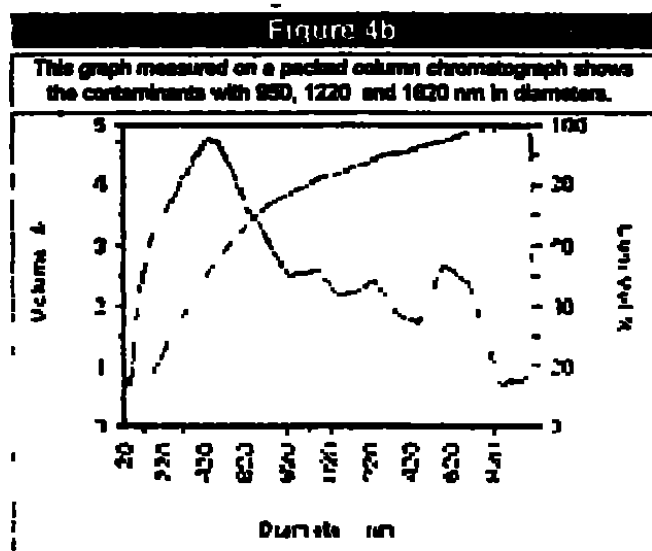


Figure 4b



Conclusion

Amongst the ensemble methods, a back scattering system coupled with an effective photon correlator for DLS measurement and adjustable cell position feature is a viable choice for general particle size and size distribution analysis. For counting methods, an optical counter equipped with autodilution feature is ideal for the determination of oversized particle in a slurry and particle size distribution ($>0.5 \mu\text{m}$). In the category of separation method, packed column chromatographic method is easy to use and seems to be able to provide the separation needed for a mixture samples.

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12/01 Analyzing Powder Particle Size

Reaping the benefits of laser diffraction

By Mark Burniller
December 03, 2001

The particle size distribution of powders is an important physical characteristic. The size and shape of powder particles influence how the material flows through plant equipment such as bins and hoppers, and affect many unit operations including size reduction, separation, blending, filtration, granulation and coating processes.

An abundance of fine particles can cause powder flow problems, and if the particulate material is later dispersed in as a liquid suspension, fines will change the rheology of the system. On the other hand, large particles can reduce final product quality through a variety of mechanisms such as increased dissolution time. They can create a poor finish on surface coatings and an unattractive texture.

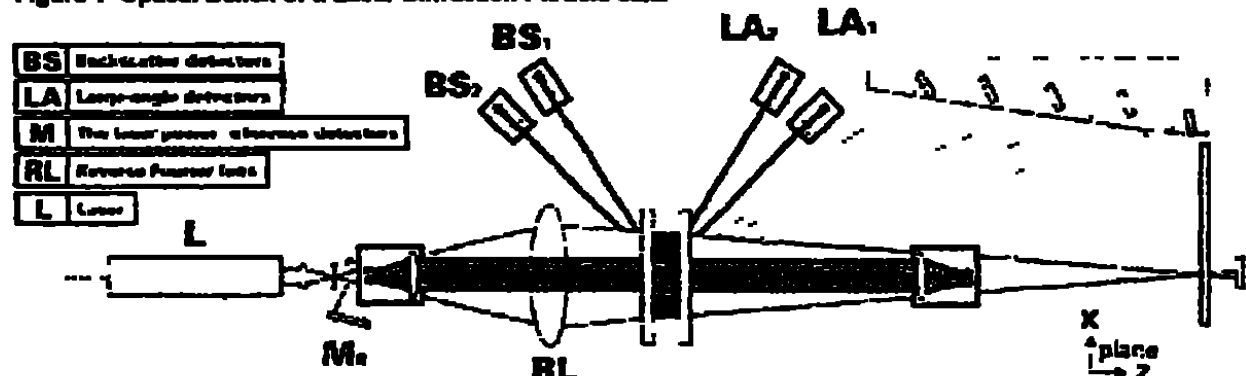
Because particle size is a critical physical property, plant engineers use a variety of analytical techniques to quantify the powder distribution. The oldest particle-sizing technique — sieving — has been around since the Egyptians and still is used in modern facilities. More advanced measurement methods currently in use include electrical sensing zone technology, sedimentation, image analysis, acoustic attenuation spectroscopy and several light-scattering techniques such as photon correlation spectroscopy (PCS) and laser diffraction.

Each of these methods has its own advantages and disadvantages. Sieving, for instance, still is the best approach for particle sizes greater than 3 millimeters (mm) but it is quite tedious and cannot generate acceptable results for fine materials. Laser diffraction has become the most popular particle-size analysis technique because it is easy to use, covers a broad dynamic range (current analyzers can measure from 0.02 μm to 2,000 μm with a single system) and is flexible enough to measure powders, suspensions and sprays. In addition, laser diffraction now can be applied not only in the laboratory but also in the process as a tool for powder process lines.

Laser diffraction in the lab

A laboratory laser diffraction particle-size analyzer consists of a light source, a detection system, a sample dispersing system to pass the particles through the optical bench and software to convert scattered light into a particle-size distribution. See Fig. 1.

Figure 1 Optical Bench of a Laser Diffraction Particle Sizer



A laboratory laser diffraction particle sizer has a light source, a detection system and a sample dispersing system to pass the particles through the optical bench. Software converts scattered light into a particle-size distribution.

The light source in the optical bench typically is a laser or lasers with different wavelengths. Adding a second light source at a lower wavelength — for example, a blue laser-emitting diode (LED) $\lambda = 432$ nanometers (nm) — improves both the ability to detect smaller particles and the ability to resolve multiple peaks in multimodal distributions in the submicron region. Detection systems also have improved over time, expanding the angles inspected from smaller than 14 degrees in the past to current instruments that measure up to 150 degrees.

The raw data file of scattered light for each of the detectors must be converted into a particle-size distribution using an iterative mathematical process. The Fraunhofer approximation was used years ago prior to the increase in

computational power available in personal computers. The Mie theory now is used because this approach generates more accurate results.

The recently published International Standard Organization (ISO) document 13320-1 "Particle Size Analysis — Laser Diffraction Methods," suggests that the Mie theory be used for particle diameters less than 40 times the wavelength of the light source — around 25 μm for a helium neon laser. Below the 25 μm size it is essential to use the Mie theory.

The Fraunhofer approximation can misrepresent the actual distribution, creating peaks of fine materials that do not really exist. To reap the benefits of the Mie theory, the refractive index of the material must be entered into the analyzer software. Many refractive index tables are available to facilitate this effort, including extensive libraries now built into the software of most diffraction analyzers. Those interested in a review of the theoretical background of laser diffraction should refer to the ISO 13320 document, which is available through the American National Standards Institute (ANSI) Web site at www.ansi.org.

From a practical standpoint, what should happen to an unknown powder that comes to the lab for laser-diffraction particle-size analysis? The first step often is to properly sub-sample the material brought to the lab. This step can be overlooked when the entire sample is measured as a dry powder. Otherwise, the sample should be split with a spinning riffler, and a portion of the total then should be placed into the analyzer's dry powder feeder. Poor sampling practices are common sources of unnecessary variations in results — up to a 30 percent variation, depending on the size and breadth of the distribution.

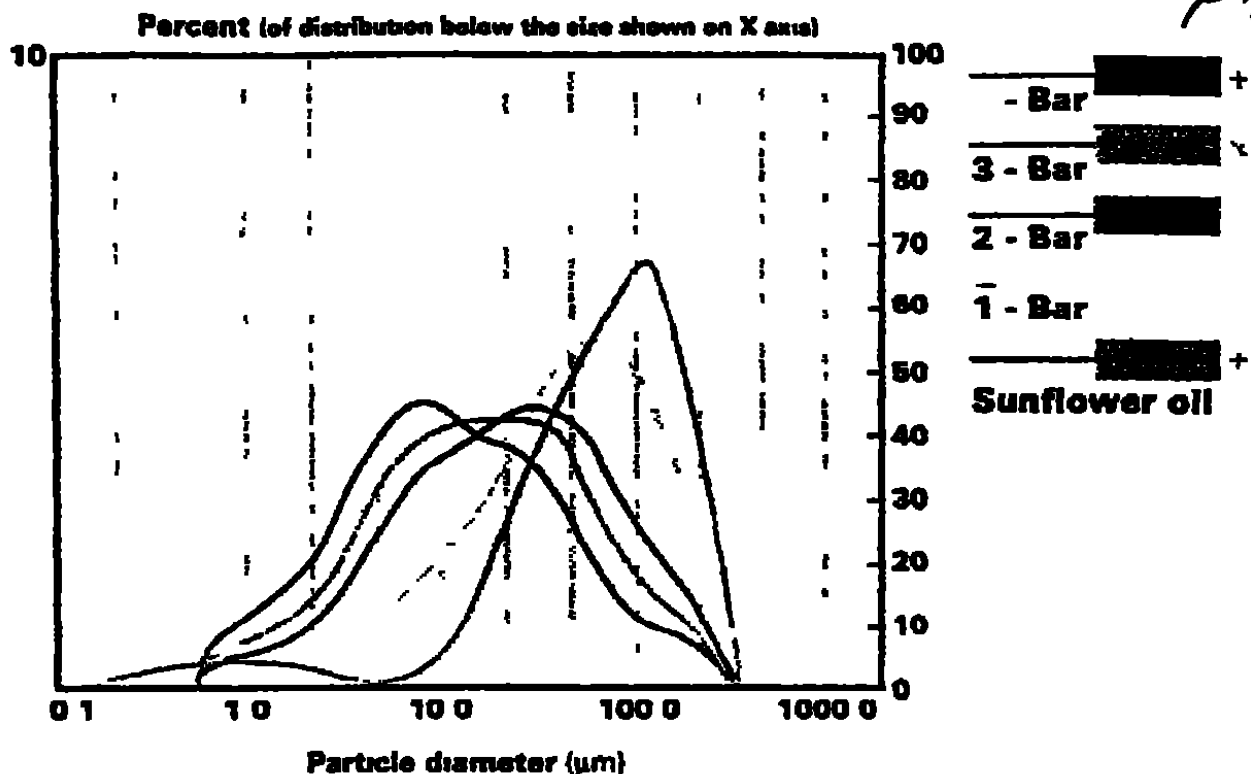
After the powder has been sub-sampled, the analyst needs to decide whether to measure the powder in its natural state or to disperse the material in a liquid medium. Measuring powders in a dry-powder feeder is preferable when the goal is to determine the distribution of the material in its natural state. Sample dispersion in a liquid might be required when the goal is to measure individual particle sizes of agglomerated materials.

Powders dispersed in liquids can be exposed to ultrasound or surfactants to break up loosely held agglomerates. Caution must be used when analyzing unknown powders with a dry-powder feeder to investigate the effect of air pressure on the size distribution; too much energy can result in comminution rather than good dispersion.

New samples should be measured repeatedly at a minimum of three pressures — 1 bar, 2 bar and 3 bar, for example — to investigate dispersion vs. comminution. Once the proper air pressure has been selected, a standard operating procedure (SOP) for that powder should be created and adhered to for future measurements. The SOP should include sampling procedures, refractive index values for the material, analysis modes and the air pressure used in the dry-powder feeder. Ideally, the air pressure is both controlled and recorded automatically by the analyzer software.

Not all powders can or should be analyzed in their natural state — some should be analyzed dispersed in a liquid suspension. Samples that are too sensitive to changes in air pressure (see Fig. 2), powders with strong cohesive forces and powders with a significant portion of submicron material should be analyzed as a suspension.

Figure 2. Effect of Pressure on Paracetamol Powder Size



Samples vary in their sensitivity to changes in air pressure

Dispersing powders in a suspension requires choosing a solvent (preferably water) and often selecting the appropriate surfactant and ultrasonic energy needed to wet the material and break up loosely held agglomerates. A typical approach might involve placement of a small quantity of the powder into a beaker, the addition of a few drops of surfactant to wet the material and then the addition of just enough solvent to create a concentrated paste that can be pipetted into the liquid sampler.

Once the sample is dropped into the sampler, the settings must be investigated to find what pump and stirrer rates are required to keep the heaviest particles in suspension without entraining air in the sample. An SOP for a powder suspended in liquid must include the sampling procedures, the choice of surfactant and solvent, any ultrasonic treatment, the refractive index of the powder and solvent, and all sampler settings.

If a powder can be analyzed as both a powder and a suspension, much can be learned by comparing the results from these two approaches. If the data closely match, then the analyst can have confidence in the results. Differences between the wet and dry results will shed light on which method is more suited to the sample under investigation. Any result showing that the reported particle sizes from the dry-powder feeder are smaller than those from a liquid dispersion should be questioned.

Laser diffraction in the plant

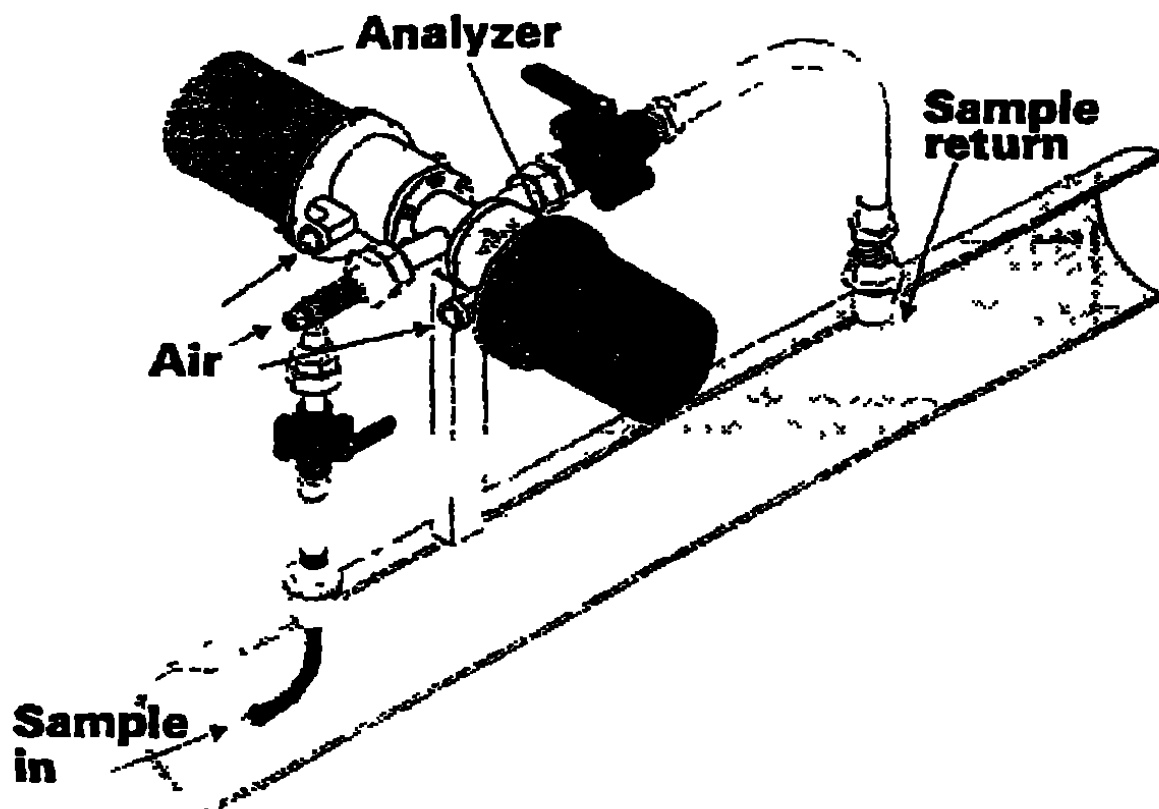
Although most particle-size analysis still is performed in the laboratory, hundreds of in-line analyzers now have been installed successfully in powder processes, including those located in cement plants, mineral processing operations, toners, pharmaceutical plants and powder coating and powder metal plants. The advantages of in-process measurement include continuous monitoring rather than batch sampling, the ability to feed size data into a centralized data acquisition system and the ability to control process operating parameters based on the measured particle size.

In-process laser diffraction analyzers perform the actual conversion from scattered light to particle size distribution in the same way laboratory instruments do. The real differences come from how the powder is introduced to the laser, the requirements for robust optics and electronics capable of withstanding harsh plant environments and the ability to operate at higher concentrations.

Most in-process analyzers remove a portion of the total product flow, pass the sample through the analyzer and then return the powder to the process stream. See Fig. 3. The optics are continuously purged with clean air to prevent any particle contamination on the windows. In a laboratory instrument operators control the sample concentration through dilution or sampler settings. In process environments, the concentration not only can fluctuate, but also can become high enough to produce multiple scattering errors that could lead to underestimating the true particle-size distribution. For this reason, in-process analyzers require automatic

corrections for multiple scattering at high concentrations.

Figure 3. In-Process Laser Diffraction Particle-Size Analyzer



In-process analyzers require automatic corrections for multiple scattering at high concentrations

Now that in-process particle-size analyzers have been proved in the field, the question arises: in which applications and process positions does the analyzer investment provide a justifiable return on investment? Most current installations are placed somewhere downstream of size-reduction steps, often immediately after mills. Steady-state milling operations can tighten product specifications and reduce batch-to-batch variations through continuous particle-size analysis. Continuous monitoring also can detect hardware failures such as screen breaks, and can be used to locate and rectify blips created by hopper flow fluctuations and compressor stoplugs. Plants using air-classifier mills have successfully used the output from the in-process analyzer to control particle size through classifier-speed control. Other advantages in-process monitoring offers over laboratory analysis include quicker startup and product changeover times and process optimization based on analyzer-generated data.

Conclusion

Laser diffraction has proved to be a valuable tool for measuring the particle-size distribution of powders, both in the laboratory and in the plant. Before performing lab analysis, however, remember to:

1. Bring a representative sample to the lab
2. Sub-sample in the lab using a spinning riffler
3. Create SOPs for all samples.
4. Always repeat measurements when creating SOPs.
5. Repeat measurements at several air pressures for unknown samples using a dry powder feeder
6. Measure and record the air pressure for all analyses.
7. Use the Mie theory for samples below 50 μm .
8. Compare wet to dry results whenever possible.

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Dynamic Light Scattering

When a beam of light passes through a colloidal dispersion, the particles or droplets scatter some of the light in all directions. When the particles are very small compared with the wavelength of the light, the intensity of the scattered light is uniform in all directions (Rayleigh scattering). For larger particles (above approximately 250nm diameter), the intensity is angle dependent (Mie scattering).

If the light is coherent and monochromatic, as from a laser for example, it is possible to observe time-dependent fluctuations in the scattered intensity using a suitable detector such as a photomultiplier capable of operating in photon counting mode.

These fluctuations arise from the fact that the particles are small enough to undergo random thermal (Brownian) motion and the distance between them is therefore constantly varying. Constructive and destructive interference of light scattered by neighbouring particles within the illuminated zone gives rise to the intensity fluctuation at the detector plane which, as it arises from particle motion, contains information about this motion. Analysis of the time dependence of the intensity fluctuation can therefore yield the diffusion coefficient of the particles from which, via the Stokes Einstein equation, knowing the viscosity of the medium, the hydrodynamic radius or diameter of the particles can be calculated.

The time dependence of the intensity fluctuation is most commonly analysed using a digital correlator such as the Brookhaven BI-9000AT. Such a device determines the intensity autocorrelation function which can be described as the ensemble average of the product of the signal with a delayed version of itself as a function of the delay time. The "signal" in this case is the number of photons counted in one sampling interval. At short delay times, correlation is high and, over time as particles diffuse, correlation diminishes to zero and the exponential decay of the correlation function is characteristic of the diffusion coefficient of the particles. Data are typically collected over a delay range of 100ns to several seconds depending upon the particle size and viscosity of the medium.

Analysis of the autocorrelation function in terms of particle size distribution is done by numerically fitting the data with calculations based on assumed distributions. A truly monodisperse sample would give rise to a single exponential decay to which fitting a calculated particle size distribution is relatively straightforward. In practice, polydisperse samples give rise to a series of exponentials and several quite complex schemes have been devised for the fitting process. One of the methods most widely used today is known as Non-Negatively Constrained Least Squares (NNLS), the Brookhaven correlator software includes this along with several other approaches to the problem.

Particle size distributions can be calculated either assuming some standard form such as log-normal or without any such assumption. In the latter case, it becomes possible, within certain limitations, to characterise multimodal or skewed distributions. The size range for which dynamic light scattering is appropriate is typically submicron with some capability to deal with particles up to a few microns in diameter. The lower limit of particle size depends on the scattering properties of the particles concerned (relative refractive index of particle and medium), incident light intensity (laser power and wavelength) and detector / optics configuration.

Dynamic light scattering (also known as Quasi Elastic Light Scattering [QELS] and Photon Correlation Spectroscopy [PCS]) is particularly suited to determining small changes in mean diameter such as those due to adsorbed layers on the particle surface or slight variations in manufacturing processes.

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90Plus - Simple Yet Powerful Submicron Particle Size Distribution Analyser

Dynamic Light Scattering (also called PCS) provides a fast, simple method for submicron particle size analysis. Random intensity fluctuations in scattered laser arising from the Brownian motion of colloidal particles are analysed to give either a simple mean size polydispersity (distribution width) or correlation data even for multimodal distributions.

Choose the 90Plus for routine measurement of particle size distributions from about 2 nm to 10 microns in virtually any liquid. It is a compact, contained unit which incorporates a powerful 3 mW diode laser and dual angle - 15° and 90° - detection system. For still higher sensitivity to extremely small or weakly scattering particles, an APD detector or even more powerful, 50mW 532nm, laser are available as options. A high specification PC computer is built into the 90Plus and Win software is used throughout facilitating transfer of data and results to other programmes.

Particle Size Analysis

Light Scattering

- 90Plus
- FOQELS
- BI-200SM

Centrifugal Sedimentation

- BI-DCP
- BI-XDC

Zeta Potential

Colloidal Particles

- ZetaPlus
- ZetaPALS

Macro Surfaces

- BI-EKA ElectroKinetic Analyser

Light Scattering

- BI-200SM
- BI-MwA
- FOQELS
- BI-9000AT

Accessories

- BI-DNDC
- BI-870
- BI-SFS

You can add all the facilities of Brookhaven's ZetaPlus and ZetaPALS to combine zeta potential determination with particle sizing in one comprehensive particle characterisation system. This can be selected at the time of purchase or later.

Typical applications of the 90Plus include polymer colloids (latex), liposomes, emulsions, microemulsions, pharmaceuticals, pigments, toners.

90Plus Specifications

Range	2 nm to 3 µm depending on refractive index, concentration & scattering angle. 10 nm to 1 µm typically with standard laser
Precision	±1% typically
Sample Type	Most colloidal-sized materials, suspended in any clear liquid
Sample Volume	1 to 3 mL. New! Small-volume cell requires only 150 µL or less of sample.
Temperature Control	10°C to 75°C ±0.1°C, active control. No external circulator required.
Laser	30 mW red, standard 50mW green optional
Scattering Angles	15° & 90°
Data Presentation	Mean diameter & width, lognormal fit, and multimodal size distribution
Correlator	Brookhaven BI-9000AT multi-tau research correlator with 5 channels, (equivalent to 10 million linearly-spaced channels) 100% efficient real-time operation over the entire delay-time range
Computer	Built-in PC Windows™ Software included. Check with Brookhaven for latest specifications. External computer optional
Printer	Colour Inkjet, standard. Others available
Monitor	Colour SVGA graphics card

ElectroKinetic Analyser

Light Scattering

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- [BI-MwA](#)
- [FQOELS](#)
- [BI-9000AT](#)

Accessories

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- [BI-870](#)
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Scientific -
Microspheres
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Sample Type	Most colloidal-sized materials, suspended in any clear liquid.
Sample Volume	1 to 3 mL New! Small-volume cell requires only 150 microlitres or less of sample
Temperature Control	10 ⁰ C to 75 ⁰ C, $\pm 0.1^{\circ}$ C, active control. No external circulator required.
Laser	30 mW, red, standard. 50mW green, optional
Scattering Angles:	15 ⁰ & 90 ⁰
Data Presentation:	Mean diameter & width, lognormal fit, and multimodal size distribution.
Correlator	Brookhaven BI-9000AT, multi-tau research correlator with 510 channels, (equivalent to 10 million linearly-spaced channels), 100% efficient real-time operation over the entire delay-time range
Computer:	Built-in PC. Windows™ Software included. Check with Brookhaven for latest specifications External computer optional
Printer	Colour inkjet, standard. Others available
Monitor	Colour, SVGA graphics card.
Power Requirements	100/115/220/240 VAC, 50/60 Hz, 300 Watts
Dimensions	267(H) x 625(W) x 445(D) mm (excluding monitor and printer)
Weight	37 Kg (excluding monitor and printer)
Environmental Characteristics:	Temperature 10 ⁰ C to 75 ⁰ C Humidity 0% to 95%, non-condensing.
Options	ZetaPlus and ZetaPALS facilities for zeta potential analysis, Small volume glass cell, Disposable square plastic cells, Round and square glass cells

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Certified Particle Size Standards

As Authorised Distributors for Duke Scientific Corporation USA, Brookhaven are pleased to supply the full range of Duke Scientific certified particle size standards. These standards provide third party traceability of calibration procedures to national or international agencies through an unbroken chain of measurements with specified uncertainties.

They are available as uniform spheres of polymer, glass or silica in a range of discrete sizes from 20nm to 2000µm calibrated with linear dimensions transferred from NIST (National Institute of Standards & Technology) by Duke Scientific using methods developed in Duke's own laboratories.

Each standard is supplied with a Certificate of Calibration and Traceability, a description of the calibration method, a table of its chemical and physical properties and a Materials Safety Data Sheet (MSDS) with handling and disposal instructions.

3000 Series Nanosphere Size Standards 20 – 900nm

Uniform polystyrene microspheres in a range of sizes, each packaged as an aqueous suspension in 15mL dropper-tipped bottles. The concentration is optimised for ease of dispersion and colloidal stability. The microspheres have a density of 1.05 g/cm³ and refractive index (589nm) of 1.58.

Nanosphere Size Standards are used for a wide variety of applications including calibration in electron microscopy, laser light scattering and colloid research.

4000 Series Polymer Microsphere Size Standards 1 – 1000µm

With the same composition and physical properties as the 3000 Series, these polystyrene microsphere standards are supplied as aqueous suspensions in 15mL dropper-tipped bottles (1 – 100µm) or in dry form in 1g screw capped bottles (200µm and larger).

8000 Series Silica Microspheres 0.5 – 1.6µm

Designed for applications requiring monodisperse inorganic microspheres, these particles have a higher density than polystyrene and provide more contrast than polymer microspheres in optical and electron beams. They are packaged as aqueous suspensions at 2% solids in dropper-tipped bottles.

The silica spheres have a density of 1.8 – 2.2 g/cm³ and an index of refraction of 1.40 – 1.48 at 589nm.

9000 Series Glass Particle Size Standards 2 – 2000µm

This range consists of borosilicate glass microspheres (mean diameters 2 – 20µm) and soda lime glass microspheres (30 – 2000µm) all with narrow size distribution and NIST traceable mean diameters.

Small borosilicate microspheres have fewer spherical imperfections and inclusions and better mechanical and thermal stability. They are packaged in 1g quantities of dry microspheres having a density of 2.50 – 2.55 g/cm³ and refractive index of 1.58 at 589nm.

The soda lime glass of the larger microspheres contains trace amounts of metallic elements making them easily detectable by non-dispersive x-ray methods and improving their contrast and reflectivity in optical, ultrasonic and electron beams. They are processed to remove most of the non-spherical or broken material, ensuring a high percentage of spherical particles.

Soda lime microspheres have a density of 2.4 – 2.5 g/cm³ and index of refraction of 1.51 at 589nm.

589nm Their softening temperature is 720°C and the dielectric constant is 7.3 at 1KHz and 20°C.

To download a brochure in Adobe Acrobat format giving full details of the Certified Particle Size Standards range including individual sizes available, [click here](#). Alternatively visit the Duke Scientific web site for more information

2000 Series Uniform Polymer Size Standards 5 – 40µm

First introduced in 1971 this range of microspheres continue to find application where moderate uniformity of particle size is required rather than the very narrow distributions (CV <5%) of the other standards. They are widely used with laser diffraction and light blockage instruments, acoustical imaging, electrolyte displacement (e.g. Coulter principle) and other methods often used to characterise coarse distributions.

Like the 3000 and 4000 Series microspheres, they are composed of cross-linked polystyrene giving them good durability and chemical stability. Their density is 1.05 g/cm³ and refractive index 1.59 at 589nm. They are packaged in 15mL, dropper tipped vials and supplied with certificate of NIST traceable calibration

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Additional certified particle size standards are described in the section on Standards for Particle Counting Methods.

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Advanced Surface Characterisation of Inhalation Microparticles

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Stephen Ebbens, Shen Luk and Nildn Patel, Molecular Profiles Ltd, 1 Faraday Building, Nottingham Science and Technology Park, University Blvd, Nottingham, UK

Introduction

The application of advanced surface analytical methods to the characterisation of inhalation particles allows direct determination of the physical and chemical properties that are critical to device function. Properties that can be determined for individual micronised particles include size, texture, roughness and surface heterogeneity. Such information is crucial to confirming that particles are engineered within respirable dimensions, and present the desired surface structure and composition. Furthermore the adhesion between particles, or between a particle and a surface can be measured. Micronisation produces particles with a high surface area, which are prone to form unstable cohesive systems, agglomerates or adhere to surfaces, such as packaging materials. These factors lead to potentially serious problems with dosage control, dispersion and delivery in inhalation devices. In this article, an overview of the capabilities of current surface analytical methods is given, along with example applications of this technology.

Determination of Particle Physical Properties

The morphology of the particulate components of an inhaler device is important in determining inhaler function. At a basic level, it is necessary to assess particle size, to ensure that delivery to the respiratory tract is possible (generally a size criteria of 1-5 μm must be satisfied). Conventional particle sizing methods such as light scattering produce average particle diameters assuming spherical particle shape, which can be inaccurate for the crystal geometries of many active ingredients. An alternative method is to use Scanning Electron Microscopy (SEM) in conjunction with image-analysis. This approach enables particle shape to be visualised and quantified, ensuring an accurate assessment of the respirable fraction (see Figure 1).

Particle roughness is another important parameter, as it plays a large role in determining the level of adhesion to other active particles, excipients and inhaler device surfaces, via its effect on contact area (Stanforth, 1995). Atomic Force Microscopy (AFM) provides an ideal method for determining surface roughness, through its ability to generate true 3D topographical images with nm resolution. AFM operates by scanning a sharp tip

attached to an ultra-light cantilever across the surface. An image is formed from the displacements required to maintain a constant tip-surface interaction, and this constant force surface forms a representation of topography. As an example of the data obtained Figure 2 displays the results of AFM analysis of active ingredient particles that have been produced using the solution-enhanced dispersion from supercritical fluids method (SEDS). In addition to the 3D and 2D data representations, virtual cross-sections can be produced to allow quantification of surface features. Here, this was used to measure the height of a crystal step, providing information about the crystal habit of the active ingredient. AFM data is also readily analysed to provide a range of surface roughness parameters. In this case there was interest in determining if the novel particle preparation method had succeeded in smoothing the particle surface compared with conventional micronisation. The roughness data presented in Figure 3 confirms that the SEDS process does produce significantly smoother particles, which is likely to reduce particle self-adhesion, and so reduce undeliverable agglomerate formation.

Phase imaging extends the use of AFM for particle characterisation. This mode allows variations in surface properties such as hardness and hydrophobicity to be imaged. For example, phase imaging is able to distinguish crystalline and amorphous material and has even been shown to differentiate two polymorphs of an active



Figure 1 SEM analysis of SEDS Salbutamol particles enables direct determination of particle dimensions and shape

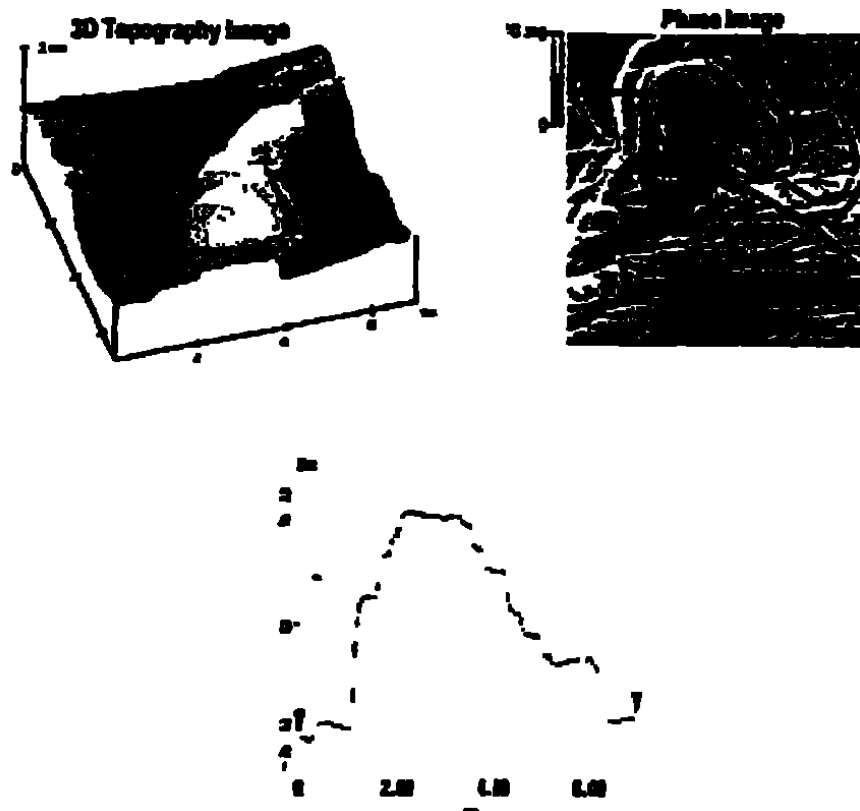


Figure 2. AFM analysis of SEDS produced Salbutamol particles. A virtual cross section is generated along the red line allowing the crystal step heights to be measured

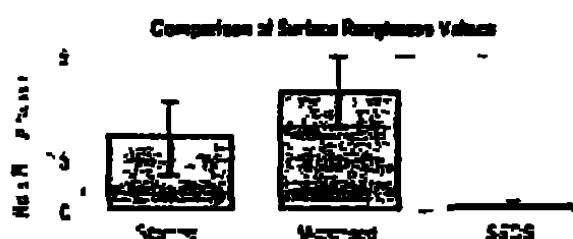


Figure 3. Comparison of surface roughness values for Salbutamol processed using conventional micronisation and the SEDS process.

ingredient (Danesh et al. 2000). In addition, by utilising the force sensing ability of AFM it is possible to measure and compare mechanical properties of particles such as elasticity and plastic deformation. These properties contribute to particle adhesion levels, and can also reveal information about the state of the particle

Chemical Characterisation of Single Particle Surfaces

In addition to characterisation of the final physical properties of inhaler active ingredients, confirmation of particle chemical composition is also important. This is

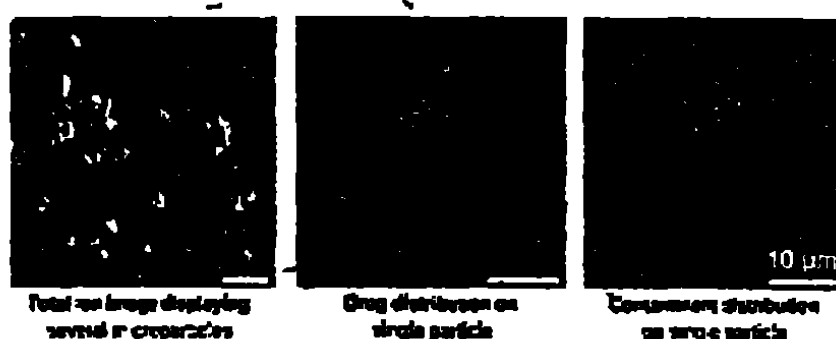


Figure 4. TOF-SIMS analysis of the contents of a dry powder inhaler reveals the presence of a contaminant distributed on active ingredient particles

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particularly important as milling processes have the potential to modify particle surfaces. One of the few chemical analysis methods with the spatial resolution to interrogate individual micronised particles is time-of-flight secondary mass spectrometry (TOF-SIMS). This advanced method allows surface sensitive mass spectrum to be obtained from regions as small as 1 nm. The technique achieves ppm sensitivity, and only samples the top monolayer of the sample. Interpretation of the mass fragments allows accurate determination of the surface chemical composition. A significant feature of TOF-SIMS is the ability to form images of the distribution of specific molecular fragments, allowing the mapping of heterogeneous surfaces with a resolution of 100 nm

An example is the chemical analysis of the contents of a dry powder inhaler using TOF-SIMS (see Figure 4). The total ion image is used to locate the position of the particles after expulsion from the inhaler device, and provides an indication of their size distribution. The retrospective analysis capability of the technique allows mass spectrum to be extracted from individual particles. In this case the spectra contained fragments that could be assigned to the active ingredient and excipients, however some additional signals were present. Reference to TOF-SIMS libraries revealed the signals to be attributable to an Irgafos 168 contaminant. Again, retrospective analysis of the data allows images of both the active ingredient and contaminant distribution to be produced (see Figure 4). From these images it is apparent that the contaminant is located on the active ingredient particles. Further analysis revealed that the Irgafos contaminant originated from the packaging material used to contain the active ingredient. This case highlights the importance of chemical characterisation of inhaler components in their final form, and allowed detection of a contaminant that may have otherwise gone unnoticed

Although TOF-SIMS has unrivalled surface sensitivity and detection levels, the data obtained is qualitative. For this

reason, a complementary quantitative surface analysis method, X-ray Photoelectron Spectroscopy (XPS) is often used in conjunction with TOF-SIMS. XPS allows surface elemental compositions to be determined, and also provides some quantitative information about the functional groups present (Davies et al. 1999).

Particle Interaction Measurements

The performance of inhaler devices is highly dependant on the interactions between their constituents. For example, in a dry powder inhaler, the active ingredient is present as a micronised powder. Due to the high cohesive energy of such small particles, the active ingredient on its own would form aggregates exceeding respirable dimensions. For this reason an excipient (usually lactose, termed the carrier) is included to aid dispersion of the active ingredient. During the inhalation process, the active ingredient must release from the lactose as individual micronised particles. It is apparent that for such a system to succeed, the balance of interactions between the lactose and the active ingredient must be carefully controlled. Furthermore, adhesion to the walls of the device provides an additional loss mechanism for the active ingredient that must be minimised.

Conventional methods for assessing particle-particle interactions include tests *in vivo*, on "electronic lungs" and using Andersen-Cascade Impactors. In addition, some experiments using centrifuges have also been performed (Podczek et al., 1995). All these experiments have the disadvantage of measuring the properties of particle ensembles, rather than individual particles, and offer no means of probing spatial variations in adhesion strength due to heterogeneity of one or both of the interacting materials.

Localised Particle Interaction Measurements using Atomic Force Microscopy

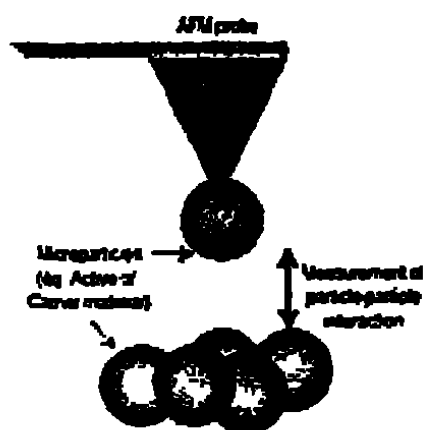


Figure 5 Schematic of the use of AFM to measure interaction forces between inhaler components.

AFM provides a method that avoids these drawbacks. By attaching a single particle of interest to an AFM cantilever, the interaction with other particles or surfaces can be probed (see Figure 5). The type of data obtained is termed "force-distance" as graphs of the force on the particle as a function of its distance from the probe material are generated. Mathematical analysis of these graphs allows quantitative parameters such as maximum adhesion energy to be extracted. These can be used to rank the strength of adhesive interaction between a series of materials.

As an example of this approach, a study examining the interactions in a dry powder inhaler comprising salbutamol (active), lactose (carrier) and

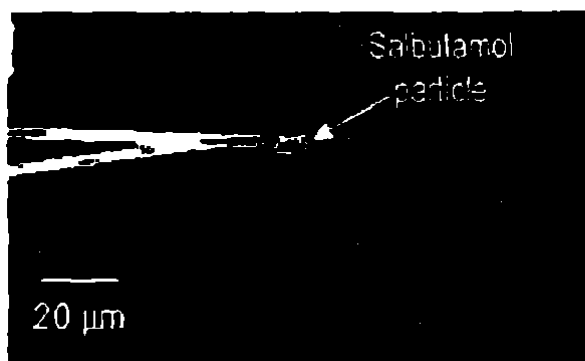


Figure 6. SEM image of a Salbutamol particle localized on an AFM cantilever.

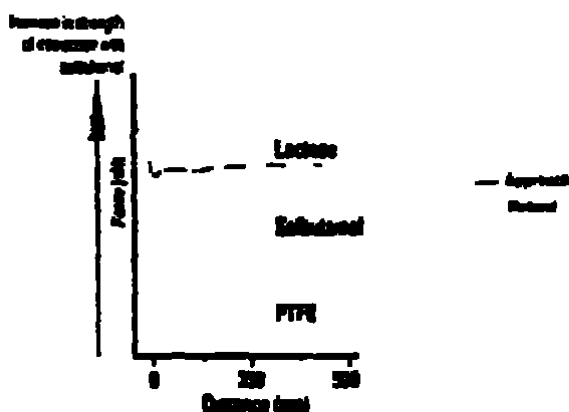


Figure 7 Typical force distance curves obtained for the interaction of a Salbutamol particle with the dry powder device components. The size of the well in the retract curve indicates the extent of adhesion.

polytetrafluoroethylene (canister coating) is described (Eve et al. 2002). The first stage of the interaction measuring experiment is to attach a Salbutamol particle to a cantilever using the micromanipulation capabilities of AFM. A SEM image of a cantilever prepared in this way is shown in Figure 6.

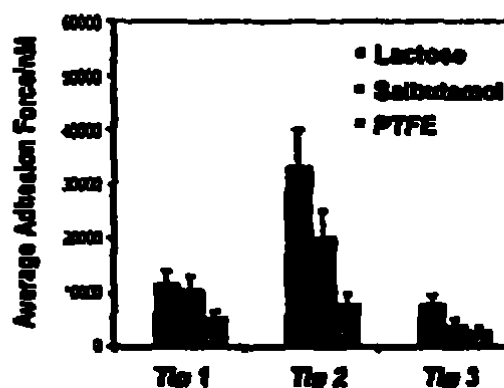


Figure 8. Average interaction forces between the components of the dry powder device

Interaction measurements are performed by challenging the modified cantilever to a disk of Salbutamol particles (self-interaction), a disk of lactose carrier and a model polytetrafluoroethylene film. Typical force distance interaction curves obtained from these experiments are shown in Figure 7. The size of the well in the force-distance curve, observed as the tip is withdrawn from the sample, reflects the strength of the adhesion between the two components. At least 100 measurements were recorded for a given functionalised tip, and averaged to provide an adhesion measurement. In addition, to allow for variations caused by the geometry of the drug particle, three different tips were employed. The results indicate a consistent ranking of adhesion of the order salbutamol-lactose > salbutamol-salbutamol > salbutamol-PTFE, (see Figure 8). It should be noted that the tip-to-tip variation in adhesion energy is a result of the different shapes of the attached particles producing different contact areas. This renders the data qualitative, although recent advances enable estimations of contact area to allow quantitative analysis. The impact that this data has, is to suggest that it is energetically favourable for the salbutamol aggregates to disperse onto the lactose carrier as desired. Furthermore, the low level of adhesion of

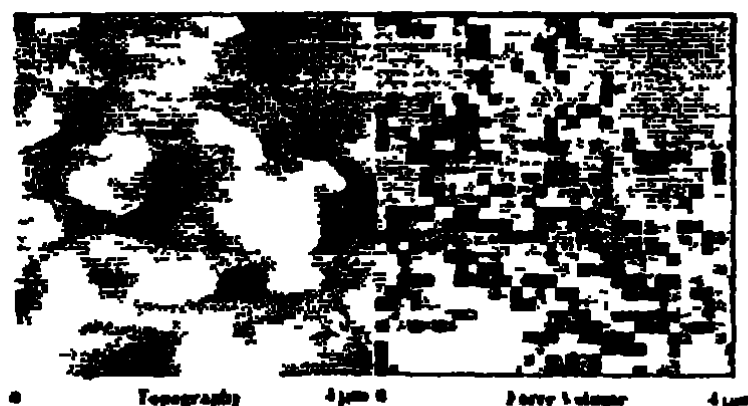


Figure 9 Force volume imaging of the interaction of a salbutamol particle with a lactose carrier particle

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active ingredient to the canister coating is desirable. This later finding was tempered by the discovery that repeated contact of the active particle with the same region of the PTFE coating produced a large increase in adhesion energy. This effect is likely to be due to contact charging, and may result in the active ingredient adhering strongly to the canister. This finding could have an impact on subsequent device design.

Atomic Force Microscopy Interaction Imaging

The above experiment can be extended to enable the spatial variation in the interaction between a particle and a substrate to be determined. To achieve this, an array of force-distance graphs is recorded over the area of interest. This method is termed "force-volume" imaging and generates a spatial map of particle adhesion simultaneously with topographical data. As an example, a force-volume image was produced to measure the spatial variation in interaction between a salbutamol particle and a larger lactose carrier (see Figure 9). The force-volume image is generated in a manner whereby darker regions correspond to increased particle-surface adhesion. It is apparent that some of the features in the adhesion map correspond to the topography, and so are likely to be due to changes in tip-sample contact area. This effect is removed by comparing regions with smooth topography. Careful examination of the force-volume images reveals that there are variations in adhesion in these regions that do not show obvious correlation to topography. This is confirmed in Figure 10, where force distance curves are

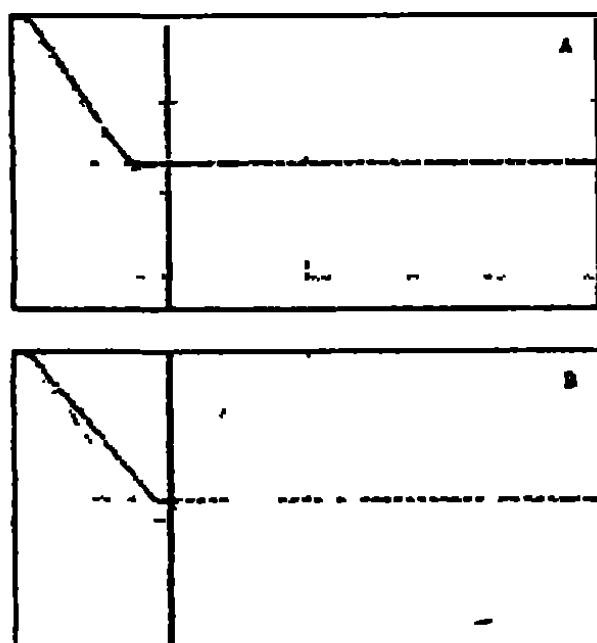


Figure 10. Force-distance curves extracted from the force-volume map shown in Figure 9. Topography independent variations in the adhesion force are seen.

extracted from two regions of interest. It can be seen from the size of the force wells, that the active particle experiences less adhesion in region A, than region B. Topography independent variations in adhesion of the active ingredient to the lactose carrier may help to explain the previously reported existence of active and passive sites for absorption.

Although the experiments described here have focused on dry powder devices, applications to pressurised aerosol inhalers also exist. The study of such devices is possible through the ability of AFM to operate in a controlled environment, or under fluids. To simulate the conditions in a pressurised inhaler, experiments are performed under a model fluorochromic solvent. To date, this approach has been used to determine the effect of a surfactant on inter-particle adhesion, and to map the variation in interaction between an active ingredient and the walls of the inhaler canister.

Summary

Advanced surface analytical methods find numerous applications for the characterisation of inhaler devices. The application of a combination of techniques (SEM, AFM and TOF-SIMS) facilitates analysis of particle size, roughness, morphology and chemical composition. Furthermore, AFM provides an ideal tool to explore the interactions between inhaler components, knowledge that can assist improvements in device performance.

Acknowledgments

Molecular Profiles would like to thank our collaborators, Peter York at Bradford Particle Design Ltd, and Anna Belu at Medtronic, Inc.

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CAPITULO 3

CONTENIDO

- 1 Tendencias emergentes en micronización**
- 2 Micronización de ingredientes farmacéuticos activos**
- 3 Avances en tecnología de procesamiento de polvos**
- 4 Micronización de compuestos potentes**

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Micron Technologies

MICRON TECHNOLOGIES - EMERGING TRENDS IN MICRONIZING

As our understanding of the impact of particle size on Active Pharmaceutical Ingredients (APIs) continues to develop, the pharmaceutical industry is faced with numerous challenges. Challenges which include, but are not limited to, achieving the desired particle size in a consistent manner, measuring particle size in a reproducible manner, and meeting current and future regulatory requirements. Below is a discussion of the existing and emerging options as related to micronizing (defined as particles smaller than 20µm)

PARTICLE SIZE REDUCTION

The most commonly used pieces of equipment are tangential fluid energy mills or pancake mills. Size reduction occurs via particle to particle collision. The benefit is that no heat is generated (as in mechanical milling). The pancake mill grinds and classifies in a single chamber. High-pressure, air/gas is introduced through specially designed nozzles. Raw materials are introduced into the grinding chamber through a venturi feed injector. The solid particles are entrained in the flow, causing them to collide. These high-velocity collisions pulverize the solids into micron and submicron particles. As the particles are reduced to the desired size, the viscous drag of the exhaust draws only the reduced particles into the discharge system.

Air or gas is introduced into the loop mill through specially designed nozzles. Solid particles are injected into this stream. The high-velocity collisions that result provide thorough and effective pulverization of the feed into smaller particles. The particle stream leaving the reduction chamber flows to the classification zone. As the stream enters the classifier, the direction of the flow is reversed. Properly sized product is entrapped by the exhaust flow and conveyed to collection equipment. Larger particles remain in chamber for further grinding.

PARTICLE CLASSIFICATION

With classification mills, air or inert gas is injected through specially designed nozzles directly into the grinding chamber of the mill. Raw material is introduced into the mill. Size reduction is accomplished by collisions between particles. Small particles are then swept towards the classifier, which rotates at high speeds above the grinding chamber. Material, which is fine enough to pass through the classifier, is collected as product. Oversized particles are recycled by the classifier, back into the grinding chambers for further reduction.

PARTICLE SIZE REDUCTION MONITORING

Monitoring of particle size reduction is typically performed using laser diffraction. This technique can be relatively simple and fast, making such methods ideal for in-process testing. Due to the potential for the formation of loose aggregates during micronization, wet dispersion methods are preferred. Care must be taken, however, in developing reproducible and robust methods. In cases where particle size will be used as a release specification, thorough method development and validation

studies are required. Method transfer studies must also be performed when using contract manufacturers, as it is not uncommon to see considerable variability between laboratories employing different sample preparation methods or instrumentation.

SURFACE AREA ANALYSIS

Surface area analysis may provide more relevant information with respect to particle dissolution and/or bioavailability, but is not a practical in-process test due to sample preparation requirements. Additional physical characterization may be required if changes in crystallinity, polymorphism, hydration/solvation or other parameters are expected. Some of the techniques employed include x-ray diffraction, thermal analysis (DSC and/or TGA), spectroscopy (Raman and/or FT-IR), NMR and so forth.

GMP IN THE MICRONIZING PROCESS

Good Manufacturing Practices (GMPs) are becoming an integral part of the micronizing process for the pharmaceutical industry. Compliance is expected in the areas of validation (for example particle size methods, computers, instrumentation), employee training (employees have been trained to perform job functions), and documentation (if it is not documented it did not happen).

The new ICH guidelines (GMPs for APIs) show a trend toward making all API manufacturing processes adhere to the same standards as pharmaceutical companies dealing in final dose forms.

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mifaco chemicals ag

mifaco chemicals ag Micronization of Active Pharmaceutical Ingredients

Dieter Krimmer*

Abstract: mifaco chemicals ag is a young and dynamic company that provides several services. The services are: a) CMC management: This involves all technical aspects during the development of a new drug. For generic drugs, mifaco chemicals' experience can also be counted on. b) Micronization of APIs: mifaco chemicals is specialized in contract micronization of APIs. Micronization is performed under cGMP conditions in multi purpose lines. Each line is located in dedicated suites. Our specialty is micronization below 10 µm.

Keywords: cGMP/GMP CMC management Consulting Micronization Particle size distribution

mifaco chemicals is the outsourcing partner for the pharmaceutical industry focusing on size reduction for active pharmaceutical ingredients and other ingredients. Our aim is to establish a partnership with our clients, not only providing the micronization capacity. We are able to provide a variety of value-added services, such as:

- validation expertise and personal contacts with the authorities in US and Europe,
- CMC management,
- marketing ideas.

Nevertheless such services are supplementary to the manufacturing capabilities that mifaco chemicals specializes in.

mifaco chemicals was founded in 1997 with micronization as the strategic focus. The technical concept has been proven in the meantime, setting new standards in the industry. The core competence of the personnel ensure that manufacture is carried out according to current Good Manufacturing Practice



Fig. 1 View of the clean rooms and HVAC systems

(cGMP). Furthermore, we have a good understanding of the pharmaceutical industry which helps to accelerate FDA or other government approval.

The equipment was constructed in 1997/1998 and the modern plant has been fully operational since the final quarter of 1998. mifaco chemicals was successful

inspected by several leading pharmaceutical companies. The two industrial micronization lines and one benchscale laboratory plant will offer following possibilities:

Micronization can be performed with nitrogen or oil free compressed air both also at lower temperatures.

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Fig. 2. Micronization line CGS 32

- Product handling is performed in closed systems and air-conditioned rooms (Fig. 1).
- Batches for micronization can be from 100 g up to several metric tons.
- Fulfillment of the latest requirements of the authorities.
- Sterile micronization

The plant offers the following properties. The mills are in completely separated cabins with locks for material and for personnel. The concept was discussed with the authorities (FDA) and accepted before construction. Each micronization line has a segregated air conditioning system to avoid any cross-contamination. Micronized and unmiconized products are stored in separated warehouses. The scientist responsible for QA ensures that

only released material will be micronized or will be sent back to the partner.

Our Personnel:

- For CMC management: 2–5 chemists/pharmacists
- For micronization: 1–2 chemists, 1–2 lab technicians, 3–5 chemical workers
- For administration: 1–2 controllers

The Equipment (Fig. 2):

- Fluidized-bed jet mills
A classifier secures the desired particle size. All equipment has been constructed from stainless steel with pharmaceutical-grade surfaces. The micronization cell is not coated to avoid any electrostatic charging.

Cleaning can be performed quickly and easily (cleaning validation).

- Preparation of the milling gas. The milling gas is oil-free compressed air or nitrogen (medical grade). The temperature of the milling gas can be chosen between 1 °C and 25 °C; possibility of adaptation of the air conditioning.

Laboratory:

- Sieving analysis for particle sizes above 100 µm. Laser scattering method for particle sizes below 100 µm. Six different methods for evaluation can be used, i.e. the Fraunhofer method. A dry powder module and a module for liquids are available. All retention samples are stored for seven years for any requests.

The Documentation:

- Master validation plan (systems and processes)
- The equipment was qualified according cGMP (DQ, IQ, OQ, PQ).
- This qualification forms the basis of a prospective validation of APIs.

Batch Documentation:

- After micronization, each customer receives a complete batch documentation in accordance with cGMP. This documentation will be stored for ten years.

The Unique Set of Capabilities Offered to our Partners:

- A constant and very tight particle size distribution, which is the best assumption for an optimal galenical process.
- Specialization for a particle size distribution less than 10 µm.
- With the micronized substances, you meet every time the demanded specifications of your dissolution profile.

CMC Management: C (Chemistry), M (Manufacturing), C (Controls)

We offer consulting in the complete technical area, for example:

- basic design of new equipment
- qualification of the equipment
- validation of systems and processes
- support in the registration and much more

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Title of Paper

**ADVANCES IN POWDER PROCESSING TECHNOLOGIES FOR
CHEMICAL, FOOD AND MINERAL APPLICATIONS**

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Abstract

Powder producers in chemical, mineral and pharmaceutical markets are exploring new processing methods to isolate smaller average particle sizes and tighter overall particle size distributions. Consumer demand for higher quality end products is driving these producers to explore new technologies in the area of powder processing. Manufacturers of powder processing equipment have, in turn, developed new and improved methods for producing powder products that meet/exceed these stringent parameters.

This paper will review the basics of particle size reduction and classification, and describe recent developments in powder manufacturing technologies. A summary of available technologies will assist the participant to determine the optimal powder processing method for his/her specific application. The presentation will conclude with an overview of recent case studies within the powder processing industry.

Submitted for ChemShow '99 The 48th CPI Expo
Jacob K. Javits Center, NY, NY
November 16-19, 1999

Session "Powder & Particle Process Applications"

INTRODUCTION

Solid particle size reduction and classification techniques have been used for a number of years, in order to modify particles for a variety of chemical, pharmaceutical, food and mineral applications. Virtually any powder used in commercial production has passed through some type of machine to alter its size or shape. Practical examples include the powdered sugar on confectionery products, the toner used in copy machines, the powder coating material used for automotive finishes; the talc used in baby powder; the starch used in a variety of food products, the active ingredients used in prescription drugs. These represent a small sample of the applications where the raw material has been altered in some way to improve the quality of the finished product as well as the efficiency of the manufacturing method.

The science of size reduction and grinding has changed dramatically in order to keep up with the demand for improved consumer products. In addition, this demand is derived by the desire of the manufacturer to produce a product more efficiently, with less off spec material to recycle or discard. This paper will review size reduction and classification methods, in addition to the advances made in this area.

PARTICLE SIZE REDUCTION

Three main principles govern the size reduction of solid particles. impact, compression and shear. Mechanical-impact grinding mills utilize the impact principle of grinding; either impacting a particle with an outside force or accelerating the particle against a particle. Compression involves size reduction caused predominantly by pressure but also by friction from the surfaces of the neighboring particles. Shearing, or stressing by cutting, is used for soft or fibrous materials such as plastics and animal and vegetable products. These machines make use of rotary knife cutters, which consist of rotating and stationary knives that cut materials on the shearing edges.

Mechanical-impact mills are ideal for easy to grind ("soft") materials requiring "medium" fineness (see Table 1). Harder materials (typically defined as solids with a hardness of the Mohs scale of greater than 3) require special processing techniques which will be described in a later section.

TABLE 1

Degree of Hardness	Mohs Scale	Example
Soft	1	Talcum
Soft	2	Gypsum
Soft	3	Calcite
Medium-hard	4	Fluorite
Medium-hard	5	Apatite
Medium-hard	6	Feldspar
Hard	7	Quartz
Hard	8	Topaz
Hard	9	Corundum
Hard	10	Diamond

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Mechanical impact mills are limited in their usage to relatively soft materials. Harder materials will cause wear and abrasion to occur rapidly inside and impact mill.

Types of Impact Mills

Technological advances have led to a whole host of machine configurations designed to reduce particle size. These mills include (but are not limited to) Cutting Mills/Crushers, hammer and screen mills, universal and pin mills and mills with classifiers. Each machine offers its own unique processing characteristic in order to achieve a specific product upon discharge

Cutting Mills/Crushers

Cutting mills or crushers utilize shear for size reduction and are used when material is required in a coarse to medium fine product range (see Table 2). Cutting mills (also known as granulators) make use of rotating and stationary knives that cut materials on the shearing edges. Sets of rotor-knives rotate inside a set of stationary knives, thus mimicking the action of high-speed scissors doing hundreds of cuts per minute (See Figure 1). The knife design can be varied depending on the material to be processed.

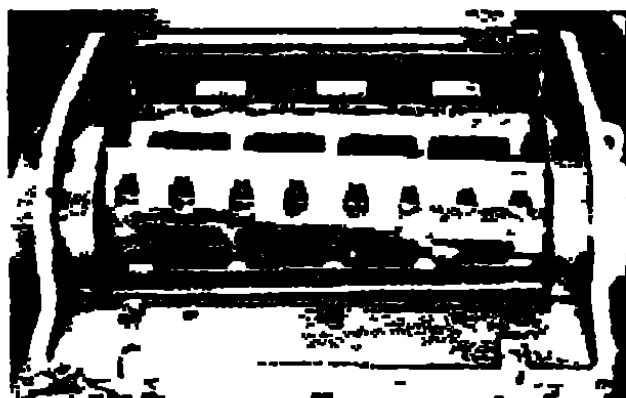


Figure 1 Rotary-knife Cutting Mill

Applications for cutting mills include the size reduction of fibrous materials such as vegetable matter, spices, herbs, plastic bottles and film, automobile components (bumpers, dashboards and door linings) for end-product particle size in the range of 1-6 mm.

Coarse crushers utilize the compressive force between two solid surfaces to cause size reduction. These crushers are used mostly for the size reduction of minerals, gravel and ores resulting in particle size distributions in the range of 1 mm-100 mm. A specialty use is as a pre-crusher, to provide a uniform feed material for the next step in size reduction. Most crushers are located at mine sites, for immediate size reduction prior to being loaded for transportation.

Universal and Pin Mills

Universal mills are often referred to as fine-grinding impact mills. Particle size reduction occurs by impact against the grinding media, and through inter-particle collision and attrition. These mills typically utilize a variety of grinding media within the same milling chamber to allow for complete flexibility in the resulting particle size distribution (see Figure 2)

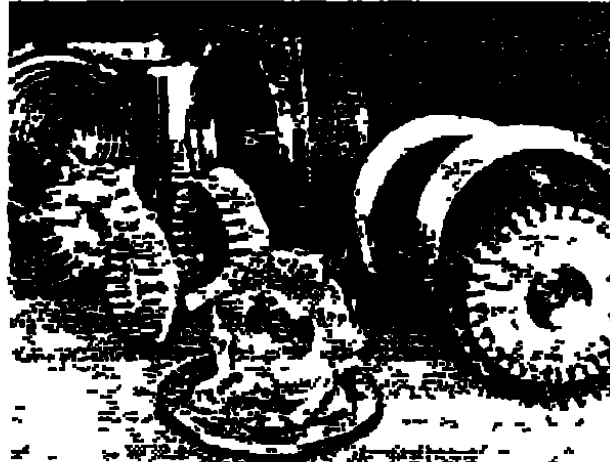


Figure 2 Universal (pin) Mill

A universal mill equipped with pin discs consists of one stationary set of pins and one rotating set of pins. Material enters the center of the grinding chamber via gravity, and is accelerated by centrifugal force against the meshing pins. The speed of the discs sets the strength of this force. The feed rate and the peripheral speed of the pin discs determine particle size. These mills do an ideal size reduction when the desired particle-size distribution is narrow. Milling of pharmaceuticals, food confectioneries, animal feeds, mineral powders, pesticides, paints pigments as well as the cryogenic milling of herbs and spices can be accomplished using the universal mill.

Hammermills

Size reduction in a hammermill is accomplished by impacting the solid particles against a rigid surface, namely the mill housing. A retaining screen on the discharge end of the mill "rejects" oversized particles and prevents them from exiting the grinding chamber. Three basic variables affect the grinding process: hammer type, screen hole size and peripheral speed of the hammers.

Hammermills (see Figure 3) are ideal for a wide variety of particle sizes in the medium to medium-fine particle size range (20-150 microns). Applications include the grinding of pigments, various industrial chemicals and food ingredients. Hammermills are ideally suited for a cryogenic impact-milling set-up that embrittles the material prior to size reduction. This makes possible the grinding of tough, fibrous materials or thermoplastics as well as heat-sensitive products.

Mills with Classifiers

A recent advancement in the area of impact milling has been the incorporation of a classifier wheel as an integral part of the grinding machine. The classifier acts as a rejection mechanism that only allows particles below a specified size to pass through the wheel. Material to be ground is conveyed into the mill chamber to a rotor equipped with pins or hammers. As particle size reduction occurs, the particles are picked up by the airstream and eventually pass

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through the classifier wheel to the product collector. Those particles that are rejected by the classifier are continuously recycled back to the hammers for further size reduction (See Figure 4)

Rotor speed, classifier wheel speed and airflow control particle size in an air-classifier mill. Due to the constant airflow passing through the air-classifier mill, the overall temperature remains relatively low, allowing for low-melting or softening point materials to be ground with this device



Figure 3. Hammermill



Figure 4 Air-classifier mill

Application examples for the air-classifier mill include a variety of heat-sensitive materials and minerals such as kaolin, talc and diatomaceous earth. Powder coating materials are ideally suited for this grinder, due to the need for temperature control in the mill as well as control of particle size on the top end of the distribution. Average particle sizes as fine as 30 microns are possible, depending upon the material and application.

Long-gap Mills

A further advancement in the area of impact milling has been the development of the long-gap mill. The design of the long-gap mill includes a variable rotor height to diameter ratio as well as an adjustable gap clearance between the impact hammers and the mill liner (See Figure 5).

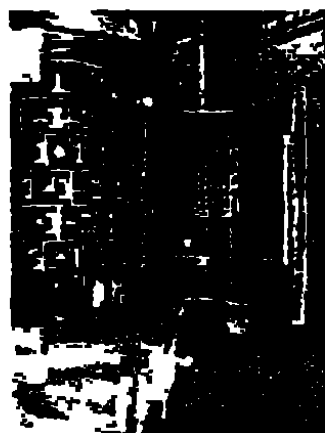


Figure 5 Long-gap mill

The unit includes an independent or single shaft classifier, for controlling the top end of the resulting particle size distribution. Grit-reduction in the processing of carbon-black is a popular application for the long-gap mill, as well as the simultaneous drying/grinding of a variety of minerals and metal oxides

Fluid Energy Impact Mills

Fluid energy impact (jet) mills utilize the principle of size reduction via particle-to-particle collision. Particles are accelerated in a high-velocity gas stream and are reduced by inter-particle collision or impact against a solid surface. Unlike impact milling devices, fluidized bed jet mills are suitable for the fine and ultra-fine size reduction of any material up to a hardness of 10 that can be fluidized by the expanding compressed gas in the grinding chamber. In addition, heat sensitive and abrasive materials can be easily processed in this type of mill.

Two general types of jet mills exist: those that do not have an internal classifier and those that do. A pancake or spiral jet mill has no internal classifier (See Figure 6). A fluidized bed jet mill incorporates an internal air classifier which allows material of a given fineness to exit the mill, while rejecting over-sized particles back into the grinding chamber for additional size reduction (See Figure 7).



Figure 6- Spiral Jet Mill



Figure 7 Fluidized-bed Jet Mill

Applications for these fluid energy mills include fine chemicals, ceramic materials including oxides, pharmaceutical powders, resins, waxes pigments, dyes, pesticides and rare earth powders. The fluidized-bed jet mill is specially suited for toners due to their requirement for very fine particles in narrow, overall particle size distribution

AIR CLASSIFICATION OF POWDERS

Air classification is used in processing industries where a high degree of uniformity is required in the finished product. Oversized particles can spoil the surface finish of plastics, paints and coatings, cause failure of electronic components and profoundly affect the flow or packing characteristics of powdered products. Particles that are too fine can also cause problems in powder performance and handling: flow properties deteriorate, airborne dust increases and process loss and waste can become a serious factor. In addition, very fine particles may cause ruboff in coating applications or cannot be recycled upstream in the process.

While the simplest means of separating a powder into two distinct fractions is through sieving, developments in air classification have resulted in more economical classification

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processes. Sieves depend on the size of the screen mesh to divide material into a coarse and a fine fraction. Screens are susceptible to blinding when high throughput rates are desired or if the product being classified contains moisture. Air classification is used where when screens cannot effectively make the separation, increased throughput is desired, plant space is limited or when the cutpoint is more easily varied with air classification.

Air classification relies on the fact that there are always two forces that affect particles in an airstream. mass force is exerted on the particle by acceleration due to gravity, inertia or centrifugal force. Drag force is always the force exerted on a particle by the surrounding medium as affected by its aerodynamic properties. Drag force depends on several variables including velocity of the particles in the surrounding medium, the density of the fluid and the drag coefficient of the particles.

Dispersion of solid particles is often the most critical material characteristic affecting classification. A classifier cannot effectively classify the individual particles into fractions if the particles cannot be physically separated and distributed evenly in the fluid. Moisture, oil or fat content or electrostatic interaction can inhibit dispersion and negate classification. Advancements in the dispersive capabilities of classifiers have been made which improve the performance and efficiency of these machines.

Centrifugal Classifiers with Mechanical Dispersion

A centrifugal classifier with mechanical dispersion (Figure 8) uses low energy dispersion to disperse material. Material enters the classifier and is dispersed at the top of the classifier wheel prior to actual classification. A further result of this dispersion is the equal dispersion around the classifier wheel. Airflow and classifier wheel speed determines the cutpoint for the material being classified.

A further method for improving the performance of classifiers by operating two classifiers in series. The first classifier's coarse fraction is highly dispersed as it is immediately fed to the second classifier. This results in improved product quality and especially higher product yield. A unique tandem classifier design has advanced the principle and applied it to a single unit. This new development in high performance classification (Figure 9) is intended for products that are from the coarse classification fraction.

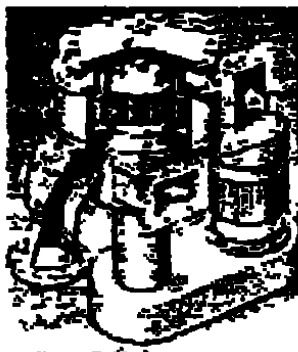


Fig. 8-Centrifugal classifier w/mechanical dispersion



Figure 9- Tandem Classifier

The tandem classifier has become an ideal machine for use in toner manufacture. In recent years, the particle size requirement has become finer, as the demand for higher image

quality in terms of resolution and color saturation has increased. An extremely sharp top size cut ($d_{97}=12$ micron) and a very sharp fines cut at 3 microns or less is required to achieve these desired parameters. The tandem classifier is capable of achieving these specifications in the finished product. Powder coating material, while slightly coarser than toner, also requires tight particle size control. While powder-coating materials are typically ground on a mechanical air classifier mill to control maximum particle size, further classification is required to remove the fraction of fine particles that remain after grinding.

CONCLUSION

Manufacturers of powder products continue to innovate in order to increase product quality and manufacturing efficiency. These product innovations have led to unique machine configurations designed to process materials to the more exacting specifications required in the marketplace.

The applications and examples outlined in this paper represent a small sampling of those that have been optimized through the use of new processing technology. In order to keep up with the changing demands of the powder processing industry, the science of size reduction and classification has advanced dramatically. All industries have been affected and can benefit from improved particle size distributions of powders and better overall control of the process.

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Micronization of potent compounds. An integration with the isolation technology

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He has 18 years of experience in micronization technologies and has registered patents for spiral Jetmill Systems. In 2002 he invented a new concept of miniaturization jet milling and feeding technology which has received awards worldwide.

Since 1996 Mr. Lasso has been managing the JETPHARMAS new technology development program and the company's FDA approved facilities in Europe and the US.

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• Containment, characterized from a negative pressure environment.

Considering the contrasting particularities of the above technologies, the combination is difficult to adequately execute but this is a must.

Micronization defined as controlling and reducing the size of powder particles into microscopic particles of 0.1-20 μm (microns). In particular, this technology has become evermore important to the pharmaceutical industry where particle size is a primary parameter. In parallel during the last 10 years the pharmaceutical market has increasingly utilized highly potent active ingredients (in 1990 the HPAs were 5% of the produced API, in 2002, they are increased to 30%). The increasing production and utilization of these potent and high potent compounds has forced the design and concept of isolators to consider both high containment levels as well as a high level of protection against Operator Exposure. The last 10 years have testified a dramatic upgrade in the requested containment systems, i.e. the first isolators installed in the pharmaceutical field were for sterile applications, and then they were adapted to containment applications. This concept is currently no longer acceptable. 10 years ago the containment (OEL) requested for these applications was about 50 $\mu\text{g}/\text{m}^3$, later it was updated to 10 $\mu\text{g}/\text{m}^3$, then to 1 $\mu\text{g}/\text{m}^3$ and now is being reduced to 0.1 $\mu\text{g}/\text{m}^3$. This tendency follows the increased potency of products and the knowledge of R&D products, that 10 years ago were more generic.

To address this actual need, two different technologies must be strictly connected with Micronization in Containment:

- Micronization, Fluid Jet Mills technology using high-pressure gas (from 7 to 12 bar); and

The Fluid Jet Mill technique is well established and well known in the field of the drug delivery for lung diseases, as it allows to accelerate the absorption of medication in comparison with absorption through the intestinal tract, allowing smaller dosages with the same efficacy. The micronization technologies are considered a relatively new technology applied to several product application and it is being utilized more for the advantages obtained using different "dosage form," especially when it is utilized for potent compounds.

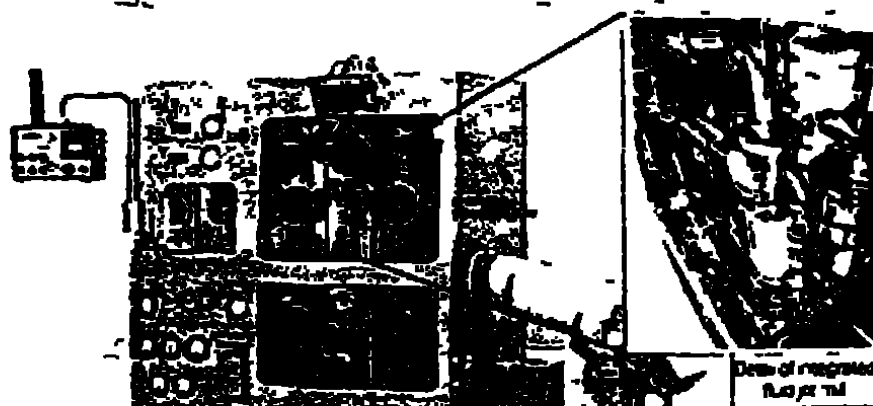
The most widely used instrument for the micronization of pharmaceutical active ingredients is the Spiral Jet Mill, introduced in the late 1940s. The spiral jet mill technology operates under strictly controlled constant temperature and pressure conditions and can reach very fine particle sizes, from 0.1 to 20 microns; these features - constant temperature and very fine particles - being not easily achievable with other micronizing technologies.

The micronization process with spiral jet mill begins with the feeding of powder particles (tangentially) into a (cylindrical) milling chamber by means of a Venturi system that creates an initial negative pressure, followed by a sub-sonic acceleration (50 m/sec). A series of "De Laval" nozzles, quickly increases the acceleration of the particles to a supersonic speed (300-500 m/sec) in a spiral movement. The micronization is generated by the collision between the particles entering and the particles rotating into the milling chamber (using the kinetic energy). The micronized particles are

transported to the centre by the exhaust air. At the same time centrifugal force retains the larger, heavier particles at the periphery of the milling chamber, where they continue to accelerate until collision reduces the particle size.

Inside of a jet mill unit, there is a positive high pressure.

Figure 1 - Glove box Isolator for HPAs



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Company of JETPHARMA

(up to 12 bar), and this particular technology has to be integrated into an Isolator. The challenge is: how to accomplish this? The Jet Mill concept could appear to dramatically contrast with the basic concepts of the isolator itself, which has an internal environment under constant negative pressure. As each technology are radically different conceptually; to control the SAFETY and the PERFORMANCE of both containment and milling processes, it is necessary to create a perfect dialogue, or feedback between them.

Though two different technologies, each systems process parameters must perfectly communicate in order to avoid compromising safety and performance of each. The perfect feedback across the system and the reaction of each system is difficult, but necessary, to achieve. The goal is a perfect integration of all process controls. a true integration of two technologies into one system. Nothing less will allow high performance. We use as example the difficulties encountered when creating a high-performance race-car: the engine is one important component, but we must also consider the perfect combination with the other components to generate an excellent result.

How to design and create the right combination Isolator/Micronizer?

- Firstly, the designer needs the end-user's perspective and the design expertise of a manufacturer of both technologies in order to focus all particularities of each process, thus creating the optimised process dialogues. A typical mistake is encountered when a generic Jet Mill is adapted into generic Isolators without particular modifications, or worse, ill-conceived modifications. This situation is quite frequent and is due to generic knowledge of the user, sometimes addressed in "economy" solutions present on the market.

In this application field any compromise in term of safety and performance is not welcomed.
COMPROMISE = RISK = HAZARD X EXPOSURE

- The designer must have the necessary knowledge to modify the Jet Mill unit to be integrated into an Isolator in order to reach the configuration required
- The designer must be able to create a tailor made Isolator around a Jet Mill able to guarantee the performance in this particular configuration.

The **MUST** in the design criteria for a potent compound Isolator has to focus especially on the **HIGH LEVEL of SAFETY** of the operator and the **CONTAINMENT LEVEL**. That means the same safety level should be maintained even during accidental and/or emergency situations.

Considering an Isolator configured with a Jet Mill enclosed, some of these situations are summarized as

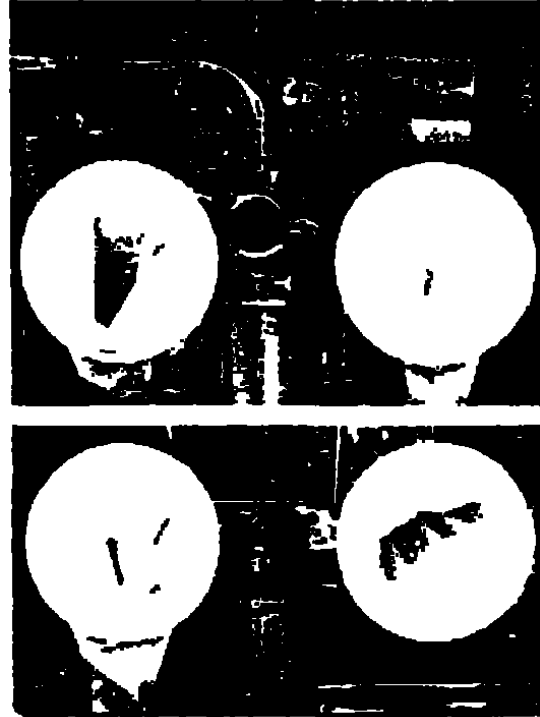
- failure of electrical power;
- breaking of elements (as Gloves) by incorrect utilization,
- incorrect fittings or leakage by process gas pipe lines

The worst case situations mentioned above have also to be considered in the safety design criteria of an Isolator-Micronizer: that means to constantly measure the Isolator performances (OEL) expressed in $\mu\text{g}/\text{m}^3$

The conclusions are summarized in two words

Safety
 Speaking of potent, high potent, and cyto-toxics the word safety is a **MUST**. Any compromise accepted with the technology in use is translated in a potential future risk for the operator. Actually the OEL requested $< 1 \mu\text{g}/\text{m}^3$ is a starting point, the ultimate goal is to lower this value down towards the range of $0.1 \mu\text{g}/\text{m}^3$ TWA (8 hours time-weighted-average). But what does an OEL $0.1 \mu\text{g}/\text{m}^3$ mean? It means that this value must be achieved, monitored, and guarantee within life cycle of the Isolator during any

Figure 2 - Alternative ergonomic solution: operator's comfort of the working arm



circumstances and events, for example during emergency situations, maintenance in/out process, leakage/breakage, etc.

Performances
 The Jet Mill must be conceived and tailor made for an Isolator configuration. As example the containment for this kind of JetMill (alone) must be quite high in order to maximize the containment performance in the Isolator.

The ergonomics is another important aspect of the Isolation technology. This means that all components of the JetMill must be light and easily disassembled. For a laboratory scale JetMill the Isolator is normally provided with gloves in order to reach the internal environment through the front panels where one or more pairs of gloves are located. For a production scale JetMill in Isolation there should be one or more Half Suits in order to maximize the ergonomic. This solution allows a better efficiency when the parts to be manipulated into the Isolator are quite big and heavy, as can be the case with production systems. In effect, the Half Suit has similar ergonomics as compared to 6-8 pairs of Gloves.

These two goals "safety" and "performance" are achievable only when a user creates the technology

CONTENIDO

- 1 Principios y métodos para incrementar la disolución y absorción de fármacos**
 - 2 Incremento biodisponibilidad de fármacos muy poco solubles en agua**
 - 3 Mecanismo para incrementar la disolución del Diazepam Temazepam en dispersiones sólidas de PEG 6000**
 - 4. Tecnología supercrítica fluida para la reducción del tamaño de partícula**
 - 5 Incremento de la solubilidad del Intraconazol utilizando la tecnología supercrítica fluida**
 - 6 Estado morfológico sólido de partículas preparadas por proceso supercrítico fluido**
 - 7 Diseño del equipo para micronización fluida supercrítica acorde con las BPM**
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Complejos multicomponentes de Sulfametuzol**
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 - 12. Efecto del tamaño de partícula en la biodisponibilidad de la Ciclosporina en dispersiones submicrón**
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 - 14. Caracterización físico química de soluciones sólidas preparadas por extrusión por fusión**
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 - 17 Precipitación controlada una tecnología para la obtención de nanopartículas con rápida disolución**
 - 18 Establecimiento de las especificaciones del fármaco y del medicamento**
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The aqueous solubility of drug substances plays an important role in the formulation of drug dosage forms. For the oral route of administration it is well experienced that, unless the substance has an aqueous solubility above 10 mg/ml over the pH-range 1-7, then potential absorption problems may occur. A solubility less than 1 mg/ml is likely to give dissolution-rate limited absorption because solubility and dissolution rate are interrelated.

The proportion of drug substances showing aqueous solubilities below 1 mg/ml seems to increase steadily along with increasing specificity in the biological action of new chemical substances. A review of new monographs (1992-1995) in the European Pharmacopoeia by the author shows that more than 40 per cent of the drug substances have aqueous solubilities below 1 mg/ml, and that 32 per cent have an aqueous solubility below 0.1 mg/ml. The implementation of dissolution and absorption enhancing methods is, therefore, a major field in the formulation of drug dosage forms, in particular for the oral route of administration.

A wide range of principles and methods is available for the purpose of enhancing dissolution and/or dissolution rate of 'low-solubility' substances for example

- selection of salt form for weak acids and bases,
- reduction of particle size and, thereby, increased specific surface area,
- use of surfactants for increased wettability
- complex formation with excipients, e.g. hydrophilic polymers or cyclodextrins,
- preparation of solid dispersions,
- change of crystal form by precipitation with hydrophilic polymers,
- lipophilic formulations, i.e. emulsions, microemulsions etc.,

Selection of an appropriate salt form - or in case of liquid preparations, adjustment of pH - is first choice for acidic and basic drug substances. The selection of a salt form is essentially a preformulation task because the choice has implications to the regulatory aspects of drug research and development. The survey of monographs in the European Pharmacopoeia shows that the main part of substances having aqueous solubilities above 10 mg/ml was hydrochlorides, sulphates, maleates, citrates etc. of basic drugs or for acidic drugs potassium, sodium, calcium or other salts. Once the proper drug substance has been selected, preformulation studies are needed to characterise the physical and physico-chemical properties of the substance, e.g. pKa, pH-solubility profile, intrinsic solubility and dissolution rate, polymorphisms, hygroscopicity, log P etc. Although these characteristics may give some idea about potential absorption and bioavailability problems, there is, at present, insufficient knowledge about the systematics on how to formulate a given substance. It is difficult to predict the factors limiting the dissolution and absorption rates. It is believed that present industrial practice is the trial and error method based upon laboratory experiments and animal testing.

Marketed formulations of very slightly soluble substances, for example steroids, show that particle size reduction and hence, increased specific surface area are important means to achieve a satisfactory dissolution rate. In principle, the lower the aqueous solubility, the lower particle size is required. For the practically insoluble substances (< 0.1 mg/ml) the required particle size is so low that it may be technically difficult to prepare the desired size range. Significant progress has been made in recent years in the field of 'nano-particle' technology. On the other hand, physical instability of the size distribution is introduced when the size range is reduced to micrometer and sub-micrometer scale.

Physical instability is a major problem also with other dissolution enhancing methods where the state of the drug substance is made 'high energetic' i.e. solid dispersions and coprecipitates with hydrophilic polymers where the drug substance typically is present in an amorphous state. Despite the great interest these systems had 1-2 decades ago, few products based on such means have

been marketed

Physical and chemical stable compounds can be made by the synthesis of inclusion complexes with cyclodextrins. The potentials of the various types of cyclodextrins for solubility and absorption enhancement are well documented in the literature. In this field, there is also a limited number of marketed products probably because documentation of the safety aspects of cyclodextrins for the various routes of administration are not yet fully clarified. Another reason might be that manufacturers apply for marketing authorisation of the inclusion complex as such and not for a formulation based upon the cyclodextrin.

Research on the effect of the luminal liquids on dissolution and absorption of low solubility drugs has disclosed the significant role of natural surfactants such as bile salts, degradation products of triglycerides and enzymes for the dissolution, solubilisation and transport of hydrophobic substances. Effects of fat-enriched diets on the bioavailability of for example giteofulvin can probably be attributed to effects of the formation of mixed micelles and solubilisation of the drug substance. It is likely that the effects of the luminal liquids are dependent on the hydrophobicity as expressed by the log P value of the drug substances.

The newest trend in the formulation of low-solubility drugs is accordingly the use of so-called lipidic formulations, in particular microemulsions and other self-emulsifying systems which can dissolve a sufficient amount of the substance. Microemulsions are liquid systems which can be dispensed in the form of soft capsules. The absorption promoting effect of such systems may be attributed to the presence of triglycerides as well as the direct effect of the high concentration of surfactants upon the permeation of the gut wall.

An apparently over-looked means to improve drug dissolution is the possibility to form soluble complexes by means of widely accepted excipients, for example to make benefit of the reactive sites in the molecule and their interactions by hydrogen bondings with excipient materials. For example acetylates may interact with boric acid or povidone to create a soluble compound. If the compound is stable and the complex constant not excessive, this might be a fruitful way to enhance the drug dissolution.

In the presentation practical examples of dissolution enhancing methods are given. Complex formation between diflunisal and borate buffer, preparation of an inclusion complex between steroids and beta-cyclodextrin, and preparation of a co-precipitate of sulfasalazin and povidone.

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Lipid-Based Systems for Oral Drug Delivery: Enhancing the Bioavailability of Poorly Water Soluble Drugs

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Eli Lilly and Company

Developing an effective oral dosage form is the *sine qua non* for the successful launch of a new drug product in the marketplace. For well over a decade, the pharmaceutical industry has embraced combinatorial chemistry as a means to expedite the discovery of new drug molecules. This technology, which utilizes increasingly available drug receptor structural information, often results in the synthesis of polycyclic, highly hydrophobic compounds with poor aqueous solubility. Indeed, it has been estimated that nearly half of all potential new drug molecules identified by combinatorial chemistry fit the category of poorly water-soluble. Although the inherent lipophilicity of many of these compounds often allows for facile permeation of gastrointestinal barrier membranes, the combined impediments of poor aqueous solubility and slow dissolution rate frequently result in low and erratic absorption. This is particularly problematic for compounds requiring high levels of systemic exposure to achieve clinical efficacy or for compounds with a narrow therapeutic index, where erratic bioavailability translates into either unexpected toxicity or treatment failure. In many instances, an otherwise promising new chemical entity (NCE) will be removed from development due to the inability to formulate an acceptable oral dosage form using conventional excipients. For some time now, a considerable gap has existed between our ability to synthesize poorly water-soluble NCEs and our ability to effectively and efficiently formulate these compounds for oral delivery.

Excipients used in conventional oral formulations perform the following functions.

- Bind and provide bulk to the dosage form
- Facilitate or control drug release from the excipient matrix
- Allow manufacturing on high-speed, automated production equipment

Conventional formulations have proven cost-effective, relatively easy to produce and are well-suited to drugs for which an efficacy dose can be readily solubilized in the gastrointestinal tract (GIT). Compounds amenable to this formulation approach include either highly soluble drugs or highly potent, poorly soluble drugs for which the dose is sufficiently small to permit rapid and complete solubilization in the GIT.

Traditional approaches to improving the bioavailability of poorly water-soluble drugs most frequently involve salt selection or, less frequently, prodrug synthesis.

Salt Selection

For compounds possessing ionizable functional groups, the method of choice for improving absorption is through salt formation. Salts of poorly soluble compounds typically dissolve more quickly in the GIT, thus improving absorption, which is typically limited by the slow dissolution of the parent free acid or base compound. Limitations to this approach involve identifying a non-toxic counter-ion that will yield a pharmaceutically-acceptable salt. Additional salt requirements include the ability to prepare, in sufficient yield, a chemically stable, non- or minimally hygroscopic crystalline product of sufficiently high melting point to withstand milling and formulation processing.

Prodrug Synthesis

A less frequently employed method for improving NCE solubility involves attaching a solubilizing moiety such as an amino acid which is cleaved by an endogenous enzyme subsequent to absorption, thereby regenerating the active parent molecule. The added complexity of prodrug development, which requires additional studies for verifying bioconversion and demonstrating lack of toxicity, has limited the application of this approach.

Another infrequently used method for improving the bioavailability of poorly soluble compounds involves stabilizing the drug in the amorphous, or 'high energy solid' state, thereby facilitating its dissolution relative to that of the stable crystalline form. Although this technology has been effectively applied in a few instances, it is not a method of choice due to the metastable nature of most amorphous solids, which can spontaneously revert to the less soluble, stable crystalline form, with a concomitant reduction in bioavailability.

While several novel approaches to improving NCE solubility have been proposed and have in some instances formed the basis for the creation of companies, all are basically variations on 3 central themes discussed below.

Particle Size-Reduction

Particle size-reduction effectively increases the surface area to volume ratio, thereby increasing the dissolution rate in the GIT and promoting absorption. Various technologies used for particle size reduction include micronization, nanonization and, most recently, super critical fluid technology, which deposits nanometer-sized drug particles on a pharmaceutically-acceptable support matrix. Particle size-reduction must include a method for preventing aggregation, which commonly occurs after milling and effectively negates any improvement in dissolution effected by particle size reduction.

Solubilization in the Explant Matrix

Formulations which solubilize a drug in a lipid or water-miscible co-solvent system can provide dramatic improvements in bioavailability by eliminating the need for pre-absorptive dissolution in the GIT. Due to their immiscibility with water, lipids can maintain a poorly soluble drug in solution unlike water miscible co-solvent systems, which often precipitate the drug following dilution in the predominantly aqueous GI fluids. Lipid systems can also be formulated to have self-emulsifying properties, which provides further enhancement to absorption by increasing the surface area of the lipid dispersion presented to the GIT.

Inclusion Complexes

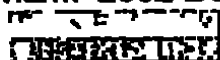
Cyclodextrins are water-soluble molecules containing a hydrophobic pocket, which can form a dissociable inclusion complex with a hydrophobic drug molecule. This typically results in improved water solubility and bioavailability for poorly water-soluble drugs.

The application of this approach is limited by the ability of the cyclodextrin to form the inclusion complex, which is strongly dependent on the molecular characteristics of the drug molecule and can be very specific.

Standard Requirements for an Oral Formulation

The success of any oral formulation is determined by several factors, including

- Development of a stable, market-image product amenable to efficient and cost-effective mass production on conventional or readily available manufacturing equipment
- Availability of simple and accepted testing methods to assure product quality and batch-to-batch consistency
- Acceptance of the formulation by regulatory agencies
- Ability to manufacture the formulation 'in-house'



Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions

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Solid dispersion literature, describing the mechanism of dissolution of drug-polyethylene glycol dispersions, still shows some gaps, (A) only few studies include experiments evaluating solid solution formation and the particle size of the drug in the dispersion particles, two factors that can have a profound effect on the dissolution (B) Solid dispersion preparation involves a recrystallisation process (which is known to be highly sensitive to the recrystallisation conditions) of polyethylene glycol and possibly also of the drug. Therefore, it is of extreme importance that all experiments are performed on dispersion aliquots, which can be believed to be physico-chemical identical. This is not always the case (C) Polyethylene glycol 6000 (PEG6000) crystallises forming lamellae with chains either fully extended or folded once or twice depending on the crystallisation conditions. Recently, a high resolution differential scanning calorimetry (DSC)-method, capable of evaluating qualitatively and quantitatively the polymorphic behaviour of PEG6000, has been reported. Unraveling the relationship between the polymorphic behavior of PEG6000 in a solid dispersion and the dissolution characteristics of that dispersion, is a real gain to our knowledge of solid dispersions, since this has never been thoroughly investigated. The aim of the present study was to fill up the three above mentioned gaps in solid dispersion literature. Therefore, physical mixtures and solid dispersions were prepared and in order to unravel the relationship between their physico-chemical properties and dissolution characteristics, pure drugs (diazepam, temazepam), polymer (PEG6000), solid dispersions and physical mixtures were characterised by DSC, X-ray powder diffraction (Guinier and Bragg-Brentano method), FT-IR spectroscopy, dissolution and solubility experiments and the particle size of the drug in the dispersion particles was estimated using a newly developed method. Addition of PEG6000 improves the dissolution rate of both drugs. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface of drug crystals after dissolution of the polymer. Formulation of solid dispersions did not further improve the dissolution rate compared with physical mixtures. X-ray spectra show that both drugs are in a highly crystalline state in the solid dispersions, while no significant changes in the lattice spacings of PEG6000 indicate the absence of solid solution formation. IR spectra show the absence of a hydrogen bonding interaction between the benzodiazepines and PEG6000.

Furthermore, it was concluded that the reduction of the mean drug particle size by preparing solid dispersions with PEG6000 is limited and that the influence of the polymorphic behavior of PEG6000 (as observed by DSC) on the dissolution was negligible

ENHANCING WATER-SOLUBILITY OF POORLY SOLUBLE DRUG, ITRACONAZOLE WITH WATER-SOLUBLE POLYMER USING SUPERCRITICAL FLUID PROCESSING

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ABSTRACT SUMMARY

To improve solubility and bioavailability of a poorly water-soluble anti-fungal agent, itraconazole, its solid dispersion particles were prepared using supercritical fluid anti-solvent (SAS) processes with water-soluble carriers, hydroxypropylmethylcellulose (HPMC). In each case, the morphology was characterized by scanning electron microscopy (SEM), and the polymorphic characteristics were investigated by differential scanning calorimetry (DSC) analysis and X-ray diffraction (XRD) method. And water solubility of itraconazole was also determined. At the DSC profile, all the processed products showed a wider melting endotherm with a lower heat-flow peak than that of pure itraconazole. XRD profile also reflected its decreased crystallinity. After the processing, we obtained its solid dispersion nanoparticles, together with remarkable water-solubility and bioavailability.

Keywords: solubility, bioavailability, itraconazole; supercritical fluid anti-solvent, nanoparticles

INTRODUCTION

Itraconazole is one of the poorly water-soluble drugs and also many efforts were made to improve its solubility including conjugation with hydroxy- β -cyclodextrin¹, preparation of fluidized-bed coating of pellets or melt extrusion with water-soluble polymers and so on^{2,3}. However, enhancing its water solubility remains challenging works up to these days and many patents have been issued for this purpose. In this study, we have used supercritical fluid processing to make a solid dispersion of the drug with water-soluble polymer, HPMC for the purpose of enhancing its water-solubility.

EXPERIMENTAL METHODS

Preparation of solid dispersion particles by SAS

Itraconazole and water-soluble polymer, HPMC were dissolved in mixture of methylene chloride and ethanol as a feed solution. And then solid dispersion particles were prepared by spraying the solution into the vessel filled with supercritical carbon dioxide as an anti-solvent^{4,5}.

Scanning electron microscopy

Samples were sputtered-coated Au/Pd using a vacuum evaporator and examined using a scanning electron microscope at 20 kV accelerating voltage at the magnification of 5000 $\times$.

Differential scanning calorimetry

DSC was performed on itraconazole raw material and SAS processed particles using Rheometric Scientific model DLOS. Samples of 3~4 mg were sealed in aluminum pans and the DSC thermograms were recorded at heating rate of 10 $^{\circ}$ C from 40 $^{\circ}$ C to 200 $^{\circ}$ C.

X-ray diffraction

X-ray diffraction patterns of the samples were obtained by X-ray diffractometer. Each diffractogram was recorded from 10 $^{\circ}$ to 70 $^{\circ}$ of angle (2 θ), at a scanning speed of 3 $^{\circ}$ /min with a step size of 0.01 $^{\circ}$. Cu-K α radiation was used as the X-ray source, which was operated at the voltage 40 kV and the current 45 mA.

Solubility test

The solubility of prepared particles was investigated in the pH 1.2 simulated gastric juice (without pepsin). The simulated gastric juice of 6 ml was added to the particles equivalent to 6 mg itraconazole in a test tube. The tube was vortexed for 5 minutes and then sonicated for 30 minutes. It was kept on shaking with the conditions of 60 rpm, 37 $^{\circ}$ C for 24 hours in the shaking water bath. A portion of the solution was taken and filtered with a membrane filter (0.45 μ m). The concentration of itraconazole was determined by HPLC.

In vivo absorption test

In order to investigate the bioavailability of the prepared particles, in vivo absorption tests were carried out as follows. The product shown highest solubility and Spornox tablet (marketed product) were orally administered into the male Sprague-Dawley rats, respectively, in a dose of 20 mg itraconazole/kg body weight of the rat. Drug concentrations in plasma were determined by HPLC method.

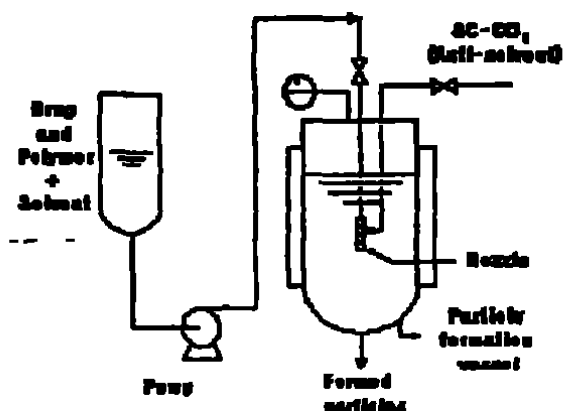


Fig. 1. Schematic diagram of the SAS equipment

RESULTS AND DISCUSSION

Particle morphology

To investigate the effects of the process parameter temperature and pressure on morphology several experiments were performed in the range of 80~150 bar at 45°C and also 80~150 bar at 60°C. The shape of untreated drug particles was irregular and crystalline and particle size distribution was also broad. On the contrary, SAS-processed particles had a relatively regular and spherical shape with narrow size distribution. The particle size of all the samples was reduced to less than 1 µm.

The smaller particles were formed at higher pressure. Smallest particles were obtained at 45°C, 100 bar. Such results can be explained that increased density of supercritical fluid with increasing pressure caused enhancing its solvating power for the solvent. With the same way, much smaller particles will be expected to prepare at a higher-pressure conditions.

DSC and XRD

The DSC thermogram of itraconazole exhibited an endothermic peak at about 168°C with a enthalpy of 121.89 J/g, corresponding to its melting point. The location of endothermic peak and enthalpy (ΔH) for the prepared particles were determined. All the processed products showed a melting endotherm with much lower heat-flow peak than that of pure itraconazole and the location was shifted to 163~165°C. A remarkable reduction of the intensity of itraconazole endothermic peak suggests decrease in its crystallinity. Further, at the condition of 60°C, 100 bar, the endothermic peak was not observed. It means an alteration in the physical state of itraconazole from crystalline state to amorphous state during SAS processes.

In the x-ray diffractogram of raw itraconazole powder, many diffraction peaks with high intensity were observed due to its crystallinity. While the particles prepared at the conditions of 45°C, 150 bar showed smallest size at SEM analysis, they still have diffraction peaks showing crystallinity of itraconazole. This data and DSC results suggest that they are mixture of small solid dispersion particles and crystalline itraconazole. On the other hand, the particles prepared at the conditions of 60°C, 100 bar showed the smaller XRD patterns with HPMC and any peaks for crystalline itraconazole were not observed. This result is identical with the DSC thermogram of the sample and indicates that the amorphous state of itraconazole was formed at that processing condition.

Solubility

The solubility data was shown at Table I. The solubility studies have shown that SAS-processed products have much more enhanced solubility compared to the raw material.

In vivo absorption

Fig. 2 shows the average serum concentration-time curves of marketed product, Sporanox tablet and prepared particles by SAS which shows highest solubility after oral administration.

It can be said that from the pharmacokinetic data, bioavailability of prepared particles has been enhanced as much as marketed product.

Table I Solubility data from itraconazole powder and SAS processed products (n = 3).

	Temp (°C)	P (bar)	Solubility (µg/ml)
SAS-processed products	45	100	81.49±8.53
		120	11.63±0.41
		150	5.51±1.19
	60	100	122.40±1.70
		120	16.14±0.69
		150	5.22±0.31
Raw itraconazole	-	-	0.23±0.04

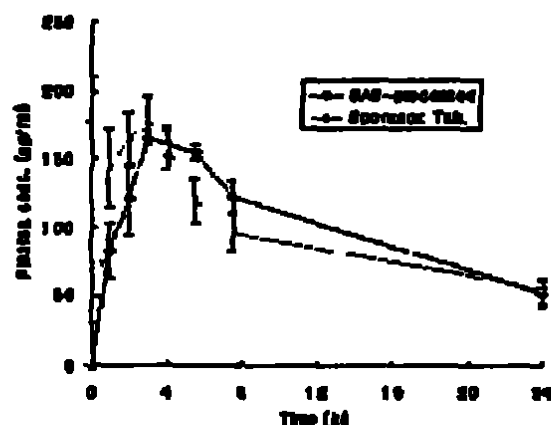


Fig. 2 Average plasma concentration vs. time of SAS processed particles and Sporanox tablet (n = 3)

CONCLUSIONS

Supercritical anti-solvent method is a promising new technique for preparing size-reduced particles and enhancing solubility and bioavailability of poorly soluble drug. And in order to reduce particle aggregation and stable bioavailability, further works are needed including adding surfactants or other excipients.

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Supercritical Fluid Technology for Particle Size Reduction

Principal Investigator: Steven L. Nail

Graduate Student Investigator: Greg Sacha

Project Status as of January 1999

Broad Objective:

Determine the feasibility of using supercritical fluid technology as a unit operation for particle size reduction which is precisely controllable, compatible with aseptic operations, and amenable to containment of potent drugs.

Specific Aims:

- 1 Build a research/pilot system for particle size reduction using the supercritical non-solvent approach.
- 2 Determine critical process variables affecting particle size and particle size distribution, as well as the reproducibility of these parameters when the process is repeated under the same set of conditions
- 3 Compare the degree of crystallinity of supercritically "milled" drug with that of the same drug after mechanical particle size reduction
- 4 Determine, using suitable model drugs, the degree to which residual carrier solvent is a problem when using the supercritical non-solvent technique.

Background and Significance:

A uniformly small particle size and a narrow particle size distribution are often critical quality attributes of pharmaceutical solids, particularly for sparingly soluble drugs and for drugs intended for aerosol administration. The reduction of particle size can affect such properties as dissolution rate, solubility, accessibility to the lungs and, therefore, bioavailability. The processing required to obtain these desirable attributes can adversely affect the physical properties of the pharmaceutical solid. Properties that may be affected include powder flow, agglomeration, and suspendability, which can be critical in the manufacture of such dosage forms as injectable suspensions and dry powder aerosols.

Current methods of reducing particle size utilize mechanical methods such as the ball mill, hammer mill, or fluid energy mill. The energy input from these operations may induce amorphous regions in crystalline material. Water may be absorbed by the amorphous regions and lead to physical or chemical instability of the product during subsequent processing or storage. This was observed after milling albuterol sulfate and was reported by Ward and Schultz (1995).

For injectable suspensions, in addition to providing consistently small (no more than a few microns) particles, there is the additional concern for sterility of the final product. Since the final suspension cannot, in general, be terminally sterilized, a sterile powder must be combined with the sterile vehicle using aseptic processing. While sterilization of the vehicle can be easily done by filtration, production of

a sterile powder is more challenging. The most common method for powder sterilization is ethylene oxide gas, however, ethylene oxide is a surface sterilant only, and will not penetrate the drug crystal to kill occluded microorganisms. For this reason, many pharmaceutical companies have invested millions to carry out the crystallization process under aseptic conditions. After aseptic crystallization, the drug is micronized, followed by ethylene oxide sterilization in order to kill any microorganisms on the surface of the drug particles prior to aseptically incorporating the drug into the suspension vehicle. While this process is effective, it does not eliminate the use of ethylene oxide. This is a disadvantage, since ethylene oxide is under continuing regulatory scrutiny from the standpoints of worker exposure to the gas itself, as well as residual levels of EtO and EtO byproducts in the drug product. This method of processing points to the need for a size reduction process which would combine aseptic crystallization with aseptic particle size reduction, thus providing a more efficient process and eliminating the need for ethylene oxide sterilization.

Containment of drug powders during pharmaceutical processing is an ongoing concern from the standpoint of worker safety, particularly with the trend in drug discovery toward lower doses of more potent compounds. The need for containment is most evident in size reduction operations, whether by conventional milling or by air micronization. Both processes generate a considerable amount of dust, which is difficult to contain adequately. A size reduction process which operates as a closed system, generating no dust, is a largely unmet need in the pharmaceutical industry.

Use of Supercritical Fluid Technology for Particle Size Reduction

Supercritical fluids are highly compressible, have high diffusivities, liquid-like densities, and viscosities intermediate between the gas and liquid extremes. These properties offer, in principle, a process which could provide consistent small particles with a narrow particle size distribution where crystallization and size reduction take place simultaneously in a closed, aseptic environment.

There are two basic approaches to using supercritical fluids for size reduction. The first is rapid expansion of a supercritical solution (RESS), where drug is first dissolved in a supercritical fluid, then the supercritical solution is rapidly expanded through a nozzle. This causes a sudden large decrease in solubility of drug, and an aerosol of fine particles is created as a result of the rapid expansion. The second approach is called the supercritical non-solvent approach (SAS), where drug is first dissolved in a carrier solvent, where the carrier solvent is at least partially miscible with the supercritical fluid and the supercritical fluid is a non-solvent for the drug. Mixing of the carrier solution with the supercritical phase causes, in principle, precipitation of a fine particles of drug.

This project uses the SAS approach, primarily because the main limitation of the RESS approach is that the drug must be soluble in the supercritical phase. The SAS approach seems more flexible, since this requirement is avoided.

Description of Equipment:

A photograph of the system is shown in Figure 1. It consists of a 2 liter, bolted closure, stirred autoclave (Autoclave Engineers) which houses supercritical carbon dioxide (CO₂) and acts as a precipitation vessel. The autoclave is jacketed for temperature control by a circulating water bath. A steady flow of CO₂ through the autoclave is established using a 6000 PSI double-ended gas compressor (Newport Scientific). Constant system pressure is maintained by a backpressure regulator. The system pressure is read by a test gauge which monitors the pressure of the supercritical fluid entering the autoclave. A feed solution containing a drug and an organic solvent is injected into the top of the autoclave by a double-headed high pressure metering pump (Milton-Roy) through stainless steel, 0.0625 inch OD tubing. The

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supercritical fluid / organic solvent mixture exits through the bottom of the autoclave leaving behind the precipitated drug. The precipitation vessel contains a collection basket which is constructed to slide into the cylindrical bore of the autoclave (Figure 2) The bottom of the basket contains a removable 2 mm sintered metal filter plate (Fuji) which collects the precipitate, allowing the supercritical fluid phase to pass through. An inverted cup style baffle with four holes in the top is placed over the filter plate to avoid the possibility of fluid passing through the vessel without adequate mixing. To further facilitate mixing, the autoclave is equipped with variable speed, turbine agitator.

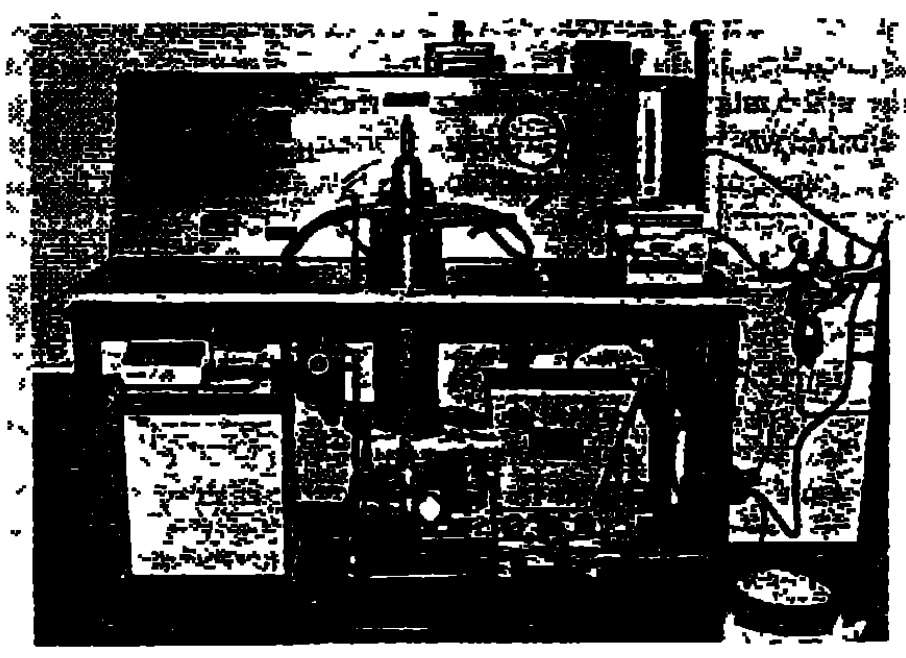


Figure 1 - Photograph of Supercritical Fluid "Mill"

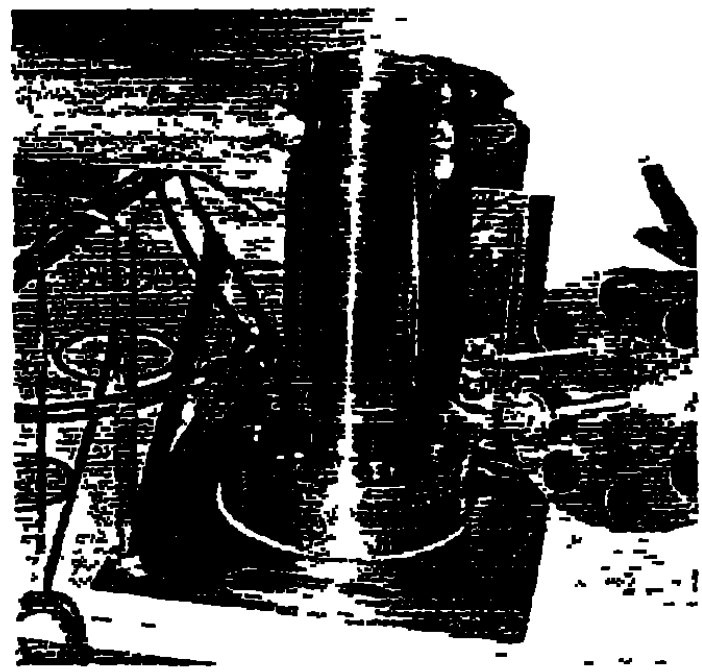


Figure 2 - Photograph of Inner Basket in Autoclave for Collection of Powder

Current Project Status

Set up of the equipment was complete as of December 1996 and thereafter the operating limits of the equipment were determined. The operating limits included determining the maximum and minimum carbon dioxide flow rates at specific pressures, and calibration of the feed solution flow rate as well as the speed of the agitator

Next, recrystallization experiments began using aspirin as a model compound. It was determined through these experiments that aspirin is soluble in supercritical carbon dioxide and, therefore, would not be suitable for SAS recrystallization. Methylprednisolone acetate (MPA) was chosen as the new model compound based on its use in previous recrystallization experiments completed by W. J. Schmitt. Experiments were conducted by feeding a 10% subsaturated solution of methylprednisolone acetate and tetrahydrofuran (THF), at 2.5 ml/min, into supercritical carbon dioxide at 2300 PSI and 45°C. A steady state flow of carbon dioxide was maintained throughout the experiments which included a post-precipitation extraction time of one hour. The product yield was determined at the end of each experiment as well as characterization of the resulting powder.

Particle size analysis of MPA was completed using the Microtrac Full Range particle size Analyzer. Solutions of MPA (1mg/ml) and 0.1% Tween 80 in distilled water were used for each analysis. Three samples were analyzed for each run and the average value was reported. MPA as received was milled by Pharmacia & Upjohn using a fluid energy mill and it was found that at least 50% of the particles had a diameter of 2.82 µm or less with a standard deviation of 0.01 µm by Microtrac analysis. Three different runs operated under the same conditions were tested by Microtrac analysis and the reported value represents the average of the three runs. At least 50% of the particles of recrystallized MPA had a diameter of 16.14 µm or less with a standard deviation of 1.71 µm. Figure 3 shows the average particle size distributions recorded for MPA before and after recrystallization. The particle size

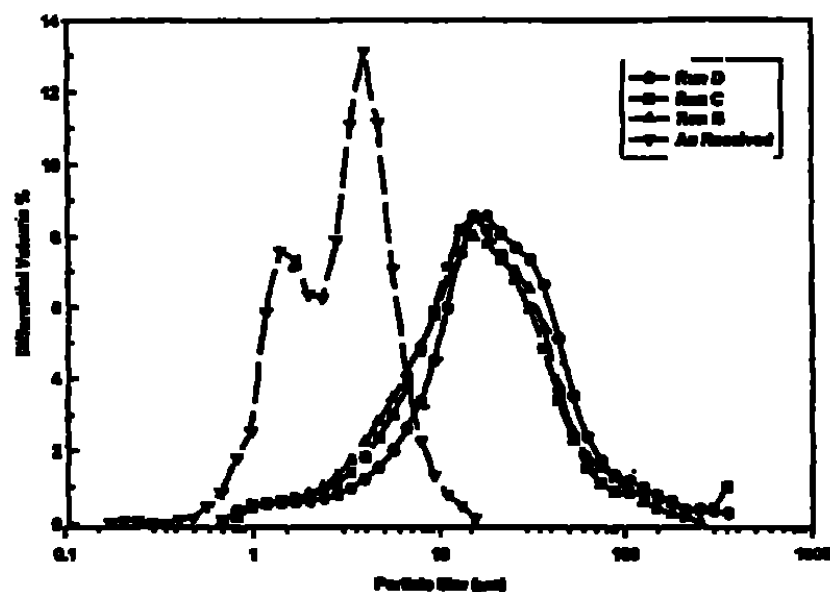


Figure 3 - Particle Size Distributions of Methylprednisolone Acetate for Starting Material and Three Runs of Drug "Milled" by Supercritical Carbon Dioxide

distributions for the recrystallized MPA are labeled as runs B, C and D. The average particle size obtained after recrystallization is still larger than the value reported by Schmitt, et al, of 3 µm for recrystallization under similar operating conditions. Further adjustment of the equipment, such as spacing the injection ports 180° apart, may improve the particle size obtained.

Plan for Second Quarter 1997

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The objectives for the next quarter include the addition of a spray nozzle to reduce the feed solution droplet size in order to obtain a mean particle size of not more than 5 μ m. The nozzle will consist of either a laser drilled plate or a fused silica capillary tube having orifice sizes of 25-100 μ m. Critical process variables will then be identified, including temperature, pressure, bleed rate of carbon dioxide from the autoclave, feed solution flow rate, and degree of saturation of the feed solution. Quantitation of residual solvent will be done by gas chromatography, and the effect of post-precipitation extraction time on residual solvent level will be determined.

Literature References:

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The Process

The basic process by which CntiTech will produce sub-micron drug particles involves a procedure referred to as Precipitation with Compressed Antisolvent (PCA). PCA precipitation is based upon unique properties of carbon dioxide when that gas is raised above its critical pressure (P_c) and temperature (T_c) (i.e., supercritical CO₂). The critical pressure (or temperature) of a compound is that pressure (or temperature) above which the material undergoes a phase transition. In the case of carbon dioxide, the critical temperature is a relatively mild 31.1° C and the critical pressure is 73.8 bar, or about 1,100 psi.

Supercritical CO₂ has properties that are mid-way between those of a gas and those of a liquid. Along a near-critical isotherm (between 1.0 and 1.2 T_c), the density, transport properties (e.g., viscosity, diffusivity), and other physical properties (e.g., dielectric constant, solvent strength) can be varied in a continuum from gas-like to liquid-like with relatively small changes around the critical pressure (0.9 - 2.0 P_c). The net result is that at selected pressures and temperatures supercritical CO₂ has nearly the diffusivity of a gas and the viscosity of a liquid.

Carbon dioxide is a non-polar solvent. This property, and the above-mentioned properties combine to make supercritical CO₂ an ideal medium for pharmaceutical processing. Processing can take place at temperatures lower than 35° C and at pressures, which although high, are not unusual in the chemical processing arena.

Particle Formation Using Supercritical Carbon Dioxide top

The Company's process takes advantage of the fact that most organic solvents, in essence, can be dissolved in supercritical CO₂. As supercritical CO₂ is mixed with organic solvents containing drug compounds, the solvent "expands" into the supercritical CO₂ effectively increasing the concentration of the solute in the solution making it supersaturated and causing the solute to precipitate or crystallize out of solution. The precipitate can then be separated from the

solvent/supercritical CO₂ mixture for packaging The solvent/supercritical CO₂ mixture is partially depressurized allowing facile separation of the solvent from the now gaseous carbon dioxide This latter step allows for the recovery of all solvents used in the process, and prevents venting of the solvent to the atmosphere

In practice, the procedure is more complicated The size of the droplet from which the drug is precipitated and the propensity of the drug particles to agglomerate into larger particles determine the ultimate size of the drug particle The former is dependent upon the droplet forming process which is a function of the size of the droplet when created by atomization, and the tendency of droplets to coalesce before precipitation of the drug from the supersaturated droplet The latter is a function of the inherent and induced self-attractiveness of the particles, which in turn is primarily determined by surface properties of the particles themselves

CritiTech uses ultrasonic energy produced by a converging/diverging nozzle or an electromechanical oscillator to shatter droplets into even droplets This alone would not enable the formation of submicron particles, as the droplets have a tendency to immediately coalesce into larger drops. In the CritiTech procedure, the drug-laden solvent is sprayed into a flowing stream of supercritical CO₂ which allows for a rapid mass transfer of solvent into the stream of supercritical CO₂ This rapid mass transfer forces precipitation or crystallization to occur prior to the coalescence of droplets. It is this combination of techniques that allows CritiTech to produce sub-micron particles of drugs or other chemicals.

Nanoparticles [top](#)

A major application of CritiTech's core technology will be the production of GMP grade pharmaceuticals in sub-micron or nanoparticulate form The pharmaceutical industry has exhibited substantial interest in the availability of processes to produce nanoparticulate drugs primarily because of the problem of limited bioavailability of poorly water-soluble compounds By some estimates as many as

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40% of all compounds considered for formulation as drugs have such limited water solubility as to make their use as drugs impossible. Evidence of the industry's interest in the fine particle solution to the bioavailability conundrum exists in the form of contracts in place between large pharmaceutical companies and the two operating fine particle-producing companies active today. SmithKline Beecham, Janssen, Mimetex, Merck, Wyeth-Ayerst, Warner-Lambert, and others have entered into collaborative research agreements with either NanoSystems or Bradford Particle Design to develop micronized or submicron preparations of their respective experimental compounds.

The process of producing nanoparticulate drugs begins with a research contract to determine the conditions under which the client's drug can be manufactured as nanoparticles. The client will provide the drug in bulk form along with sufficient information to identify a suitable solvent for the drug. CritiTech will use this material and information to produce test batches of the client's drug as nanoparticulate material. The nanoparticulate material is returned to the client for bioavailability and other testing and in an iterative process an optimal formulation is developed.

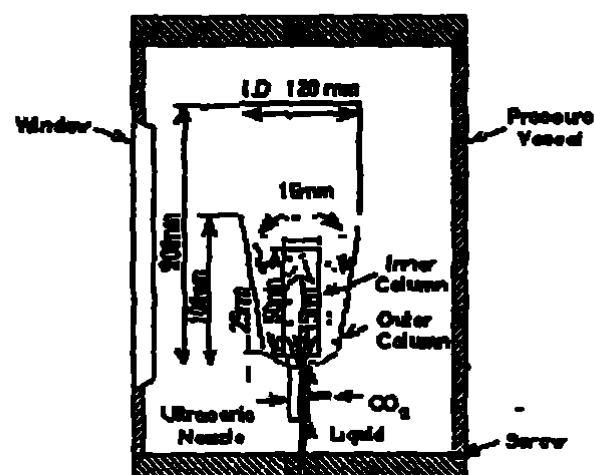
At this stage, a second contract would be negotiated to produce adequate amounts of the nanoparticulate drug under GMP conditions to perform Phase I and/or Phase II clinical trials. If these trials were successful, production would then be scaled up to produce amounts adequate for phase III clinical trials. Each of these steps will produce income for the company. Finally, if NDA approval is obtained, a contract for manufacture of the commercial product could be negotiated and would likely include production fees and royalties on future sales of the drug.

Coating Technology too

A - Particle Coating

A novel use of the fine particle formation process is to perform the process in the presence of large particle, water-soluble substrates. In this embodiment of the technology, the solute chemical (drug or coating) is deposited as a fine film or nanoparticulate coating on the surface of the substrate. One application of this technique would be to apply an ultrathin coating of a taste-masking chemical onto the surface of an unpleasant tasting drug.

In this embodiment of the technology, a substrate (e.g., drug particles) is fluidized, or lifted, by a stream of supercritical or near-critical CO₂ flowing upward through a conical chamber. CntiTech's coating process is similar to the commercial Wurster coater except that the hot air stream which serves to fluidize and to dry the spray droplets is replaced with the thermally mild supercritical CO₂. As illustrated in figure 2, the beads are lifted and circulated in a continuous process that isolates each bead. Because the beads are suspended in a flowing stream of supercritical or near-critical CO₂, chemical-laden (e.g., drug, taste-masking coating, time-release coating) organic solvent can be sprayed into the flowing stream causing the chemical to precipitate on the surface of the substrate. In this way this process is analogous to the nanoparticle formation process except that the particles are allowed to aggregate on the surface of the substrate.



Schematic of particle coating device using SCF to lift particles and remove solvent

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Potential uses of this embodiment are taste masking, delayed or sustained release of drug material, rapid dissolution of drug from the surface of slowly dissolving beads and sequential release of more than one drug substance. An advantage of this process versus the air fluidization process currently in use is that a variety of organic solvents

can be used because the system is closed and solvents can be recaptured. Another advantage is that operating temperatures are substantially lower since the process is not an evaporative one. Finally, because the coating chemical is dissolved in non-aqueous solvents, and supercritical CO₂ is essentially non-polar, water-soluble substrates can be easily coated with this technique.

As with the production of nanoparticulate drugs, commercial utilization would begin with a research contract to optimize the conditions of coating for the client company and would progress through the various stages of drug approval until the ultimate stage of mass production was reached. Income will be derived from research contracts, production fees, license fees and royalties.

B - Stent Coating

Using its patented supercritical fluid-based coating technology, CritiTech, Inc., has succeeded in coating expanded cardiac stents with ethylcellulose containing yellow Opaspray to facilitate viewing of the coated stent. Stents can be fluidized in a stream of near critical carbon dioxide in a chamber that is similar in design to a Wurster coater.

Polymer, dissolved in suitable organic solvent, is sprayed into the near critical carbon dioxide in close proximity to the fluidized stents. Thickness of coating can be controlled by duration of spraying. Texture can be controlled by alteration of temperature above and below the glass transition temperature of the polymer used. Drugs can be substituted for the dye in order to create a timed-release drug delivery device.

This stent coating procedure is an extension of CntiTech's patented technology that is used for coating water-soluble substrates with organic-soluble coating materials. CntiTech can coat substrates in the size range from 300 microns to 1/4-inch tablets uniformly, rapidly and in bulk.

Advantages of the Technology top

Industry insiders estimate that as much as 40% of the roughly 100,000 new chemical entities synthesized annually by pharmaceutical companies have inadequate water solubility. These roughly 40,000 compounds often cannot even advance to the stage of animal trials due to low water solubility, or require extreme measures to perform the exploratory pre-clinical research that will allow the drug companies to make a go/no go decision for further trials. CntiTech's technology can be of substantial value to such companies by allowing a simple, rapid, easy to apply solution to this problem. New chemical entities manufactured as nanoparticles can be easily tested for suitability for advancement to clinical trials. The cost to the drug company for this service (<\$50,000) is a fraction of the cost of subsequent clinical trials (estimated to be as much as \$75,000,000 [Zivin, J A., Scientific American 282, 69-75, 2000]) and an even smaller fraction of eventual sales of an approved drug. This market represents a potential early profit stream for CntiTech and serves as the entrée to those compounds that will require CntiTech's service to go to market.

CntiTech's particle coating technology has significant advantages over the current system of spray coating that is standard in the industry. The use of supercritical carbon dioxide allows the process to work with coating materials that are only soluble in organic solvents, or are sensitive to elevated temperatures. Both of these factors preclude the use of Wurster-type fluidized bed coaters.

Pharmaceutical compounds requiring taste masking, time-release, or an increased oral absorption by coating with drug nanoparticles are example markets for this process.

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A final advantage of CntiTech's SCF based technologies lies in the environmentally friendly nature of the processes. Organic solvents traditionally used in the industry may be hazardous to the environment or toxic to humans and animals. Because of the closed loop nature of the supercritical processes employed by CntiTech, the release of harmful substances to the atmosphere is substantially reduced, if not totally eliminated.

Advantages Over Other PCA Techniques top

CntiTech's approach to PCA uses a supercritical CO₂-powered ultrasonic nozzle. Other companies in the industry that use PCA, including CntiTech's competitor Bradford Particle Design, Ltd., report techniques that use conventional capillary spray nozzles.

The main advantages of CntiTech's approach over conventional PCA techniques follow:

- The ultrasonic nozzle-based process is capable of producing discrete nanoparticles in a narrow size range.
- A key step in the formation of nanoparticles is to enhance the mass transfer rate between the droplets and the antisolvent before the droplets coalesce to form bigger droplets. With CntiTech's ultrasonic nozzle, the sound waves assist the antisolvent's break up into small droplets, increasing the interfacial area. In addition, the turbulence created by the focused sound waves also enhances the mass transfer rate between the droplets and the CO₂.
- Sound waves, rather than inertial or frictional forces, are exploited for droplet formation. Hence, the diameter of the line into which the spray solution is introduced can be larger than that of either capillary or micro-orifice nozzles. This larger diameter allows for higher solution throughput and reduces the probability of nozzle plugging, dramatically increasing manufacturing efficiency.
- CntiTech's proprietary particle harvesting device allows continuous processing of compounds. Conventional SCF techniques require processing in batch lots.

Advantages Over Milling Techniques oo

CntiTech's PCA method is superior to milling techniques (ball mill or jet mill) like

those practiced by CntiTech's competitors NanoSystems and RTP

Pharmaceuticals

These advantages are

- Particle formation occurs in a far shorter time - minutes/hours as opposed to days/weeks.
- PCA produces a much narrower range of particle sizes than milling
- Milling processes induce the creation of electrostatic charge on the particles, which necessitates coating of the resulting particles to prevent re-agglomeration. PCA methods do not induce such electrostatic charges onto particles.
- PCA processing does not require removal of the milling agent.
- PCA processing is safely conducted in closed systems with complete recovery of solvents and CO₂ for reuse or safe disposal

Advantages Over Fluidized Air Coating Techniques 100

The CntiTech coating process has the following advantages over conventional fluidized air based coating processes

- A significantly reduced risk of fire and explosion when using organic solvents due to operation at lower temperatures (31-45°C) with dense carbon dioxide
- Enormous flexibility for controlling the size and morphology of particulate coatings. Several of the operating parameters (pressure, temperature, solute concentration, type of nozzle, type of solvent) are adjustable to achieve the desired coating. Using an ultrasonic nozzle with supercritical CO₂ as the energizing gas, nanoparticle coatings are possible
- Easy separation and recycling of the organic solvent and the CO₂
- Coatings that are virtually solvent-free can be obtained in a relatively short time

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SOLID STATE MORPHOLOGY OF PARTICLES PREPARED BY A SUPERCRITICAL FLUID PROCESS

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The solid state morphology of many compounds is a key-parameter for their further utilization when several forms can co-exist either as crystalline and amorphous, and/or as different polymorphs (allotropes) this is particularly important for pharmaceutical drugs as their morphology can have a significant impact on their bio-availability and stability. Supercritical Fluid (SCF) technology is now considered to be an innovative and promising way to design particles, as reviewed by Kompella and Koushik (2001) and Jung and Ferrut (2001). We present a review of the results already published in literature and our own results on morphology changes and stability of particles generated by SCF processes, focusing on neat particles and not on composite ones.

1 INTRODUCTION

Generally, a dramatic change of the solid morphology is observed after processing by SCF. Average particle size and size distribution, particle shape and porosity and consequently specific area and dissolution rate, are often completely different from those of the starting material. However it seems that, in most cases, the crystal pattern is not modified, although relatively few results, attested by XRD and DSC measurements, have yet been published.

1. SCF CONTACT

Surprisingly, contacting a solid with a SCF induces a re-crystallization with crystalline morphology modification in certain cases, as shown in several documents.

In a patent granted to Graser and Wickrehaeuser (1984), a process for re-crystallization of finely divided crude organic pigments in C3-C5 alkanes or alkenes, or C1-C3 chloro-alkanes is claimed to lead to pigments with deeper and more brilliant colorations than the starting material.

Recently the conversion of carbamazepine (an anticonvulsant drug) by contacting the solid with SCF carbon dioxide was reported by Bettini et al. (2001). This drug presents four polymorphs and a dihydrate forms. Form I (m.p. 190°C) and form III (m.p. 177°C) – the commercial product – form an enantiotropic pair. Form III is stable at ambient temperature whereas form I is stable at higher temperature (>70°C). Different mixtures of Form I / Form III were contacted with supercritical carbon dioxide in static conditions that causes a rapid conversion of Form I into Form III although not

complete. The authors suspect that this transformation results from the fact that these two forms have different solubilities in SCF carbon dioxide. It is to be noted that Kikic et al. (2000) reported a significant increase in dissolution rate in water after anti-solvent re-crystallization of *carbamazepine* from acetone solution either in crystalline form (the polymorph was not identified), or in composite micro-spheres of PEG 4000. We can propose the following "qualitative" interpretation. When a solvent is contacted with a solid it gets saturated into this compound but this saturation is not "static". In permanence, molecules are exchanged between the solid and the fluid phases especially in SCF solvents where mass transfer is fast, causing a "re-crystallization" of the solid into the more stable polymorph at the operating temperature, the transformation being limited by the kinetic of dissolution/re-crystallization.

2. SCF Atomization

The three main processes using SCF for atomizing pure compounds in order to reduce the particle size lead to solid morphology changes or not, depending on the compound, and the process operating conditions.

2.1 RESS

Few publications deal with scientific evaluation of the microscopic solid morphology

- The first evaluation of the solid formed by RESS was published by Larson and King (1986). The XRD patterns of the starting material and the RESS-atomized particles of *naphthalene*, *Mevinolin* (anti-cholesterol drug) and an undisclosed steroid show "that crystalline materials retain their crystallinity after precipitation from supercritical fluids" however, the diffraction patterns vary somewhat, possibly due to the presence of amorphous material.
- DSC characterization of *Griseofulvin* particles shows that particles obtained by RESS (using CHF_3) exhibit the same melting temperature and the same melting enthalpy as the micronized crystalline material (Martin et al., 2000).
- *Anthracene* and *Phenanthrene* were either precipitated or co-precipitated by RESS from a SCF CO_2 solution by Nagahama and Lu (1997), forming dendritic particles of anthracene while the starting material was in form of hexagonal crystals and phenanthrene needles. But coprecipitation of a mixture leads to a *solid solution* different from a simple eutectic as attested by XRD.
- *Ibuprofen* (a chiral non-steroidal anti-inflammatory drug) was micronized from SCF CO_2 , leading to micro-particles exhibiting the same XRD pattern as the starting material, although the peak intensities seemed lower which shows "the decrease in the degree of crystallinity" according to Kyrak et al. (2001).
- *Pure-Hydroxybenzoic acid* was micronized from solutions in SCF CO_2 or SCF CO_2 added with methanol (3.5 wt%) by Jaarao et al. (1997), leading to crystalline nano-particles and a few large irregular non-crystalline particles.

We just obtained very attractive results according to a process described in a recent patent (Ferrut et al., 2002). *Celecoxib* (a COX-2 inhibitor registered for arthritis cure) was dissolved in SCF CO_2 (30°C, 29 MPa) and the solution rapidly depressurized to atmospheric pressure. We operated either according the classical way where the atomization vessel is maintained at around 20°C (sample a), or by injecting an additional stream of liquid CO_2 in order to generate carbonic snow that trapped the particles (sample b) at very low temperature immediately after their nucleation, as

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described in an earlier patent (Ferrut, 1999). On figure 1 is presented a SEM picture after dry ice evaporation, showing fluffy agglomerates of elementary nano-particles.



Figure 1 SEM picture of Celecoxib particles (sample b)

The XRD patterns of these particles after storage at low temperature during one day (sample b lower curve and sample a intermediate curve) are compared on figure 2 with the starting material one (upper curve), the two latter curves being presented with an offset of 2,000 and 3,000 counts per second respectively for ease of interpretation. It clearly appears that the starting material is highly crystalline and the generated particles are completely amorphous when the temperature in the atomization vessel is kept low and mostly amorphous - but not free of crystals - when this temperature is near ambient. We consider that the very short RESS nucleation leads to amorphous material that immediately tends to re-crystallize during the particle residence time in the atomization vessel and on the collection filter, if the temperature is not kept lower than a "re-crystallization temperature" that is much below (at least 30°C according to some estimations) the solid glass transition temperature. So, the amorphous morphology must be "frozen" just after particle generation in order to prevent any re-crystallization.

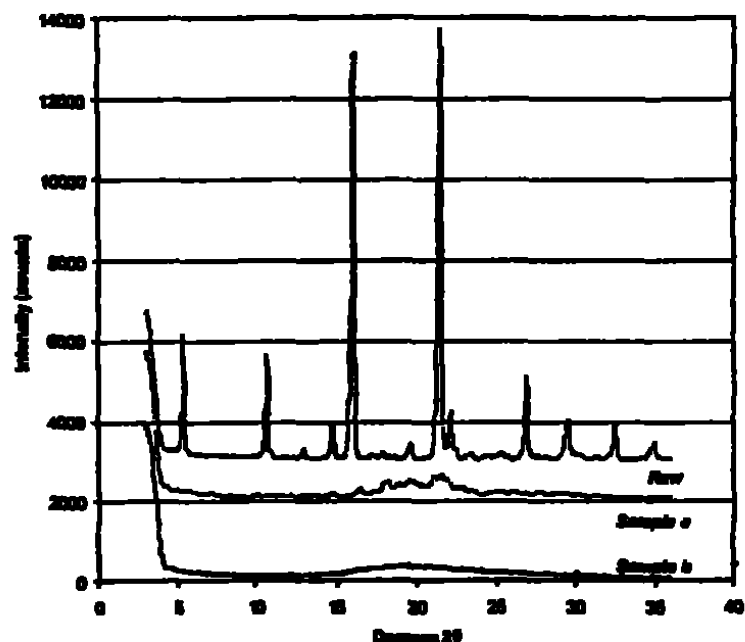


Figure 2 XRD profiles for Celecoxib raw material and RESS-CO₂ samples.

2.2 Anti-Solvent

- *Salmeterol xinafoate* polymorphic forms can be controlled by varying the anti-solvent crystallization parameters according to Hanna and York (1995) and Hanna et al. (1998) using the SEDS technology this compound was re-crystallized from acetone or methanol solutions using SCF CO₂ at various temperatures and pressures. At temperatures below 60°C, only the pure Form I was obtained meanwhile polymorphic transformation to Form II was observed since 60°C and is complete at 90°C. It is to be noted that this anti-solvent process permits to reach this Form II at a much lower temperature than by heating Form I alone (the transformation happens near to the melting temperature of Form I which is 124°C). Moreover the authors claim that the pure Form II obtained by SEDS is extremely stable when stored free from light during 5 years. This demonstrates that anti-solvent re-crystallization can be used to obtain very pure polymorphs that are the more stable because no other polymorph "impurity" may induce transformation to the other form(s).
- Sugars can be re-crystallized from aqueous solutions using SEDS as reported by Hanna and York (1996), Hanna et al. (1998) and Palakodan et al. (1998). *Lactose* was obtained in crystalline form with different particle shapes *maltose* and *trehalose* in form of spongy spheres of amorphous nature as shown by XRD, and *sucrose* as a free-flowing crystalline powder.
- *Sulfasalazine* was subjected to the most detailed study on polymorphism control by Kondikowski et al. (2000), by SEDS of a methanol solution in SCF CO₂. SEM, XRD and DSC showed temperature is the key-parameter. Three

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- pure polymorphs (Form I over 80°C, Form III around 40°C, Form IV below 0°C) and mixtures of polymorphs at intermediate temperatures were obtained.
- *Ibuprofen*, *ketoprofen*, *salicylic acid* and *nicotinic acid* were recrystallized in the same morphology by a SCF process where the compound is primarily dissolved or suspended into a first SCF and this solution/suspension is contacted with a second fluid (nitrogen) which causes precipitation of the compound into fine particles as disclosed by Hanna et al. (1999).
 - *Acetaminophen* and *P-Acetaminophenolide* were co-crystallized by SEDS from an ethanol solution of both compounds by Shklovskiy (2000) in form of a solid solution with incorporation of PAA in the crystals of A (XRD and DSC).
 - Subramaniam et al. (1997) reported GAS recrystallization in the same morphology (by DSC) of *phenytoin* by bubbling CO₂ into an acetone solution.
 - Similarly Lee et al. (2000) observed by XRD that crystal morphology is always identical to the starting material one when re-crystallizing *NTD* (Nitrotriazolone) from a DMF solution in CO₂ under various conditions.
 - On the contrary Jearno et al. (1997) prepared either crystalline or amorphous particles of *Sodium Cromoglycate* starting a methanol solution. The crystalline particles are very similar to the commercial product (same polymorph according XRD) completely amorphous spherical micro-particles were also obtained and did not show any crystallinity after 5-month storage. The authors stated that the most important parameter affecting crystallinity and stability was the residual concentration of methanol that can be drastically reduced by adding a small amount of water to the organic solution.
 - Thuring et al. (1998) reported comparative results on re-crystallization of *Pure-Hydroxybenzoic acid* using GAS and ASES (and RESS see before), the particle shape, size and crystallinity strongly depend on the temperature, the organic solvent, and the rate of addition of the anti-solvent in the batch GAS process (crystalline particles at low addition rate and amorphous ones at high addition rates), as a result of different nuclei formation kinetics.
 - Muehle et al. (2001) recently presented results obtained by GAS on an undiluted pharmaceutical showing that either amorphous (with Ethanol) or crystalline forms (with Acetone or Acetonitrile) can be reached.

2.3 DELOS

The DELOS (Depressurization of an Expanded Liquid Organic Solution) process, very recently disclosed by Sala et al. (2001) and Ventosa et al. (2001a, 2001b), consists in precipitating a solute dissolved in an organic solvent by the fast and homogeneous temperature decrease caused by depressurizing the organic solution previously expanded by a compressed gas. This can be considered as an original variant of RESS as the expanded liquid phase is homogeneous. Provided that a "solute/organic solvent/SCF" system existing as a homogeneous liquid solution can be found, this process leads to nano-/micro-particles. For several compounds, the particles showed a high degree of crystallinity with XRD patterns similar to those of the starting material.

- *Aspirin* and *Colorant Solvent Blue 35* from Acetone/CO₂ solutions
- *Acetaminophen* from Ethanol/CO₂ solutions.

2.4 PGSS

Few results have been published on morphology of particles generated from Gas-Saturated Solutions. Weidner et al. (1994) and Kacz (2000) obtained particles of

alifedipine (a calcium antagonist) that are significantly different from the starting material in size, shape and dissolution rate the authors suspected that the processed particles "have a more amorphous character compared with the product obtained by conventional process" However, no structure measurement supported this assessment.

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EQUIPMENT DESIGN FOR SUPERCRITICAL FLUID MICRONIZATION IN COMPLIANCE WITH GMP FOR PHARMACEUTICAL APPLICATIONS

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Supercritical Fluid (SCF) technology is now considered as a very innovative and promising way to design particles, especially for therapeutic drug formulation. We will present examples of equipment designed and built in compliance with the GMP rules enforced in the pharmaceutical industry incorporating several innovations in terms of mechanical, instrumentation and process control, environment and workforce protection.

1. PARTICLE DESIGN AND DRUG FORMULATION

Among the most original applications of supercritical fluids, particle formation processes using Supercritical Fluids (Jung and Perrut, 2001) are now subjected to an increasing interest especially in the pharmaceutical industry with three aims: increasing bio-availability of poorly-soluble molecules, designing sustained-release formulations and formulation of active agents for new types of drug delivery less invasive than parenteral delivery (oral, pulmonary transdermal). The most complex challenge is related to therapeutic delivery as it is extremely difficult to obtain a satisfactory therapeutic effect due to bio-molecules instability and very short half-life *in vivo*.

Several processes are proposed to address these different problems and to prepare such different types of formulation:

1.1 Rapid Expansion of Supercritical Solutions (RESS) consists in atomizing a solution of the product in a supercritical fluid into a low-pressure vessel. This process could find valuable applications at commercial scale only when product solubility in the supercritical fluid is not too small ($\geq 10^{-3}$ kg/kg), limiting the process application to non-polar or low-polarity compounds when carbon dioxide is used as solvent.

1.2 Supercritical Anti-Solvent (SAS) process applies to most molecules that can be dissolved in a very wide range of "strong" organic solvents. Recent development, especially for preparation of very fine drugs dedicated to pulmonary delivery opens a bright future for "engineering" new types of particles of drugs or micro-spheres of drug embedded in an excipient for sustained-release.

1.3 Supercritical Fluid Drying can be used to "extract" water from aqueous solutions with a polar Supercritical Fluid, this is of special interest for obtaining stabilized powders of bio-molecules or micro-capsules of bio molecules without denaturation.

1.4 Micro-encapsulation can be performed using Supercritical Fluids according to various processes among which the one developed and patented by Perrut (2000b) can lead to micro-capsules of proteins prepared in "mild" conditions without loss of bio-activity

1.5 Impregnation High diffusivity and tunable solvent power of SCF are the basis of supercritical impregnation. In supercritical state, the fluid is a powerful solvent of the product to impregnate and an excellent vector, even in the smallest pores of the matrix (when porous). Moreover for polymeric non-porous matrices, the swelling effect permits an easy penetration of the solute throughout the solid. Many impregnation applications have been reported including pharmaceutical patches, sponges, and catheters. Perrut and Majewski (1999a) recently obtained attractive results and patented a new process for on-line impregnation after extraction, especially attractive for natural products processing as one sole operation leads directly to the usable product (active agent on excipient powder).

2. EQUIPMENT REQUIREMENT

As all high pressure systems, the first requirement is obviously *safety*, which is obtained by applying the high-pressure vessel and equipment standards enforced in the country of operation, but also by incorporating the constructor know-how on both hardware and software (process control system).

The second requirement is *reliability* as for all industrial systems, demanding the right choice of all components and a sophisticated control system to help operation, meanwhile a preventive maintenance is applied.

Specifically to equipment used for drug formulation either for clinical lots preparation or for commercial lots manufacture, design, construction and operation shall be in compliance with *GMP rules* enforced by the official authorities like the Food & Drug Administration in the USA. This implies to establish and follow very detailed procedures for all design and construction steps, documentation of all parts and operations, and validation of all functions, including the process control software.

In most cases, the operator wishes to benefit of a great *flexibility*, permitting to operate one particle design process or the other, over the wider range of parameters (pressures, temperatures, flow-rates, co-solvents, ...), what dramatically complicates the task of the designer and constructor that must find compromises between the contradictory requirements related to each process.

3. EQUIPMENT DESIGN AND SCALE-UP

In fact, most parts of SCF drug formulation plants are similar to those used in classical SCF operations (extraction, fractionation, reactions, chromatography, aerogel drying, ...). For example, a plant used to implement a RESS process uses a classical SCF extractor designed according the rules known for extraction from solid granular or powder material. Similarly, fluid pumps, heat exchangers, separators, control and relief valves, instrumentation, ... are identical to those used on earlier plants designed at any scale (lab to pilot and very large commercial scale). So, we will focus our attention on the characteristics specific to particle design plants.

3.1 Atomization nozzles Nozzle scale-up is presently one of the unknowns when scaling-up a SCF process. Obviously a pure geometric scale-up would not work. As jet turbulence – that controls droplet formation – is related to the Weber number when

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atomizing liquids, we suggest to try to maintain this adimensional number as we guess it will lead to similar atomization whatever is the fluid state, that means that, for a given system, all other parameters being the same, the nozzle scale-up should maintain constant $u^2.D$, where u (m/sec) is the fluid velocity through the nozzle and D (m) the nozzle characteristic diameter. We honestly say that this needs yet to be confirmed on several examples. One original design of large flow-rate nozzles consists in using a sintered disk as depressurization/atomization system, as described for RESS process by Domingo (1997), however, we raise some doubts on the possibility to obtain particles with a narrow size distribution, as the disk porosity is not perfectly distributed and may vary along time with plugging of the smallest pores.

On the other hand, large fluid flow-rates induce thermal effect that are much more complicated to handle than when operating at lab-scale. This is especially the case for RESS process for which the rapid decompression of the fluid requires a large enthalpy input to avoid formation of liquid droplets that runs the particle formation process for those fluids that may be in liquid state at the atomization chamber pressure. As in most cases, it is not possible to pre-heat the fluid solution at the required temperature to avoid droplet formation - as the solute would be destroyed or altered at that temperature - this imposes either that the pressure in the atomization vessel be maintained below the triple point pressure of the fluid, or that supplementary enthalpy be brought by one of the following means: Hot inert gas flow, hot liquid flow with particle collection in form of a suspension in that liquid.

3.2 Particle collection and harvesting This is probably the most acute problem, especially when very fine particles (below 5 μm) are formed, as they have to be collected without losses and without re-agglomeration. Basically particles can be collected under two forms:

- **Liquid suspension** Scrubbing the particle-loaded fluid with a liquid in which both the fluid and the particles are not significantly soluble is a very efficient way of collection, similar to what is used for very fine dust collection (Bausch et al., 1999, Henriksen et al., 1997). Addition of a surfactant in the liquid (or possibly onto the particles during their formation) may stabilize the suspension when needed (Jung et al., 2002). However, this collection system is very restrictive and can be used only in a limited number of cases. Obviously scale-up is not an issue and harvesting the suspension does not raise any difficulty. On the other hand, recycling the suspension as scrubbing medium permits to control the particle content and to reach high particle loadings.

- **Dry powder** This is the general case where the particles must be collected in dry form. For very fine particles (< 5 μm), there is almost a sole possibility: Filtering the particle-loaded fluid onto an adequate filter medium. But, this raises several issues:

- i) Collection efficiency is not always total, as the finest particles may "creep" through the medium,
- ii) Re-agglomeration is frequent as the filter cake presents an increasing pressure drop that induces powder compression: this re-agglomeration may also result from solvent adsorption onto the particles when operating the anti-solvent process
- iii) This filtration operation is difficult to scale-up and to operate for significant mass production
- iv) Final harvesting of the particles is very difficult, especially in compliance with GMP

However, each of these issues can be addressed. Right choice of the filtering medium, alternate use of several atomization chambers to limit the filter cake thickness, residual solvent stripping prior to particle harvesting, special design of filter "bags" that can be closed prior to be removed from the atomization chamber for particle removal under strict atmosphere control. We also proposed other systems adapted to different cases. Particle collection by filtration on a deep bed of excipient to obtain the active-excipient mixture directly (Perrut, 1999b), particle collection into carbonic snow (Perrut, 1999c), particle collection/micro-encapsulation (Perrut, 2000a).

3.3 Fluid recycle Depending on the type of process, the fluid shall be or not recycled:

- **RESS** When the pressure in the atomization chamber is low near the atmospheric pressure, fluid recycling is always an issue. When carbon dioxide is used as solvent, either the atomization is made at high pressure and the fluid is recycled, or it is vented. When other fluids are used – especially if costly or flammable – venting is not possible and recycling mandatory, demanding gas recompression in the case where a low pressure atomization is required to avoid formation of liquid droplets.
- **Anti-solvent** In this case, the atomization being operated under high pressure, it seems easy to recycle the fluid after particle collection – in fact, the difficulty is related to the separation of the organic solvent from the fluid prior to its recycling. Experience shows that most organic solvents are volatile and the total separation from the fluid is not possible if operated at a pressure permitting an easy fluid recycling (a few tens of bars). But, it is not mandatory that the fluid is completely rid of organic solvent for succeeding in particle formation, at the condition it is at a low and constant level, as can be performed through our proprietary technology (Perrut and Jusforgues, 1986) however, the final stripping of the collected particles – on which organic solvent is adsorbed – must be operated with pure fluid, either through make-up or purification of the recycle fluid onto an adsorbent.
- **Supercritical fluid drying** As this process is mainly dedicated to bio-molecules on a very small scale, fluid venting/disposal can be preferred as a complete water separation from the fluid is difficult.
- **Micro-encapsulation** As the fluid is dissolved into the active-excipient mixture, the consumption is very limited and there is no need for recycling.
- **Impregnation** As impregnation is operated under high pressure, it is easy to recycle the fluid according to the classical means used in Supercritical fluid Extraction.

4. GMP COMPLIANCE

As SCF drug formulation and particle design is a new technology for pharmaceutical companies and authorities, a great effort has to be made to teach about the technology its advantages, its safety and reliability and to respect all the commonly enforced rules of traceability and documentation. A special difficulty is related to cleaning of these high-pressure systems that must be designed to permit a total cleaning without discounting all tubings and vessels (no dead-volumes, draining points for liquid solvent used for cleaning...) cleaning validation is also a basic procedure to be adapted to this type of equipment.

Experience gathered on design and construction of four plants built for clinical lots preparation (see picture 1), showed us that no major issue is met when this GMP

compliance is taken into account from the very beginning of plant design and the constructor procedure is planned and documented carefully

5. STERILITY

Processing bio-molecules requires sterility. It is now, clearly established that Supercritical Fluids, and especially carbon dioxide, are biocides vis-à-vis most living micro-organisms including fungi, bacteria and viruses. Not only SCF processes do not increase the bio-burden, but they contribute to sterilize the processed products. In fact, the major difficulty is rather concentrated on particle harvesting and handling from the SCF equipment, as for any other formulation process.

6. WORKFORCE AND ENVIRONMENT PROTECTION

As all biologically-active products are potentially harmful to humans, and should not be released in atmosphere, a special interest must be paid to avoid any release of the processed materials both in the working area or outside in the environment. Because SCF processes require high pressure with possible leakage at any moment (powder or aerosol release) or unpredictable release through the vent system, great care must be taken

- Protection of the operators by placing the equipment in an isolator (lab-scale as shown on picture 2) or in a room with access limited to persons with closed respiratory equipment,
- Collection and scrubbing of all the vent streams
- Automation of drug collection

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Use of Supercritical Fluid Technology for Particle Size Reduction

Supercritical fluids are highly compressible, have high diffusivities, liquid-like densities, and viscosities intermediate between the gas and liquid extremes. These properties offer, in principle, a process which could provide consistent small particles with a narrow particle size distribution where crystallization and size reduction take place simultaneously in a closed, aseptic environment.

There are two basic approaches to using supercritical fluids for size reduction. The first is rapid expansion of a supercritical solution (RESS), where drug is first dissolved in a supercritical fluid, then the supercritical solution is rapidly expanded through a nozzle. This causes a sudden large decrease in solubility of drug, and an aerosol of fine particles is created as a result of the rapid expansion. The second approach is called the supercritical non-solvent approach (SAS), where drug is first dissolved in a carrier solvent, where the carrier solvent is at least partially miscible with the supercritical fluid and the supercritical fluid is a non-solvent for the drug. Mixing of the carrier solution with the supercritical phase causes, in principle, precipitation of a fine particles of drug.

This project uses the SAS approach, primarily because the main limitation of the RESS approach is that the drug must be soluble in the supercritical phase. The SAS approach seems more flexible, since this requirement is avoided.

Staff

Gerhard Muhrer

RESEARCH ACTIVITIES - PROGRESS REPORT 1998

Separation Process Technology

Crystallization using Supercritical Fluid Antisolvents

G MUHRER and M MAZZOTTI

Keywords crystallization, micronization, supercritical fluids, antisolvent, RESS, PCA, GAS

'Ultra fine particles with narrow size distributions are gaining importance in a wide range of fields from ceramics precursors to controlled release drugs. Production generally follows either size reduction or direct generation routes such as dispersion reaction, spray drying or controlled recrystallization. Of the latter, several variants utilizing environmentally benign compressed gases as either solvents or anti-solvents are showing a high potential for industrial application. The main processes are termed rapid expansion of supercritical solutions (RESS), precipitation with compressed antisolvent (PCA) and gas antisolvent crystallization (GAS).

RESS processes require dissolution of the product in a dense gas (liquid or supercritical) at elevated pressure. This 'supercritical solution' is then expanded through a nozzle, where instantaneous nucleation and crystal growth takes place at very high supersaturation. Depending on the fluid state after the nozzle, the crystals may continue to grow or coagulate in the expanding free jet.

PCA processes avoid the drawback of insufficient solubility of many organic substances in dense gases. The product is first dissolved in a liquid organic solvent and this solution then sprayed into a dense gas antisolvent which rapidly absorbs the organic solvent from the spray droplets thus causing rapid precipitation.

GAS crystallization is complementary to the above spray processes in that it offers slower, more easily controlled precipitation which is achieved by adding the dense gas antisolvent to a batch of product dissolved in a suitable organic solvent.

This project aims at elucidating the influence and importance of operating parameters in GAS and PCA crystallization with the goal of

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micronizing difficult-to-communite pharmaceuticals reproducibly and in accordance with U S FDA standards. A sound understanding of system fluid dynamics, thermodynamics and mass transfer including nucleation, crystal growth and agglomeration will be pursued and operational aspects such as collection and recovery of product, on-line measurement and control investigated. Product specifications like crystallinity, shape and particle size distribution will be accounted for by standard off-line analytical tools

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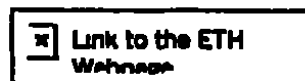
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Complexation and Protein Binding

Metal Complexes

Organic Molecular Complexes

Inclusion Compounds

Methods of Analysis

Protein Binding

Thermodynamic Treatment of

Stability Constants

Complexes or coordination compounds, according to the classic definition, result from a donor-acceptor mechanism or Lewis acid-base reaction (p 144) between two or more different chemical constituents. Any nonmetallic atom or ion, whether free or contained in a neutral molecule or in an ionic compound, that can donate an electron pair may serve as the donor. The acceptor, or constituent that accepts a share in the pair of electrons, is frequently a metallic ion, although it can be a neutral atom. Complexes may be divided broadly into two classes depending on whether the acceptor component is a metal ion or an organic molecule; these are classified according to one possible arrangement in Table 11-1. A third class, the inclusion/occlusion compounds, involving the entrapment of one compound in the molecular framework of another, is also included in the table.

Intermolecular forces involved in the formation of complexes are the van der Waals forces of dispersion, dipolar, and induced dipolar types. Hydrogen bonding provides a significant force in some molecular complexes, and coordinate covalence is important in metal complexes. Charge transfer and hydrophobic interaction are introduced later in the chapter.

METAL COMPLEXES

A satisfactory understanding of metal ion complexation is based upon a familiarity with atomic structure and molecular forces, and the reader would do well to go to texts on inorganic and organic chemistry to study those sections dealing with electronic structure and hybridization before proceeding.

Inorganic Complexes This group constitutes the simple inorganic complexes first described by Werner in 1891. The ammonia molecules in hexamminecobalt(III) chloride, as the compound $[\text{Co}(\text{NH}_3)_6]^{3+}\text{Cl}_3^-$ is called, are known as the *ligands* and are said to be

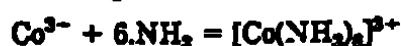
TABLE 11-1 *Classification of Complexes**

I	Metal Ion Complexes
A.	Inorganic type
B.	Chelates
C.	Olefin type
D.	Aromatic type
1.	$\text{PI}(\pi)$ complexes
2.	Sigma (σ) complexes
3.	"Sandwich" compounds
II	Organic Molecular Complexes
A.	Quinhydrone type
B.	Picric acid type
C.	Caffeine and other drug complexes
D.	Polymer type
III	Inclusion/Occlusion Compounds
A.	Channel lattice type
B.	Layer type
C.	Clethrates
D.	Monomolecular type
E.	Macromolecular type

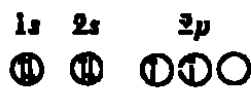
*This classification does not pretend to describe the mechanism or the type of chemical bonds involved in complexation. It is meant simply to separate out the various types of complexes that are discussed in the literature. A highly systematized classification of electron donor-acceptor interactions is given by R. S. Mulliken, *J. Phys. Chem.* 58, 801 (1952).

coordinated to the cobalt ion. The coordination number of the cobalt ion, or number of ammonia groups coordinated to the metal ions is six. Other complex ions belonging to the inorganic group include $[\text{Ag}(\text{NH}_3)_2]^+$, $[\text{Fe}(\text{CN})_6]^{4-}$, and $[\text{Cr}(\text{H}_2\text{O})_6]^{3+}$.

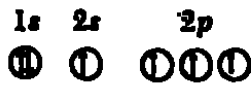
Each ligand donates a pair of electrons to form a coordinate covalent link between itself and the central ion having an incomplete electron shell. For example,



Hybridization plays an important part in coordination compounds in which sufficient bonding orbitals are not ordinarily available in the metal ion. The reader's understanding of hybridization will be refreshed by a brief review of the argument advanced for the quadrivalence of carbon. It will be recalled that the ground state configuration of carbon is



This cannot be the bonding configuration of carbon, however, since it normally has four rather than two valence electrons. Pauling¹ suggested the possibility of *hybridization* to account for the quadrivalence. According to this mixing process, one of the 2s electrons is promoted to the available 2p orbital to yield four equivalent bonding orbitals:

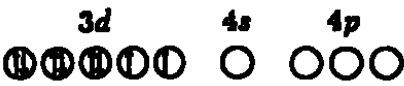


These are directed toward the corners of a tetrahedron, and the structure is known as an *sp³* hybrid because it involves one *s* and three *p* orbitals. In a double bond, the carbon atom is considered to be *sp²* hybridized, and the bonds are directed toward the corners of a triangle.

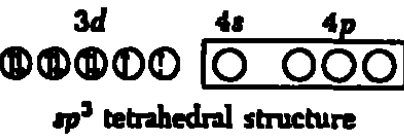
Orbitals other than the 2s and 2p orbitals can become involved in hybridization. The transition elements, such as iron, copper, nickel, cobalt, and zinc, seem to make use of their 3d, 4s, and 4p orbitals in forming hybrids. These hybrids account for the differing geometries often found for the complexes of the transition metal ions. Table 11-2 shows some compounds in which the

central atom or metal ion is hybridized differently and it shows the geometry that results.

Ligands such as H₂O, H₃N, NC⁻, or Cl⁻ donate a pair of electrons in forming a complex with a metal ion, and the electron pair enters one of the unfilled orbitals on the metal ion. A useful but not inviolate rule to follow in estimating the type of hybridization in a metal ion complex is to select that complex in which the metal ion has its 3d levels filled or that can use the lower-energy 3d and 4s orbitals primarily in the hybridization. For example, the ground-state electronic configuration of Ni²⁺ may be given by



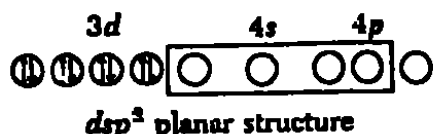
In combining with 4CN⁻ ligands to form [Ni(CN)₄]²⁻, the electronic configuration of the nickel ion may become either



or

TABLE 11-2. Bond Types of Representative Compounds

Coordination Number	Orbital Configuration	Bond Type	Examples	
			Formula	Structure
2	<i>sp</i>	linear	O ₂	O—O
3	<i>sp²</i>	trigonal	BCl ₃	
4	<i>sp³</i>	tetrahedral	CH ₄	
4	<i>dsp²</i>	square planar	Cu(NH ₃) ₄ ²⁺	
5	<i>dsp³</i>	bipyramidal	PF ₅	
6	<i>d²sp³</i>	octahedral	Co(NH ₃) ₆ ³⁺	

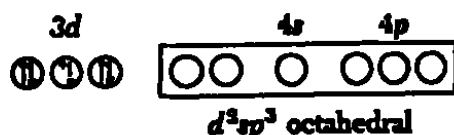


in which the electrons donated by the ligand are shown as dots. The dsp^2 or square planar structure is predicted to be the complex formed since it uses the lower-energy $3d$ orbital. By the preparation and study of a number of complexes, Werner deduced many years ago that this is indeed the structure of the complex.

Similarly, the trivalent cobalt ion Co(III) has the ground state electronic configuration



and one may inquire into the possible geometry of the complex $[\text{Co}(\text{NH}_3)_6]^{3+}$. The electronic configuration of the metal ion leading to filled $3d$ levels is

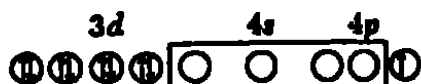


and thus the d^2sp^3 or octahedral structure is predicted as the structure of this complex. Chelates (see following section) of octahedral structure can be resolved into optical isomers, and in an elegant study, Werner used this technique to prove that cobalt complexes are octahedral.

In the case of divalent copper Cu(II) , which has the electronic configuration

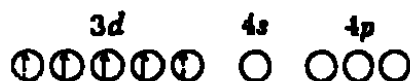


the formation of the complex $[\text{Cu}(\text{NH}_3)_4]^{2+}$ requires the promotion of one d electron of Cu^{2+} to a $4p$ level to obtain a filled $3d$ configuration in the complexed metal ion, and a dsp^2 or planar structure is obtained.

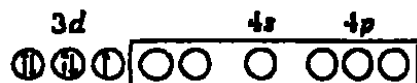


Although the energy required to elevate the d electron to the $4p$ level is considerable, the formation of a planar complex having the $3d$ levels filled entirely more than "pays" for the expended energy.

The metal ion Fe(II) has the ground-state configuration



and in forming the complex $[\text{Fe}(\text{CN})_6]^{4-}$, no electron promotion takes place.



since no stabilization is gained over that which the d^2sp^3 configuration already possesses. Compounds of this type, in which the ligands lie "above" a partially filled orbital, are termed *outer-sphere complexes*, when the ligands lie "below" a partially filled orbital, as in the previous example, the compound is termed an *inner-sphere complex*. The presence of unpaired electrons in a metal ion complex can be detected by *electron spin resonance spectroscopy* (pp 90, 91).

Chelates. A substance containing two or more donor groups may combine with a metal to form a special type of complex known as a *chelate* (Greek: *kelos*, claw). Some of the bonds in a chelate may be ionic or of the primary covalent type, while others are coordinate covalent links. When the ligand provides one group for attachment to the central ion, the chelate is called *monodentate*. Pilocarpine behaves as a monodentate ligand toward Co(II) , Ni(II) , and Zn(II) to form chelates of pseudotetrahedral geometry. The donor atom of the ligand is the pyridine-type nitrogen of the imidazole ring of pilocarpine (Fig 3-4, p 72, shows the pyridine-like nitrogen of pilocarpine). Molecules with two and three donor groups are called *bidentate* and *tridentate*, respectively.² Ethylenediaminetetraacetic acid (EDTA) has six points for attachment to the metal ion and is accordingly *hexadentate*, however, in some complexes, only four or five of the groups are coordinated.

Chelation places stringent steric requirements on both metal and ligands. Ions such as Cu(II) and Ni(II) , which form square planar complexes, and Fe(III) and Co(III) , which form octahedral complexes, can exist in either of two geometric forms. As a consequence of this isomerism only *cis-coordinated ligands*—ligands adjacent on a molecule—will be readily replaced by reaction with a chelating agent. Vitamin B_{12} and the hemoproteins are incapable of reacting with chelating agents, because their metal is already coordinated in such a way that only the *trans*-coordination positions of the metal are available for complexation. In contrast, the metal ion in certain enzymes, such as alcohol dehydrogenase, which contains zinc, can undergo chelation, suggesting that the metal is bound in such a way as to leave two *cis* positions available for chelation.

Chlorophyll and hemoglobin, two extremely important compounds, are naturally occurring chelates involved in the life processes of plants and animals. Albumin is the main carrier of various metal ions and small molecules in the blood serum. The N-terminal portion of human serum albumin binds Cu(II) and Ni(II) with higher affinity than that of dog serum albumin. This fact partly explains why humans are less susceptible to copper poisoning than are dogs. The binding of copper to serum albumin is important since this metal is possibly involved in several pathologic conditions.³ The synthetic chelating agent, ethylenediaminetetraacetic acid (Fig 11-1), has been used to tie up or *sequester* iron and copper ions so that they cannot

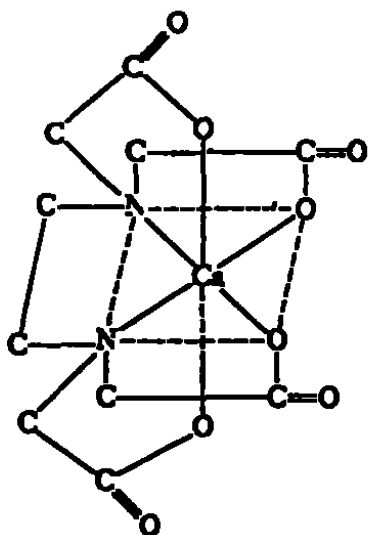


Fig. 11-1 Calcium ions sequestered by ethylenediaminetetraacetic acid (EDTA).

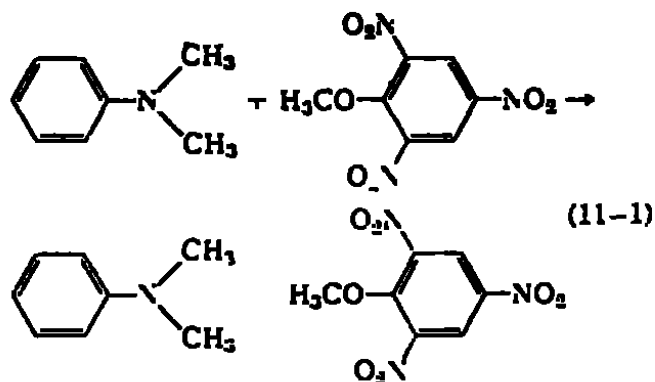
catalyze the oxidative degradation of ascorbic acid in fruit juices and in drug preparations. In the process of sequestration, the chelating agent and metal ion form a water-soluble compound. EDTA is widely used to sequester and remove calcium ions from hard water.

Chelation can be applied to the assay of drugs. A calorimetric method to assay procainamide in injectable solutions is based on the formation of a 1:1 complex of procainamide with cupric ion at pH 4 to 4.5. The complex absorbs visible radiation at a maximum wavelength of 380 nm.⁴ The many uses to which metal complexes and chelating agents can be put are discussed by Martell and Calvin.⁵

ORGANIC MOLECULAR COMPLEXES

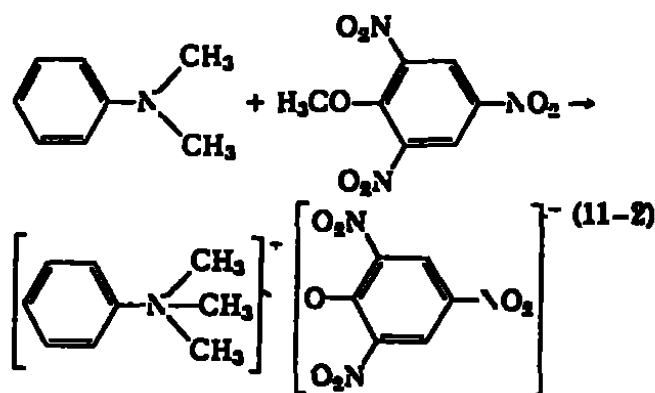
An organic coordination compound or molecular complex consists of constituents held together by weak forces of the donor-acceptor type or by hydrogen bonds.

The difference between complexation and the formation of organic compounds has been shown by Clapp.⁶ The compounds, dimethylaniline and 2,4,6-trinitroanisole, react in the cold to give a molecular complex.



On the other hand, these two compounds react at an elevated temperature to yield a salt, the constituent

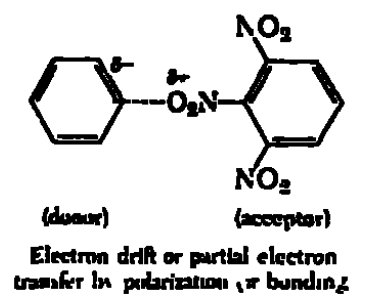
molecules of which are held together by primary valence bonds.



The dotted line in the complex of equation (11-1) indicates that the two molecules are held together by a weak secondary valence force. It is not to be considered as a clearly defined bond but rather as an overall attraction between the two aromatic molecules.

The type of bonding existing in molecular complexes in which hydrogen bonding plays no part is not fully understood, but it may be considered for the present as involving an electron donor-acceptor mechanism corresponding to that in metal complexes but ordinarily much weaker.

Many organic complexes are so weak that they cannot be separated from their solutions as definite compounds, and they are often difficult to detect by chemical and physical means. The energy of attraction between the constituents is probably less than 5 kcal/mole for most organic complexes. Since the bond distance between the components of the complex is usually greater than 3 Å, a covalent link is not involved. Instead, one molecule polarizes the other, resulting in a type of ionic interaction or charge transfer, and these molecular complexes are often referred to as *charge transfer complexes*. For example, the polar nitro groups of trinitrobenzene induce a dipole in the readily polarizable benzene molecule, and the electrostatic interaction that results leads to complex formation.



X-ray diffraction studies of complexes formed between trinitrobenzene and aniline derivatives have shown that one of the nitro groups of trinitrobenzene lies over the benzene ring of the aniline molecule, the intermolecular distance between the two molecules being about 3.3 Å. This result strongly suggests that the interaction involves π bonding between the π

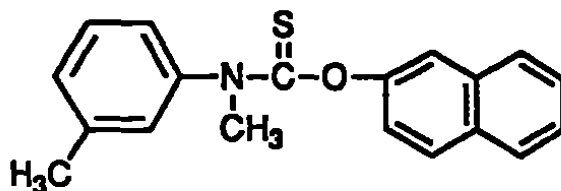
electrons of the benzene ring and the electron-accepting nitro group

A factor of some importance in the formation of molecular complexes is the steric requirement. If the approach and close association of the donor and acceptor molecules are hindered by steric factors, the complex is not likely to form. Hydrogen bonding and other effects must also be considered, and these are discussed in connection with the specific complexes considered on the following pages

The difference between a *donor-acceptor* and a *charge-transfer* complex is that in the latter type resonance makes the main contribution to complexation, while in the former, London dispersion forces and dipole-dipole interactions contribute more to the stability of the complex. Resonance interaction is shown in Figure 11-2 as depicted by Bullock.⁷ Trinitrobenzene is the acceptor, A, molecule and hexamethyl benzene is the donor, D. On the left side of the figure weak dispersion and dipolar forces contribute to the interaction of A and D, on the right side of the figure the interaction of A and D results from a significant transfer of charge, making the electron acceptor trinitrobenzene negatively charged (A^-) and leaving the donor hexamethylbenzene positively charged (D^+). The overall complex, Donor-Acceptor, is shown by the double-headed arrow to resonate between the uncharged D-A and the charged D^+-A^- moieties. If, as in the case of hexamethylbenzene-trinitrobenzene, the resonance is fairly weak, having an intermolecular binding energy ΔH of about -4700 calories, the complex is referred to as a *donor-acceptor complex*. If, on the other hand, resonance between the charge-transfer structure (D^+-A^-) and the uncharged species (D-A) contributes greatly to the binding of the donor and acceptor molecule, the complex is called a *charge-transfer complex*. Finally, those complexes bound together by van der Waals forces, dipole-dipole interactions, and hydrogen bonding but lacking charge transfer are known simply as *molecular complexes*. In both charge-transfer and donor-acceptor complexes, new absorption bands occur in the spectra, as shown in Figure 11-13, p 286. In this book we shall not attempt to separate the first two classes but rather refer to all interactions that produce absorption bands as charge-transfer or as electron donor-acceptor complexes without distinction. Those com-

plexes that do not show new bands are called molecular complexes

Charge-transfer complexes are of importance in pharmacy. Iodine forms 1:1 charge-transfer complexes with the drugs disulfiram, chlomethiazole, and tolnaftate. These drugs have recognized pharmacologic actions of their own. Disulfiram is used against alcohol addiction, chlomethiazole is a sedative-hypnotic and anticonvulsant, and tolnaftate is an antifungal agent. Each of these drugs possesses a nitrogen-carbon-sulfur moiety (see the structure of tolnaftate below), and a complex may result from the transfer of charge from the pair of free electrons on the nitrogen and/or sulfur atoms of these drugs to the antibonding orbital of the iodine atom. Thus, by tying up iodine, molecules containing the $N-C-S$ moiety inhibit thyroid action in the body.⁸

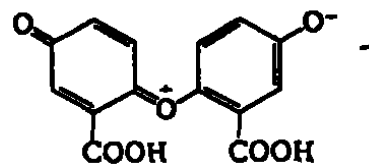


Tolnaftate (Tinactin)

Quinhydrone Complexes. The molecular complex that was referred to in Chapter 9 as quinhydrone is formed by mixing alcoholic solutions of equimolar quantities of benzoquinone and hydroquinone. The complex settles as green crystals. When an aqueous solution is saturated with quinhydrone, the complex dissociates into equivalent amounts of quinone and hydroquinone and is used as an electrode in pH determinations.

The 1:1 complex formed between benzoquinone and hydroquinone may be said to result from the overlap of the π -framework of the electron-deficient quinone molecule with the π -framework of the electron-rich hydroquinone molecule. Maximum overlap between the π -frameworks is expected if the aromatic rings are parallel and are oriented in such a way as to have their centers directly over one another. Hydrogen bonding may contribute in stabilizing this complex, but it is not the sole means of association, since hydroquinone dimethyl ether also forms a colored adduct with quinone.

An interesting quinone is obtained from salicylic acid. This compound is readily oxidized, yielding blue-black quinhydrone compounds of the type



Quinhydrone of salicylic acid

Picric Acid Complexes Picric acid, 2,4,6-trinitrophenol, $pK_a = 0.38$, reacts with strong bases to form salts

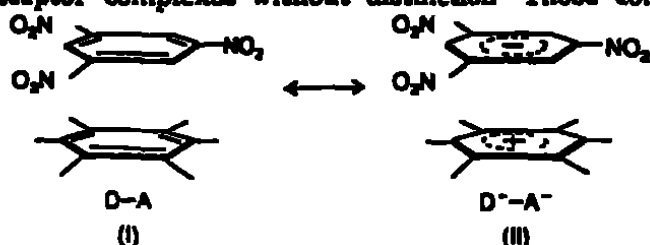
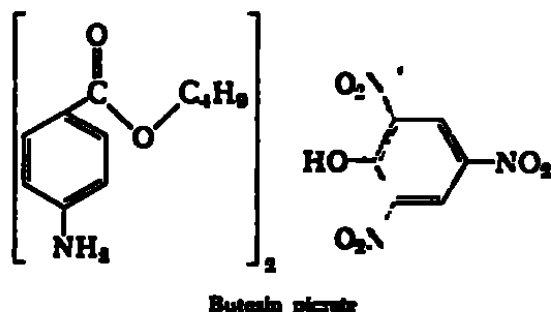


Fig. 11-2 Resonance in a donor-acceptor complex of trinitrobenzene and hexamethylbenzene. (From F. Y. Bullock, Charge transfer in biology, Chapter 3 in *Comprehensive Biochemistry* M. Florin and E. H. Stoltz, Eds. Vol. 22 of *Bioenergetics* Elsevier N.Y. 1967 pp. 82-85, reproduced with permission of the copyright owner.)

and with weak bases to form molecular complexes. Butesin picrate (Abbott Laboratories), presumably a 2:1 complex, may be represented by the formula



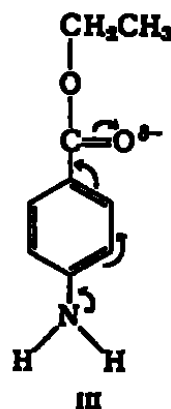
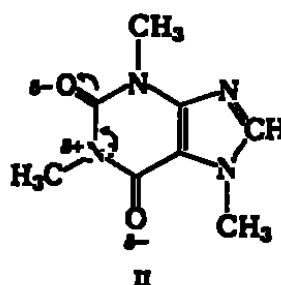
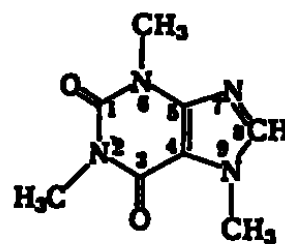
It is a yellow powder, insoluble in water but soluble in organic solvents. Butesin picrate is used as a 1% ointment for burns and painful skin abrasions. It combines the antiseptic property of picric acid and the anesthetic property of butesin.

It has been suggested that the stability of the complexes formed between carcinogenic agents and picric acid is related to carcinogenic activity, and any substitution on the carcinogen molecule that hinders picrate complexation also reduces carcinogenicity. Symmetric trinitrobenzene forms more complexes than does picric acid, and perhaps trinitrobenzene may also be used to provide a test for carcinogenicity.

Drug Complexes. Higuchi and his associates⁹ have investigated the complexing of caffeine with a number of acidic drugs. They attribute the interaction between caffeine and a drug such as a sulfonamide or a barbiturate to a dipole-dipole force or hydrogen bonding between the polarized carbonyl groups of caffeine and the hydrogen atom of the acid. A secondary interaction probably occurs between the nonpolar parts of the molecules, and the resultant complex is "squeezed out" of the aqueous phase owing to the great internal pressure of water. These two effects lead to a high degree of interaction.

The complexation of esters is of particular concern to the pharmacist, since many important drugs belong to this class. The complexes formed between esters and amines, phenols, ethers and ketones have been attributed to the hydrogen bonding between a nucleophilic carbonyl oxygen and an active hydrogen. This, however, does not explain the complexation of esters such as benzocaine, procaine, and tetracaine with caffeine, as reported by Higuchi et al.¹⁰ There are no activated hydrogens on caffeine, the hydrogen in the number 8 position (formula I) is very weak ($K_a = 1 \times 10^{-14}$) and is not likely to enter into complexation. It might be suggested that, in the caffeine molecule, a relatively positive center exists that serves as a likely site of complexation. The caffeine molecule is numbered in I for convenience in the discussion. As observed in formula II, the nitrogen at the 2 position presumably can become strongly electrophilic or acidic just as it is in an imide owing to the withdrawal of electrons by the

oxygen at position 1 and 3. An ester such as benzocaine also becomes polarized (formula III) in such a way that the carboxyl oxygen is nucleophilic or basic. The complexation can thus occur as a result of a dipole-dipole interaction between the nucleophilic carboxyl oxygen of benzocaine and the electrophilic nitrogen of caffeine.



Caffeine forms complexes with organic acid anions that are more soluble than the pure xanthine, but the complexes formed with organic acids, such as gentisic acid, are less soluble than caffeine alone. Such insoluble complexes provide caffeine in a form that masks its normally bitter taste and should serve as a suitable state for chewable tablets. Higuchi and Pitman¹¹ synthesized 1:1 and 1:2 caffeine-gentisic acid complexes and measured their equilibrium solubility and rates of dissolution. Both the 1:1 and 1:2 complexes were less soluble in water than caffeine, and their dissolution rates were also less than that of caffeine. Chewable tablets formulated from these complexes should provide an extended-release form of the drug with improved taste.

York and Saleh¹² studied the effect of sodium salicylate on the release of benzocaine from topical vehicles, it being recognized that salicylates form molecular complexes with benzocaine. Complexation between drug and complexing agents can improve or impair drug absorption and bioavailability; the authors found that

the presence of sodium salicylate significantly influenced the release of benzocaine, depending on the type of vehicle involved. The largest increase in absorption was observed for a water-miscible polyethylene glycol base.

Polymer Complexes Polyethylene glycols, polystyrene, carboxymethylcellulose, and similar polymers containing nucleophilic oxygens can form complexes with various drugs. The incompatibilities of certain polyethers, such as the Carbowaxes[®], Pluronic[®], and Tweens[®] with tannic acid, salicylic acid, and phenol, can be attributed to these interactions. Marcus¹² has reviewed some of the interactions that may occur in suspensions, emulsions, ointments, and suppositories. The incompatibility may be manifested as a precipitate, flocculate, delayed biologic absorption, loss of preservative action, or other undesirable physical, chemical, and pharmacologic effects.

Plautner-Vercammen et al.¹⁴ have studied the interaction of povidone (PVP) with ionic and neutral aromatic compounds. Several factors affect the binding to PVP of substituted benzoic acid and nicotine derivatives. While ionic strength has no influence, the binding increases in phosphate buffer solutions and decreases as the temperature is raised.

Crosspovidone, a cross-linked insoluble PVP, is able to bind drugs owing to its dipolar character and porous structure. Frömzung et al.¹⁵ studied the interaction of crosspovidone with acetaminophen, benzocaine, benzoic acid, caffeine, tannic acid, and papaverine hydrochloride, among other drugs. The interaction is mainly due to any phenolic groups on the drug. Hexylresorcinol shows exceptionally strong binding, but the interaction is less than 5% for most drugs studied (32 drugs). Crosspovidone is a disintegrant in pharmaceutical granules and tablets. It does not interfere with gastrointestinal absorption because the binding to drugs is reversible.

Solutes in parenteral formulations may migrate from

the solution and interact with the wall of a polymeric container. Hayward et al.¹⁶ showed that the ability of a polyolefin container to interact with drugs depends linearly on the octanol-water partition coefficient of the drug. For parabens and drugs that exhibit fairly significant hydrogen bond donor properties, a correction term related to hydrogen-bonding formation is needed. Polymer-drug container interactions may result in loss of the active component in liquid dosage forms.

Polymer-drug complexes are used to modify biopharmaceutical parameters of drugs; the dissolution rate of ajmaline is enhanced by complexation with PVP. The interaction is due to the aromatic ring of ajmaline and the amide groups of PVP to yield a dipole-dipole induced complex.¹⁷

Some molecular organic complexes of interest to the pharmacist are found in Table 11-3 (Complexes involving caffeine are listed in Table 11-6).

INCLUSION COMPOUNDS

The class of addition compounds known as *inclusion* or *occlusion* compounds results more from the architecture of molecules than from their chemical affinity. One of the constituents of the complex is trapped in the open lattice or cage-like crystal structure of the other to yield a stable arrangement.

Channel Lattice Type The *choleic acids* (bile acids) can form a group of complexes principally involving deoxycholic acid in combination with paraffins, organic acids, esters, ketones, and aromatic compounds and with solvents such as ether, alcohol, and dioxane. The crystals of deoxycholic acid are arranged to form a channel into which the complexing molecule can fit (cf Fig 11-8). Such stereospecificity should permit the resolution of optical isomers. In fact, camphor has been partially resolved by complexation with deoxycholic

TABLE 11-3. Some Molecular Organic Complexes of Pharmaceutical Interest*

Agent	Compounds That Form Complexes with the Agent Listed in the First Column
Polyethylene glycols	<i>m</i> -Hydroxybenzoic acid <i>p</i> -hydroxybenzoic acid salicylic acid <i>o</i> -phthalic acid, acetylsalicylic acid resorcinol catechol phenol phenobarbital iodine (in I ₂ KI solutions) bromine (in presence of HBr)
Povidone (polyvinyl-pyrrolidone PVP)	Benzoic acid, <i>m</i> -hydroxybenzoic acid <i>p</i> -hydroxybenzoic acid salicylic acid sodium salicylate <i>p</i> -aminobenzoic acid mandelic acid sulfathiazole chloramphenicol phenobarbital
Sodium carboxymethylcellulose Oxytetracycline and tetracycline	Quinine benadryl, procaine, pyrimbenzamine <i>N</i> methylpyrrolidone <i>N,N</i> -dimethylacetamide γ -valerolactone γ -butyrolactone, sodium <i>p</i> -aminobenzoate sodium salicylate sodium <i>p</i> -hydroxybenzoate sodium saccharin caffeine

*Compiled from the results of T. Higuchi et al. J. Am. Pharm. Assoc. Sci. Ed. 43, 393, 398, 456, 1954; ibid. 44, 508, 1955; ibid. 45, 157, 1956; ibid. 46, 452, 587, 1957 and from J. L. Lach et al. Drug Standards 24, 11, 1956. An extensive table of acceptor and donor molecules that form aromatic molecular complexes has been compiled by L. J. Andrews, Chem. Revs. 34, 713, 1954. Also refer to T. Higuchi and K. A. Connors, Phase solubility techniques, *Advances in Analytical Chemistry and Instrumentation*, C. N. Reilly, Ed. New York, Wiley, 1965, pp. 117-212.

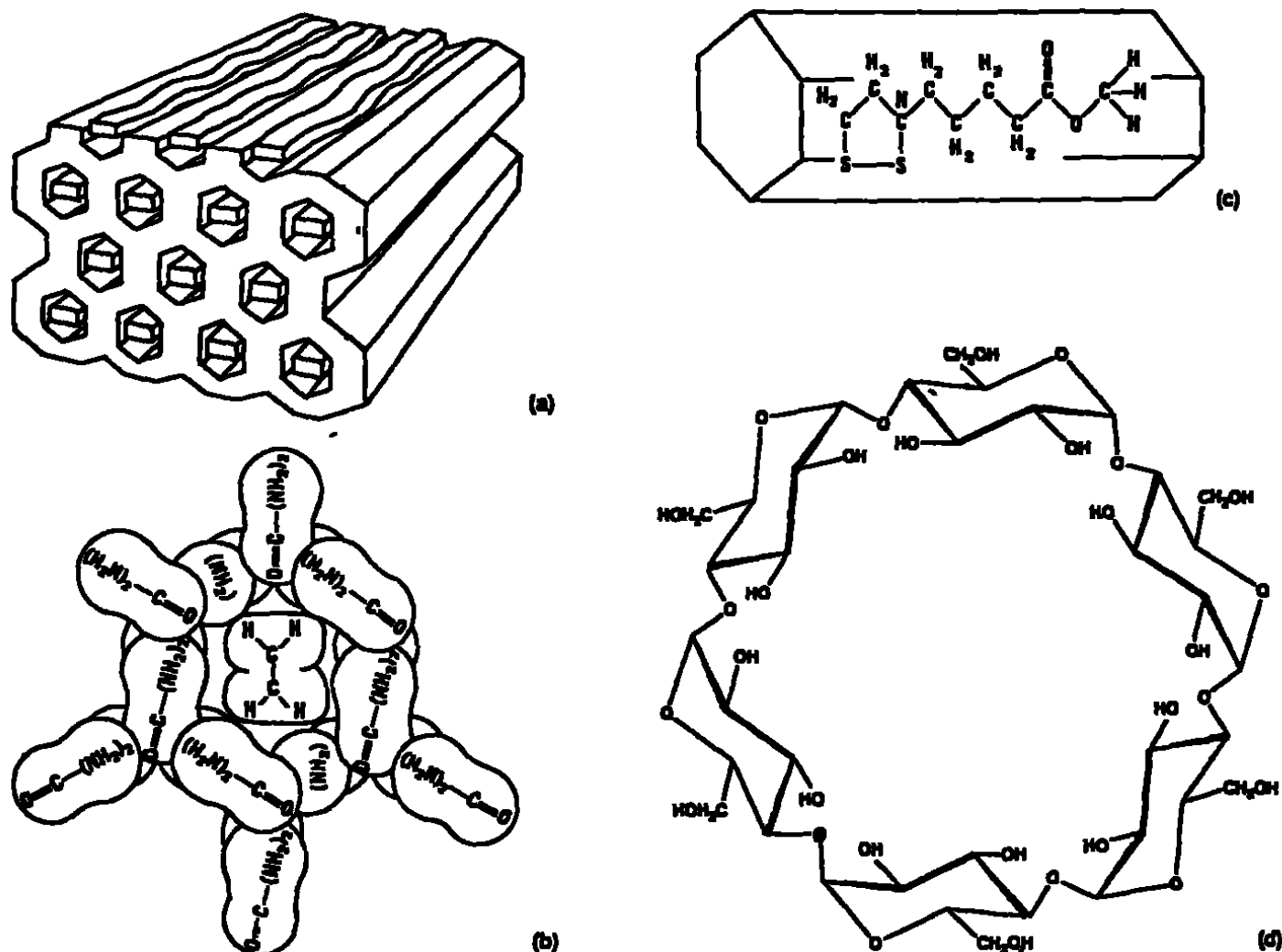
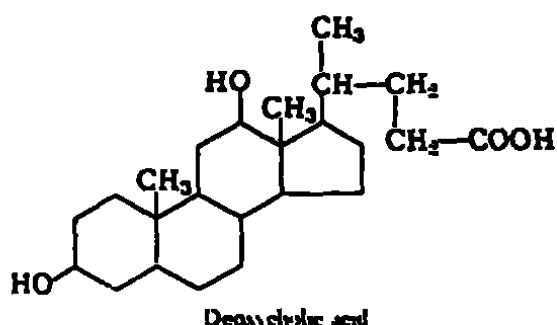


Fig. 11-3. (a) A channel complex formed with urea molecules as the host. As the lower sketch (b) shows, these molecules are packed in an orderly manner and held together by hydrogen bonds between nitrogen and oxygen atoms. The hexagonal channels, approximately 5 Å in diameter, provide room for guest molecules such as long chain hydrocarbons, as shown here. (From J. F. Brown, Jr., *Sci. Am.* 207: 82, 1962. Copyright © 1962 by Scientific American, Inc. All rights reserved.) (c) A hexagonal channel complex (adduct) of methyl α -lipoate and 15 g of urea in methanol prepared with gentle heating. Needles crystals of the adduct separated overnight at room temperature. This inclusion compound or adduct begins to decompose at 63° C and melts at 163° C. Thiourea may also be used to form the channel complex. (From H. Mima and M. Nishikawa, *J. Pharm. Sci.* 53, 931, 1964 reproduced with permission of the copyright owner.) (d) Cyclodextrin (cyclomaltoheptaose, Schardinger dextrin), See *Merck Index* Edition 12, Rahway, N.J., 1969 p. 425.

acid, and *dl*-terpineol has been resolved by the use of digitonin, which occludes certain molecules in a manner similar to that of deoxycholic acid



Urea and thiourea also crystallize in a channel-like structure permitting enclosure of unbranched paraffins, alcohols, ketones, organic acids, and other compounds, as shown in Figure 11-3a and b. The well-known starch iodine solution is a channel-type complex consist-

ing of iodine molecules entrapped within spirals of the glucose residues.

Forman and Grady¹⁸ found that monostearin, an interfering substance in the assay of diene-2-ol, could be extracted easily from dermatologic creams by channel-type inclusion in urea. They felt that urea inclusion might become a general approach for separation of long-chain compounds in assay methods. The authors reviewed the earlier literature on urea inclusion of straight-chain hydrocarbons and fatty acids.

Layer Type Some compounds such as the clay montmorillonite, the principal constituent of bentonite, can trap hydrocarbons, alcohols, and glycols between the layers of their lattices.¹⁹ Graphite can also intercalate compounds between its layers.

Clathrates²⁰ The clathrates crystallize in the form of a cage-like lattice in which the coordinating compound is entrapped. Chemical bonds are not involved in these complexes, and only the molecular size of the encaged

ponent is of importance Ketelaar²¹ observed that the stability of a clathrate may be related to the confinement of a prisoner The stability of a clathrate is due to the strength of the structure, that is, to the high energy that must be expended to decompose the compound, just as a prisoner is confined by the bars that prevent his escape

Powell and Palin²² have made a detailed study of clathrate compounds and have shown that the highly toxic agent hydroquinone (quinol) crystallizes in a cage-like hydrogen-bonded structure, as seen in Figure 11-4 The holes have a diameter of 4.2 Å and permit the entrapment of one small molecule to about every two quinol molecules. Small molecules such as methyl alcohol, CO₂, and HCl may be trapped in these cages, but smaller molecules such as H₂ and larger molecules such as ethanol cannot be accommodated. It is possible that clathrates may be used to resolve optical isomers and to bring about other processes of molecular separation.

One official drug, warfarin sodium USP, is a clathrate of water, isopropyl alcohol, and sodium warfarin in the form of a white crystalline powder

Monomolecular Inclusion Compounds. Cyclodextrins. Inclusion compounds are reviewed by Frank.²³ In addition to channel- and cage-type (clathrate) compounds, Frank adds classes of *mono-* and *macromolecular* inclusion compounds. Monomolecular inclusion compounds involve the entrapment of a single guest molecule in the cavity of one host molecule. Monomolecular host structures are represented by the cyclodextrins. These compounds are cyclic oligosaccharides

containing a minimum of six D-(+)-glucopyranose units attached by α -1,4 linkages produced by the action on starch of *Bacillus macerans* amylase The natural α , β , and γ cyclodextrins (α -CD, β -CD, and γ -CD) consist of 6, 7, and 8 units of glucose, respectively

Their ability to form inclusion compounds in aqueous solution is due to the typical arrangement of the glucose units (see Fig 11-3d) As observed in cross-section in the figure, the cyclodextrin structure forms a torus or doughnut ring The molecule actually exists as a truncated cone, which is seen in Figure 11-5a, it can accommodate molecules such as mitomycin C to form inclusion compounds (Fig 11-5b) The interior of the cavity is relatively hydrophobic because of the CH₂ groups, whereas the cavity entrances are hydrophilic owing to the presence of the primary and secondary hydroxyl groups.^{24,25} α -CD has the smallest cavity (internal diameter almost 5 Å) β -CD and γ -CD are the most useful for pharmaceutical technology owing to their larger cavity size (internal diameter almost 6 Å and 8 Å, respectively) Water inside the cavity tends to be squeezed out and to be replaced by more hydrophobic species Thus, molecules of appropriate size and stereochemistry can be included in the cyclodextrin cavity by hydrophobic interactions. (See pp. 272-273) Complexation does not ordinarily involve the formation of covalent bonds. Some drugs may be too large to be accommodated totally in the cavity As

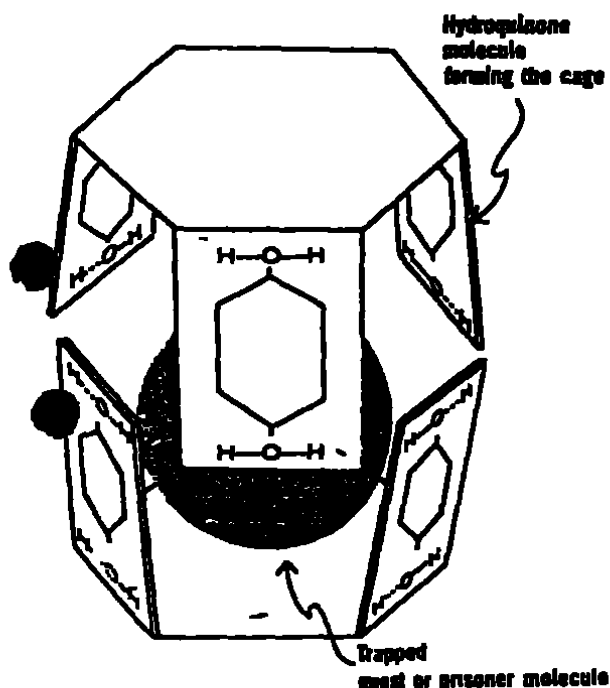


Fig. 11-4. Cage-like structure formed through hydrogen bonding of hydroquinone molecules. Small molecules such as methanol are trapped in the cages to form the clathrate (Modified from J. F. Brown Jr. Sci. Am. 207 32, 1962. Copyright © 1962 by Scientific American Inc. All rights reserved.)

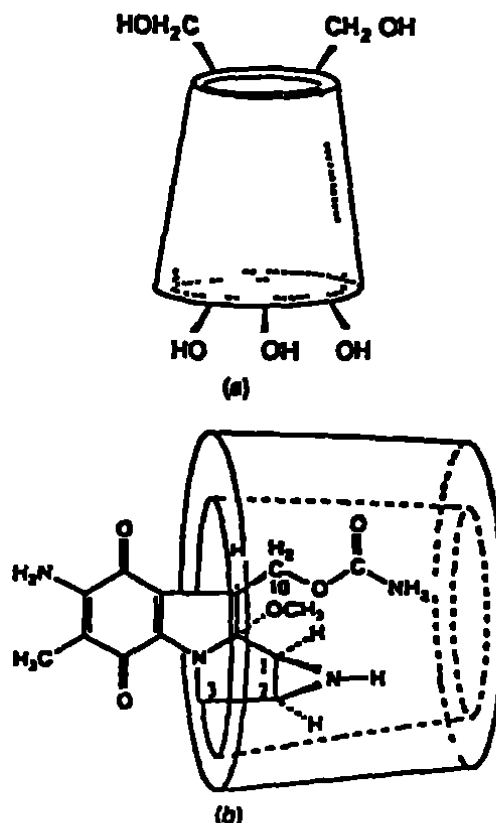
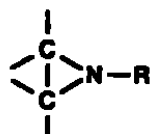


Fig. 11-5 (a) Representation of cyclodextrin as a truncated cone (b) Mitomycin C partly enclosed in cyclodextrin to form an inclusion complex. (From O. Beckers, In: J. Pharm. 52 240-247 1969 reproduced with permission of the copyright owner.)

shown in Figure 11-5b, mitomycin C interacts with γ -CD at one side of the torus. Thus, the azuridine ring



of mitomycin C is protected from degradation in acidic solution.²⁶ Bakensfield et al.²⁷ studied the inclusion of indomethacin with β -CD using an $^1\text{H-NMR}$ technique. The *p*-chlorobenzoyl part of indomethacin (shaded part of Fig 11-6) enters the β -CD ring, whereas the substituted indol moiety (the remainder of the molecule) is too large for inclusion and rests against the entrance of the CD cavity.

Cyclodextrins are studied as solubilizing and stabilizing agents in pharmaceutical dosage forms. Lach and associates²⁸ used cyclodextrins to trap, stabilize, and solubilize sulfonamides, tetracyclines, morphine, aspirin, benzocaine, ephedrine, reserpine, and testosterone. The aqueous solubility of retinoic acid (0.5 mg/liter), a drug used topically in the treatment of acne,²⁹ is increased to 160 mg/liter by complexation with β -CD. Dissolution rate plays an important role in bioavailability of drugs, fast dissolution usually favoring absorption. Thus, the dissolution rate of famotidine,³⁰ a potent drug in the treatment of gastric and duodenal ulcers, and tolbutamide, an oral antidiabetic drug, are both increased by complexation with β -cyclodextrin.³¹

Cyclodextrins may increase or decrease the reactivity of the guest molecule depending on the nature of the reaction and the orientation of the molecule within the CD cavity. Thus, α -cyclodextrin tends to favor pH-dependent hydrolysis of indomethacin in aqueous solution, whereas β -cyclodextrin inhibits it.³² Unfortunately, the water solubility of β -CD (1.8 g/100 mL at 25°C) is often insufficient to stabilize drugs at therapeutic doses, and is also associated with nephrotoxicity when CD is administered by parenteral routes.³³ The relatively low aqueous solubility of the cyclodextrins may be due to the formation of intramolecular hydrogen bonds between the hydroxyl groups (see Fig 11-3d), which prevent their interaction with water molecules.³⁴

Derivatives of the natural crystalline CD have been developed to improve aqueous solubility and to avoid

toxicity. Partial methylation (alkylation) of some of the OH groups in CD reduces the intermolecular hydrogen bonding, leaving some OH groups free to interact with water, thus increasing the aqueous solubility of CD.³⁵ According to Müller and Brauns,³⁴ a low degree of alkyl substitution is preferable. Derivatives with a high degree of substitution lower the surface tension of water, and this has been correlated with the hemolytic activity observed in some CD derivatives. Amorphous derivatives of β -CD and γ -CD are more effective as solubilizing agents for sex hormones than the parent cyclodextrins. Complexes of testosterone with amorphous hydroxypropyl β -CD allow an efficient transport of hormone into the circulation when given sublingually.³⁶ This route avoids both metabolism of the drug in the intestines and rapid first-pass decomposition in the liver (see Chapter 19), thus improving bioavailability.

In addition to hydrophilic derivatives, hydrophobic forms of β -CD have been found useful as sustained-release drug carriers. Thus, the release rate of the water-soluble calcium antagonist diltiazem was significantly decreased by complexation with ethylated β -CD. The release rate was controlled by mixing hydrophobic and hydrophilic derivatives of cyclodextrins at several ratios.³⁶ Ethylated β -CD has also been used to retard the delivery of isosorbide dinitrate, a vasodilator.³⁷

Cyclodextrins may improve the organoleptic characteristics of oral liquid formulations. The bitter taste of suspensions of femoxetine, an antidepressant, is greatly suppressed by complexation of the drug with β -cyclodextrin.³⁸

Molecular Sieves. Macromolecular inclusion compounds, or *molecular sieves* as they are commonly called, include zeolites, dextrans, silica gels, and related substances. The atoms are arranged in three dimensions to produce cages and channels. Synthetic zeolites may be made to a definite pore size so as to separate molecules of different dimensions, and they are also capable of ion exchange. See the review article by Frank³⁹ for a detailed discussion of inclusion compounds.

METHODS OF ANALYSIS³⁹

A determination of the *stoichiometric ratio* of ligand to-metal or donor-to-acceptor and a quantitative expression of the *stability constant* for complex formation are important in the study and application of coordination compounds. A limited number of the more important methods for obtaining these two quantities are presented here.

Method of Continuous Variation. Job⁴⁰ suggested the use of an additive property such as the spectrophotometric extinction coefficient (dielectric constant or the square of the refractive index may also be used) for the measurement of complexation. If the property for two

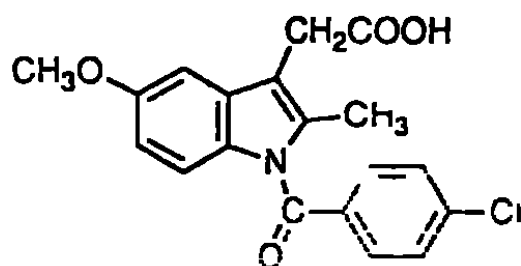


Fig. 11-6 Indomethacin (Indocin)

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SULPHAMETHIZOLE-CYCLODEXTRIN-HYDROXY PROPYLMETHYL CELLULOSE MULTICOMPONENT COMPLEXES

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Abstract

The effect of cyclodextrin complexation of sulphamethizole (SM) was studied. Two systems were prepared with two cyclodextrin derivatives, β -cyclodextrin (BCD) and hydroxypropyl- β -cyclodextrin (HPBCD): binary complexes and multicomponent systems (cyclodextrins and a hydroxypropylmethyl cellulose K4M). Inclusion complexes were prepared by freeze-drying and characterized by thermal analysis (DSC) and X-ray diffractometry. The presence of the polymer in the solution increases the effect of cyclodextrins – specially BCD – on the solubility of SM. In solid state, binary inclusion complexes enhance the dissolution behaviour of SM but, from the multicomponent complexes, the polymer controls the release of the drug.

Keywords: β -cyclodextrin, cyclodextrin inclusion complexes, DSC, hydroxypropyl- β -cyclodextrin, hydroxypropylmethyl cellulose, stability constant, X-ray diffractometry

Introduction

Cyclodextrins (CDs) are water-soluble, hydrophobic torus-shaped cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity. In aqueous solutions CDs are capable of forming inclusion complexes with many drugs. Because of these properties CDs can be used to improve some physicochemical properties of drug molecules such as stability or aqueous solubility [1–3].

For a variety of reasons including costs, production capabilities and toxicology, CDs can be incorporated into drug formulations in a limited amount, and therefore, it is important to develop methods that allow a reduction in the amount of CDs necessary in a particular pharmaceutical formulation [4]. Among these procedures, the use of water-soluble polymers has been extensively studied to enhance the complexing abilities of the CDs. In fact, it has been proven that various pharmaceutical polymers, such as cellulose derivatives, have a significant effect on the drug-CD complex formation because, as surfactants, they increase the solubilizing power of CDs. The in-

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teraction polymer-CD results in physical-chemical changes of the systems formed, and the solubility of the drug increases [5-7]. We have used a hydrophilic polymer, hydroxypropylmethyl cellulose (K4M) which is a well established pharmaceutical excipient, extensively used in controlled drug delivery systems. K4M has been previously reported useful in the improvement of CD complexation [8-10], but most of the studies carried out to analyse the effect of hydrophilic polymers on the complex formation with cyclodextrins were made in solution, not in solid state. Several papers have been published concerning the improvement of the solubility and bioavailability of drugs through the formation of binary and multicomponent complexes with cyclodextrins [11, 12]. Acid molecules - hydrochloric, citric or tartaric acids - were included in these multicomponent systems but not polymer molecules.

Sulphamethazole (SM) was used as a model drug. It is a short-acting sulphonamide used in the treatment of infections of the urinary tract, sometimes in combination with other antibacterial agents. It is very slightly soluble in water and thus could be a drawback to formulate it in controlled release dosage forms. Its formulation as an inclusion complex either with β -cyclodextrin (BCD) or hydroxypropyl- β -cyclodextrin (HPBCD) has showed a significant increase in its aqueous solubility [13].

The aim of this study was to prepare solid multicomponent systems containing cyclodextrins (BCD and HPBCD) and hydroxypropylmethyl cellulose (K4M) to be included in solid dosage forms. These systems were prepared by freeze-drying and characterized by differential scanning calorimetry and X-ray diffractometry. Drug dissolution characteristics from binary and multicomponent complexes were compared with those of the uncomplexed drug.

Experimental

Materials

Sulphamethazole was purchased from Sigma Chemical Co. (St. Louis, MO, USA). BCD and HPBCD were a gift from Lassa-Roquette (Barcelona, Spain) and Janssen Pharmaceutische (Belgium), respectively. Hydroxypropylmethyl cellulose K4M (Methocel[®]) was obtained from The Dow Chemical Company (Michigan, USA). All other reagents were of analytical reagent grades.

Solubility studies

Solubility diagrams were obtained according to Higuchi and Connors methodology [14]. Excess amounts of sulphamethazole were added to water containing various concentrations of cyclodextrins. The suspensions were shaken at 37°C for seven days.

To establish the effect of the polymer on the solubility diagrams, K4M was added (0.1% w/v). The suspensions were autoclaved at 120°C for 20 min and equilibrated for at least 3 days at room temperature, according to Loftsson *et al.* [15].

The stability constants $K_{1:1}$ were calculated using the following relationship

379
373

$$K_{1:1} = \frac{\text{slope}}{S_0(1 - \text{slope})}$$

where S_0 represents the solubility of sulphamethazole in water without cyclodextrins. Drug concentration was analysed spectroscopically (Shimadzu UV-240-Graphisord) at 264 nm ($E_{1\%}^{1\text{cm}} = 577.31$).

Preparation of the physical mixtures

Sulphamethazole, cyclodextrins and hydroxypropylmethyl cellulose were passed through 0.5 mm meshes, and 1:1 SM/CD ratio with 0.1 g of K4M (equal amount that is present in the inclusion complexes) were mixed in a Turbula T2C mixer for 10 min.

Preparation of the inclusion complexes

Equimolar amounts of sulphamethazole and cyclodextrins – BCD and HPBCD – were dissolved in 5% (w/v) aqueous ammonium hydroxide. K4M was added to obtain a final concentration of 0.1% (w/v), and the solution was left to stand for 24 h at 4°C. The dispersions were frozen by immersion in liquid nitrogen, and lyophilized in a Labconco Lyph-lock 6 apparatus.

Thermal analysis

Differential scanning calorimetry (DSC) was performed on a Shimadzu DSC-50 system with a DSC equipped with a computerized data station TA-5 WS/PC. General conditions: scanning rate 10°C min⁻¹, scanning temperature range 25–250°C.

X-ray

X-ray powder diffraction patterns were recorded on a Philips X-ray diffractometer (PW 1710 BASED) using CuK_α radiation. In the diffractograms the relative intensity of reflexion peaks were recorded as a function of diffraction angles 2θ°.

Dissolution studies

The dissolution behaviour of the complexes at 37°C was compared with that of pure sulphamethazole and of physical sulphamethazole-cyclodextrin mixtures using hard shell colorless gelatin capsules containing quantities of formulation equivalent to 50 mg of sulphamethazole. Capsules were placed in a stainless steel box to avoid their flotation. Tests were carried out in a USP24 Method II apparatus (Turu-Grau) using 900 mL of distilled water and a stirring speed of 50 r.p.m. All experiments were made in triplicate. At pre-specified times, 5 mL samples were extracted and filtered, and the concentration of sulphamethazole was determined spectrophotometrically at 264 nm. The resulting dissolution curves were characterized by the corresponding 0–60 min dissolution efficiency [16]. The statistical significance of differences among formula-

tions was estimated by one-way analysis of variance (one-way Anova) and the Scheffé test for multiple comparisons using SPSS for Windows (v 10.1.3)

Results and discussion

Phase-solubility diagrams

The effect of K4M on the solubilizing effect of BCD and HPBCD is shown in Table 1. Solubilities of the drug in aqueous CD solutions (S_w) were much higher than in water (S_0), but the introduction of small amounts of K4M to the solution medium improved the solubility even further. Thus, to obtain a significant increase of the solubility (up to 39% with BCD and 6% with HPBCD), the solutions have to be heated to 120°C for 20 min (autoclaving).

Table 1 Effect of the addition of 0.1% (w/v) K4M to aqueous 1% (w/v) HPBCD and BCD solutions on solubilization of sulphamethizole

	S_0	S'_0	S_w	S_w'	S_w''	S_w'/S_w	S_w''/S_w
BCD	2.337	3.271	7.472	6.649	10.430	0.89	1.40
HPBCD	2.337	2.854	7.125	5.938	7.578	0.83	1.06

S_0 , solubility of SM in aqueous solution (2.336 mM)

S'_0 , solubility in aqueous 0.1% (w/v) solution of the K4M (mM)

S'_w , solubility in aqueous 0.1% (w/v) solution of the K4M with autoclaving process (mM)

S_w , solubility in aqueous 1% (w/v) CD solution (mM)

S_w' , solubility in aqueous solution containing both 0.1% (w/v) K4M and 1% (w/v) CD (mM)

S_w'' , solubility in aqueous solution containing both 0.1% (w/v) K4M and 1% (w/v) CD with autoclaving process (mM)

Figures 1 and 2 show the phase solubility diagrams of SM in aqueous BCD and HPBCD solutions in the presence or absence of K4M. In all cases, the solubility of the drug increases linearly as a function of the CD concentration, A_L -type according to Higuchi and Connors classification. The slope of the diagrams is lower than 1, and therefore, the complex is responsible for the increase in drug solubility has a 1:1 molar stoichiometry [14]. K4M enhanced significantly the solubilizing effect of CDs but did not affect the type of the phase-solubility diagram.

The apparent stability constants of SM-BCD and SM-HPBCD with and without K4M were calculated from the slopes of the phase-solubility diagrams assuming a 1:1 stoichiometry (Table 2). The stability constants of the inclusion complexes show an enhancement in the presence of K4M in the case of SM-BCD complex. This effect was not found for HPBCD systems, in fact, the effect of K4M was negligible. Similar results were found by Veiga [17] with HPBCD and HPMC, in disagreement with those obtained by other authors where the solubilization enhancement is more than simple, it is synergistic [10].

The concentration of SM dissolved was higher when an autoclaving process was carried out. During this autoclaving process, the rise in temperature caused a satura-

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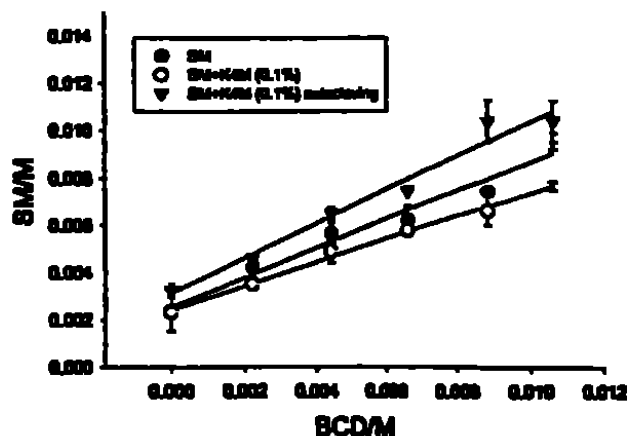


Fig. 1 Phase-solubility diagrams of SM in aqueous BCD solutions containing 0 and 0.1% K4M at 37°C

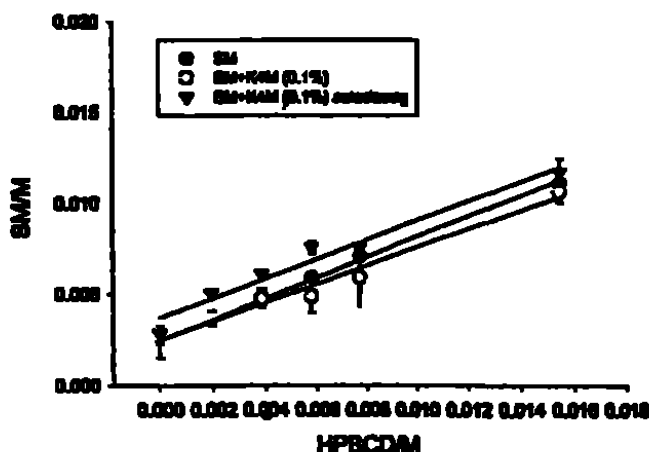


Fig. 2 Phase-solubility diagrams of SM in aqueous HPBCD solutions containing 0 and 0.1% K4M at 37°C

tion and an increase in the solubility of the drug, which could probably lead to improved interactions between SM and the CD molecules. The improved solubilization after autoclaving could be due to the various electrostatic forces involved and a facilitated fitting of the guest molecule into the cavity. For SM-HPBCD complex the increase of temperature after autoclaving could explain the lower value of the stability constant because it may well produce an overall exothermic reaction between the drug and CD [5].

Table 2 Stability constants ($K_{1:1}$) of SM complexes with HPBCD and BCD

	BCD	HPBCD
Without K4M	651.85 M ⁻¹ ($r^2=0.9684$)	563.95 M ⁻¹ ($r^2=0.9969$)
With K4M	419.93 M ⁻¹ ($r^2=0.9948$)	448.72 M ⁻¹ ($r^2=0.9715$)
With K4M and autoclaving	815.51 M ⁻¹ ($r^2=0.9721$)	409.12 M ⁻¹ ($r^2=0.9626$)

Preparation and characterization of solid inclusion complexes.

Solid inclusion complexes were obtained by freeze-drying which is a common pharmaceutical technique useful for preparing cyclodextrin inclusion complexes [18]. The drug:cyclodextrin ratio used was 1:1 mol:mol as found in the phase solubility diagrams for both CD derivatives and K4M was 0.1% w/v common polymer concentration [9, 15].

Differential scanning calorimetry and X-ray diffractometry were used to characterize the systems prepared.

DSC is a widely used analytical technique in the characterization of multi-component solid systems to analyze possible changes during heating. In the case of CDs, DSC can provide a lot of information on drug/CD interactions in the solid state. Polymers can form complexes with CDs with physicochemical properties distinct from those of individual cyclodextrin molecules [19]. Figure 3 shows the DSC curves of the physical mixtures of SM and BCD as well as those of the solid binary and multicomponent complexes prepared by the freeze-dried method. BCD shows an endothermic peak from 90 to 140°C, which may be attributed to the evaporation of the adsorbed water [20]. The endothermic peak due to fusion of the drug appears at 210°C. In the freeze-dried complexes,

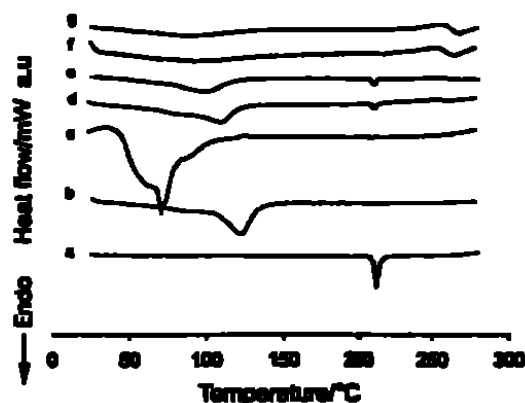


Fig. 3 DSC curves of different SM-BCD systems: a - SM, b - BCD, c - K4M, d - physical mixture SM+BCD, e - physical mixture SM+BCD/K4M, f - SM-BCD freeze-dried complex and g - SM-BCD/K4M freeze-dried complex

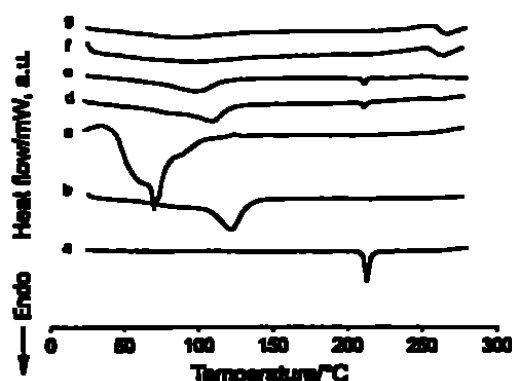


Fig. 4 DSC curves of different SM-HPBCD systems: a - SM, b - HPBCD, c - K4M, d - physical mixture SM+HPBCD, e - physical mixture SM+HPBCD/K4M, f - SM-HPBCD freeze-dried complex and g - SM-HPBCD/K4M freeze-dried complex

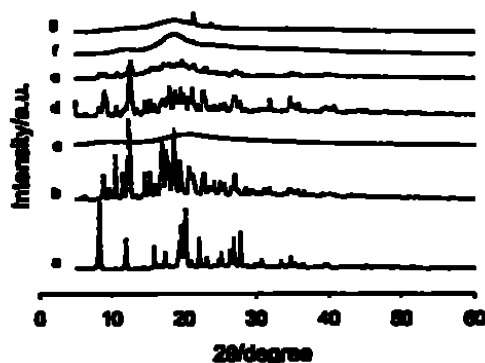


Fig. 5 X-ray diffraction patterns of different SM-BCD systems: a - SM, b - BCD, c - K4M, d - physical mixture SM+BCD, e - physical mixture SM+BCD/K4M, f - SM-BCD freeze-dried complex and g - SM-BCD/K4M freeze-dried complex

the plots show the absence of the characteristic endothermic melting peak, as compared to the physical mixtures in which this peak is clearly visible. The disappearance of the endothermic peaks of the drug is attributed to the amorphous state and the inclusion complexation of the drug inside the cavity [18].

The results of the HPBCD systems were similar to those of BCD, the peak or the drug fusion at 210°C disappeared in the binary and multicomponent complexes.

Powder X-ray diffractometry is a useful technique for the detection of CD complexation in powder or microcrystalline states. The diffraction pattern of the complex is supposed to be clearly distinct from the superposition of each component if a true complex exists.

The X-ray diffraction spectra of SM-BCD binary and multicomponent complexes in comparison with the physical mixture are shown in Fig. 5. The diffraction

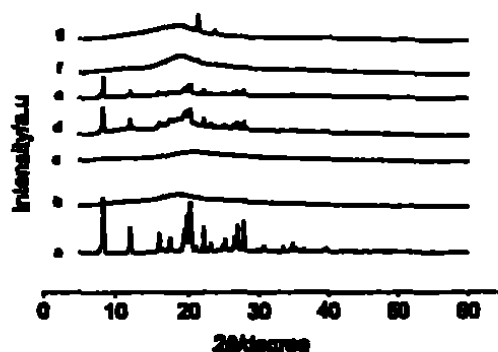


Fig. 6 X-ray diffraction patterns of different SM-HPBCD systems: a – SM, b – HPBCD, c – KAM, d – physical mixture SM+HPBCD, e – physical mixture SM+HPBCD/KAM, f – SM-HPBCD freeze-dried complex and g – SM-HPBCD/KAM freeze-dried complex.

patterns of the physical mixtures correspond to the superimposed diffractograms of SM and BCD, while those of the freeze-dried complexes show fewer and less intense peaks. This indicates that all freeze-dried compounds are markedly less crystalline than the physical mixtures or the pure components.

Similarly to BCD the X-ray diffractograms of HPBCD complexes consisted fundamentally of a single very broad band, whereas those of physical mixtures of the same compositions corresponded to superimposition of the individual components diffractograms (Fig. 6).

X-ray and DSC studies indicate the formation of amorphous binary and multi-component complexes by freeze-drying between the cyclodextrins and the drug.

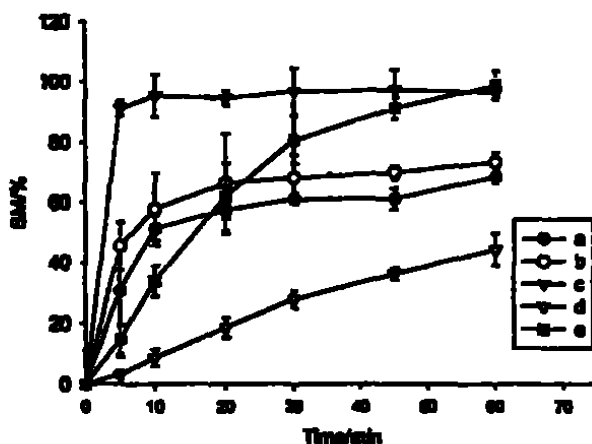


Fig. 7 Dissolution profiles of SM and different SM-BCD systems: a – SM, b – physical mixture SM+BCD, c – SM-BCD freeze-dried complex, d – physical mixture SM+BCD/KAM and e – SM-BCD/KAM freeze-dried complex.

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Effect of complexation on the dissolution of sulphamethizole

Figures 7 and 8 illustrate the dissolution profiles obtained with pure drug, physical mixtures and the inclusion complexes in water. In both cases, the liberation of the drug is delayed from the multicomponent system, showing the typical profile of a sustained release formulation. In fact, in spite of the stability constant of BCD being higher when the polymer is present, for the multicomponent system prepared with K4M, the dissolution rate of the drug is lower. This effect is also clear for HPBCD multicomponent complex. It seems that when the complex makes contact with the dissolution medium, K4M swells and controls the release of the drug [21].

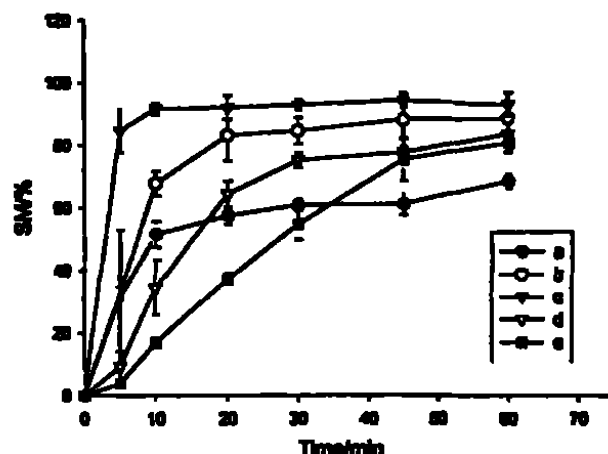


Fig. 8 Dissolution profiles of SM and different SM-HPBCD systems. a - SM, b - physical mixture SM+HPBCD, c - SM-HPBCD freeze-dried complex, d - physical mixture SM+HPBCD/K4M and e - SM-HPBCD/K4M freeze-dried complex.

One-way Anova of the dissolution efficiency 0-60 min revealed significant differences between the formulations (BCD: $F_{4,10}=74.09$, $\alpha<0.05$, HPBCD: $F_{4,10}=81.12$, $\alpha<0.05$). The Scheffé test grouped the formulations as follows:

BCD:

SM+BCD/K4M SM SM+BCD SM-BCD/K4M SM-BCD

HPBCD:

SM-HPBCD/K4M, SM SM+HPBCD/K4M SM+HPBCD SM-HPBCD

where SM+CD are the binary physical mixtures, SM-CD the binary complexes, SM+CD/K4M the multicomponent physical mixtures and SM-CD/K4M are the binary physical mixtures.

These results confirm that K4M controls the release of the drug, and in fact, the physical mixtures and inclusion complexes show, in both cases, the better dissolution profiles.

Conclusions

Our results show that K4M could enhance the complexation of SM with cyclodextrins in solution. This effect on SM solubility is only evident if an autoclaving process is included to promote the interaction between the cyclodextrin and the polymer. Solid multicomponent inclusion complexes with BCD or HPBCD and K4M can be obtained by freeze-drying and their formation has been proven using DSC and X-ray diffraction techniques. Additionally, the polymer allows to control the drug dissolution rate extending the process.

* * *

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Title Processes to generate submicron particles of water-insoluble compounds

United States Patent 6,177,103

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Appl. No. 335735

Filed: June 18, 1999

Abstract

Submicron particles of water-insoluble compounds, particularly drugs, are prepared by simultaneously stabilizing microparticulate suspensions of same with surface modifier molecules by rapid expansion into an aqueous medium from a compressed solution of the compound and surface modifiers in a liquefied gas and optionally homogenizing the aqueous suspension thus formed with a high pressure homogenizer

BACKGROUND AND SUMMARY OF INVENTION

A major problem in formulating biologically active compounds is their poor solubility or insolubility in water. For instance, over one third of the drugs listed in the United States Pharmacopoeia are either water-insoluble or poorly water-soluble. Oral formulations of water-insoluble drugs or compounds with biological uses frequently show poor and erratic bioavailability. In addition, drug insolubility is one of the most recalcitrant problems facing medicinal chemists and pharmaceutical scientists developing new drugs. Water-insolubility problems delay or completely block the development of many new drugs and other biologically useful compounds, or prevent the much-needed reformulation of certain currently marketed drugs. Although the water-insoluble compounds may be formulated by solubilization in organic solvents or aqueous-surfactant solutions, in many cases such solubilization may not be a preferred method of delivery of the water-insoluble agent for their intended biological use. For instance, many currently available injectable formulations of water-insoluble drugs carry important adverse warnings on their labels that originate from detergents and other agents used for their solubilization.

An alternative approach for the formulation of water-insoluble biologically active compounds is surface-stabilized particulate preparations. Small particle size formulation of drugs are often needed in order to maximize surface area, bioavailability and, dissolution requirements. Pace et al ("Novel Injectable Formulations of Insoluble Drugs" in Pharmaceutical Technology, March 1999) have reviewed the usefulness of the microparticulate preparations of water-insoluble or poorly soluble injectable drugs.

In U S Pat Nos. 5,091,187 and 5,091,188 to Haynes describe the use of phospholipids as surface stabilizers to produce aqueous suspension of submicron sized particles of the water-insoluble drugs. These suspensions are believed to be the first applications of the surface modified microparticulate aqueous suspension containing particles made up of a core of pure drug substances and stabilized

with natural or synthetic bipolar lipids including phospholipids and cholesterol. Subsequently, similar delivery systems exploring these principles have been described (G. G. Liversidge et al., U.S. Pat. No. 5,145,684; K. J. Ilig et al., U.S. Pat. No. 5,340,564 and H. William Bosch et al., U.S. Pat. No. 5,510,118) emphasizing the usefulness of the drug delivery approach utilizing particulate aqueous suspensions.

In U.S. Pat. No. 5,246,707 Haynes teaches uses of phospholipid-coated microcrystals in the delivery of water-soluble biomolecules such as polypeptides and proteins. The proteins are rendered insoluble by complexation and the resulting material forms the solid core of the phospholipid-coated particle.

These patents and others utilized processes based on the particle size reduction by mechanical means such as attrition, cavitation, high-shear, impaction, etc. achieved by media milling, high pressure homogenization, ultrasonication, and microfluidization of aqueous suspensions. However, these particle size reduction methods suffer from certain disadvantages, such as long process duration (high-pressure homogenization or microfluidization) and contamination (media milling, and ultrasonication). In addition, these methods may not be suitable for aqueous suspensions of compounds with limited stability in aqueous medium at the pH, high temperature and high pressure conditions prevailing in these processes.

Among the alternatives that address these problems is a procedure which uses liquefied gases for the production of microparticulate preparations. In one such method liquefied-gas solutions are sprayed to form aerosols from which fine solid particles precipitate. The phenomenon of solids precipitated from supercritical fluids was observed and documented as early as 1879 by Hannay, J. B. and Hogarth, J. "On the Solubility of Solids in Gases," *Proc. Roy. Soc. London* 1879 A29, 324.

The first comprehensive study of rapid expansion from a liquefied-gas solution in the supercritical region was reported by Krukons (1984) who formed micro-particles of an array of organic, inorganic, and biological materials. Most particle sizes reported for organic materials, such as lovastatin, polyhydroxyacids, and mevminol, were in the 5-100 micron range. Nanoparticles of beta-carotene (300 nm) were formed by expansion of ethane into a viscous gelatin solution in order to inhibit post expansion particle aggregation. Mohamed, R. S., et al. (1988), "Solids Formation After the Expansion of Supercritical Mixtures," in *Supercritical Fluid Science and Technology*, Johnston, K. P. and Penninger, J. M. L., eds., describes the solution of the solids naphthalene and lovastatin in supercritical carbon dioxide and sudden reduction of pressure to achieve fine particles of the solute. The sudden reduction in pressure reduces the solvent power of the supercritical fluid, causing precipitation of the solute as fine particles.

Tom, J. W. and DeBenedetti, P. B. (1991), "Particle Formation with Supercritical Fluids—a Review," *J. Aerosol Sci.* 22 555-584, discusses rapid expansion of supercritical solutions techniques and their applications to inorganic, organic, pharmaceutical and polymeric materials. This technique is useful to comminute shock-sensitive solids, to produce intimate mixtures of amorphous materials, to form polymeric microspheres and deposit thin films.

Most studies of rapid expansion from supercritical solution on organic materials utilize supercritical carbon dioxide. However, ethane was preferred to carbon dioxide for beta-carotene because of certain chemical interactions. Carbon dioxide is generally preferred, alone or in combination with a

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cosolvent Minute additions of a cosolvent can significantly influence the solvent properties. When cosolvents are used in rapid expansion from a supercritical solution, care is required to prevent dissolution of the particles due to solvent condensing in the nozzle. Normally, this is achieved by heating the supercritical fluid, prior to expansion, to a point where no condensate (mist) is visible at the nozzle tip.

A similar problem occurs when carbon dioxide is used. During adiabatic expansion (cooling), carbon dioxide will be in two phases unless sufficient heat is provided at the nozzle to maintain a gaseous state. Most investigators recognize this phenomenon and increase the pre-expansion temperature to prevent condensation and freezing in the nozzle. A significant heat input is required (40-50 kcal/kg) to maintain carbon dioxide in the gaseous state. If this energy is supplied by increasing the pre-expansion temperature the density drops and consequently reduces the supercritical fluid's solvating power. This can lead to premature precipitation and clogging of the nozzle.

The solvent properties of liquefied-gas are strongly affected by their fluid density in the vicinity of the fluid's critical point. In rapid expansion from liquefied-gas solutions, a non-volatile solute is dissolved in a liquefied-gas that remains either in the supercritical or sub-critical phase. Nucleation and crystallization are triggered by reducing the solution density through rapid expansion of the liquefied-gas to atmospheric conditions. To achieve this the liquefied-gas is typically sprayed through 10-50 micron (internal diameter) nozzles with aspect ratios (L/D) of 5-100. High levels of supersaturation result in rapid nucleation rates and limited crystal growth. The combination of a rapidly propagating mechanical perturbation and high supersaturation is a distinguishing feature of rapid expansion from a liquefied-gas solution. These conditions lead to the formation of very small particles with a narrow particle size distribution.

There are a number of advantages in utilizing compressed carbon dioxide in the liquid and supercritical fluid states, as a solvent or anti-solvent for the formation of materials with submicron particle features. Diffusion coefficients of organic solvents in supercritical fluid carbon dioxide are typically 1-2 orders of magnitude higher than in conventional liquid solvents. Furthermore, carbon dioxide is a small linear molecule that diffuses more rapidly in liquids than do other antisolvents. In the antisolvent precipitation process, the accelerated mass transfer in both directions can facilitate very rapid phase separation and hence the production of materials with sub-micron features. It is easy to recycle the supercritical fluid solvent at the end of the process by simply reducing pressure. Since supercritical fluids do not have a surface tension, they can be removed without collapse of structure due to capillary forces. Solvent removal from the product is unusually rapid. No carbon dioxide residue is left in the product, and carbon dioxide has a number of other desirable characteristics, for example it is non-toxic, nonflammable, and inexpensive. Furthermore, solvent waste is greatly reduced since a typical ratio of antisolvent to solvent is 30:1.

Exploiting these concepts Hennksen et al. in WO 97/14407, disclosed a process using compressed fluids to produce sub-micron sized particles of water insoluble compounds with biological uses, particularly water insoluble drugs by precipitating a compound by rapid expansion from a supercritical solution in which the compound is dissolved, or precipitating a compound by spraying a solution, in which the compound is soluble, into compressed gas, liquid or supercritical fluid which is miscible with the solution but is antisolvent for the compound. In this manner precipitation with a compressed fluid antisolvent (compressed fluid antisolvent) is achieved.

An essential element of this process is the use of phospholipids and other surface modifiers to alter the surface of the drug particles to prevent particle aggregation and thereby improve both their storage stability and pharmacokinetic properties. This process combines or integrates phospholipids or other suitable surface modifiers such as surfactants, as the aqueous solution or dispersion in which the supercritical solution is sprayed. The surfactant is chosen to be active at the compound-water interface, but is not chosen to be active at the carbon dioxide-organic solvent or carbon dioxide-compound interface when carbon dioxide is used as the supercritical solution. The use of surface modifying agents in the aqueous medium allowed making submicron particles by the compressed fluid antisolvent process without particle aggregation or flocculation.

Claim 1 of 15 Claims

What is claimed is:

1 A process of preparing a stable suspension of sub-micron particles of a water-insoluble or substantially water-insoluble biologically active compound of up to 2000 nm in size comprising the successive steps of

(a) dissolving a water-insoluble or substantially water-insoluble biologically active compound and a first surface modifier in a liquefied compressed gas solvent therefor and forming a solution of greater than 1% w/w of said compound in said solvent and thereafter,

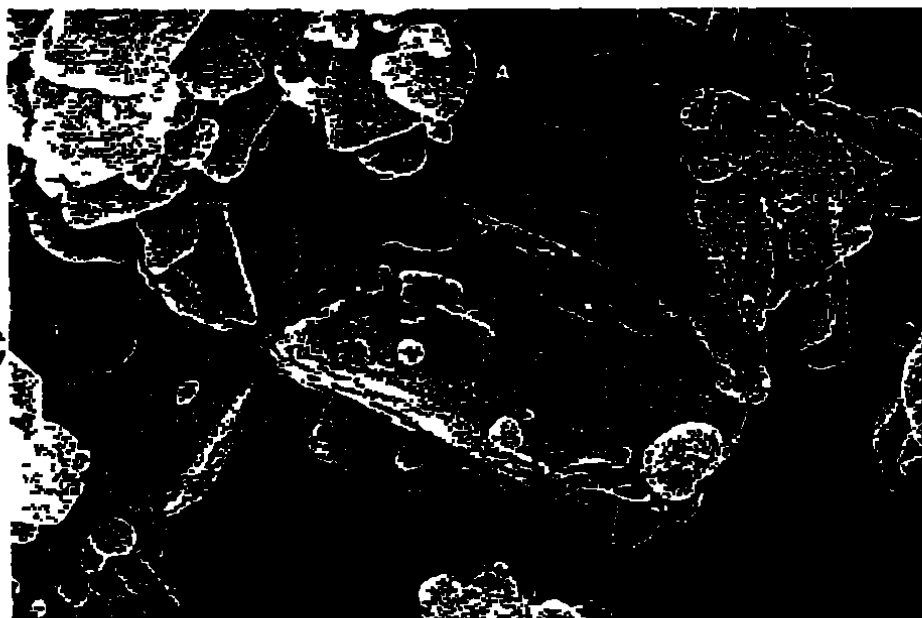
(b) expanding the compressed fluid solution prepared in step (a) into water or aqueous solution containing a second surface modifier and water-soluble agents thereby producing a suspension of microparticles, and thereafter

(c) homogenizing the suspension of step (b) at high pressure.

If you want to learn more about this patent, please go directly to the U.S. Patent and Trademark Office Web site to access the full patent.

New Particle Engineering Technology Improves Drug Solubility

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Scanning electron micrographs of the androgenic steroid danazol show significantly more complex structure and greater surface area resulting from treatment by evaporative precipitation into aqueous solution (EPAS). EPAS is one of a portfolio of proprietary solubilization technologies used by Dow Chemical's BioAqueous solubilization services. Photo A shows untreated micronized danazol crystals.

According to industry studies, more than 30% of new chemical entities developed during drug discovery efforts exhibit poor solubility characteristics, severely limiting their therapeutic usefulness. Today, however, recent advancements in particle engineering technology may be opening the door to a host of drug compounds previously considered unviable.

Because dissolution rates are related to surface area, one approach to increasing solubilization is to prepare drug particles of uniformly small size and high surface area. To take advantage of this, Dow Chemical Company (Midland, MI) has developed a series of technologies to prepare such nanostructured particles and is making them available to pharma companies through a new custom service program aimed at overcoming such dissolution-rate limited drug compounds.

The company's BioAqueous Solubilization Services currently incorporate four different technological approaches: controlled precipitation, template emulsion, and two new advanced particle engineering techniques codeveloped with the University of Texas at Austin—spray freezing into liquid (SFL) and evaporative precipitation into aqueous solutions (EPAS) (see sidebar).

As described by Dr. Ed Elder, pharmaceuticals director, Dow Pharmaceutical Technologies, "We recognized that there was a need in the industry not being addressed, so we began working with the University of Texas to combine their expertise in chemical engineering as well as pharmaceutical technology. Dr. Keith Johnston, UT professor of chemical engineering, worked in parallel with Dr. Bill Williams, professor of pharmaceuticals at UT's College of Pharmacy. Says Johnston,

"Chemical engineering and pharmaceutical science are extremely synergistic. The work wouldn't have been possible without collaboration between our two groups."

Although both the SFL and EPAS techniques are applicable to other industries and processes, Johnston points out that the techniques have been specifically modified for the drug solubilization application "For example, in SFL we do the spraying directly within the cryogenic fluid itself. This leads to smaller particles at faster freezing rates."

For pharmaceutical companies, of course the ability to industrialize processes is a primary concern. As noted by Johnston, "The beauty of SFL is that you can go from spraying solution in a semicontinuous process to the final dry powder in a relatively fast, highly integrated fashion. Solvent removal can be accomplished either via lyophilization in vials or through a fluidized-bed process using dry air with definite advantages to the fluidized-bed technology."

As described by Elder, ultimately, a number of factors have to be considered before choosing which technological approach to apply to a particular drug product. "Factors such as relative performance, cost, and complexity all must be considered before we can recommend an approach. It's absolutely essential that we completely understand all of the unique challenges associated with the molecule. In addition to our own studies, we also work to maximize the customer's existing data."

Johnston agrees, pointing out that "there are definite aspects of phase separation rates, surfactant to drug ratios, and particle morphologies, that must be considered in designing processes for particular goals. For example, SFL leads to faster phase separation than EPAS."

Ultimately, Elder says alternative solutions, each with specifically defined advantages and disadvantages, will likely be proposed to customers. "The final choice will result from a close working relationship with the customer. In addition to selecting the right technology, the optimum additives and stabilizers will also have to be determined."

Work at the University of Texas will continue as researchers look for new ways to improve existing processes and to develop

Dissolution Technologies

In the controlled precipitation dissolution process, the drug compound of interest is dissolved in a water-miscible solvent and dispersed into water. Nanostructured drug particles are formed from the solvent droplets as the solvent dissolves into the water phase. Stabilizers are added to the water and/or solvent to control particle growth and to stabilize the final particles. The stabilized particles are isolated as dry powders by standard techniques. In the complete emulsion process, an oil-in-water emulsion is prepared and then switched with a nonaqueous solution of a drug compound and stabilizers. The solvent and water are then removed, and the stabilized drug particles recovered. By changing the size of the initial emulsion droplets, the size of the drug particles can be controlled. Through selective use of solvents and stabilizers, emulsion stability is achieved with no, or suppressed, "Ostwald ripening." (Ostwald ripening describes a phenomenon in which initially many small crystals form in a system but then slowly transform to a few larger crystals.)

In the spray freezing into liquid (SFL) process, the drug and its excipients are dissolved into a solvent and injected into a cryogenic liquid (temperatures below -40°C) such as liquid nitrogen. The droplets of the drug solution freeze at a rate sufficient to minimize crystallization and form amorphous particles. The nitrogen and solvent are then removed under conditions that avoid agglomeration, or ripening, of the drug particles. The frozen SFL material is then dried either by lyophilization or atmospheric freeze drying, resulting in a highly porous material.

In the evaporative precipitation into aqueous solutions (EPAS) process, a drug is dissolved in a water-insoluble solvent and atomized into water above the solvent's boiling point. The rapid expansion and atomization of the solvent in the water phase causes the formation of nanostructured particles. The solvent and/or the water phase contain the stabilizers for the particles. The evaporated solvent is recovered, and the stabilized particles are isolated from the aqueous phase by standard techniques.

new ones. Says Johnston, "We're continually achieving a better understanding of how to stabilize these particles with very high drug to surfactant ratios, utilizing very small amounts of excipient in terms of the dosage forms. And, we're also focusing on how to further control particle sizes."

Meanwhile, Dow will be making use of its contract manufacturing facility in Midland, Michigan, to provide a commercial-scale manufacturing capability for each of the four technologies. The company is currently capable of kilo-scale production to meet the needs of Phase II and Phase III clinical trials. Says Robert Connors, Dow Pharmaceutical senior new business development leader, "We expect to be working closely with a number of pharma companies to evaluate the applicability of our technologies to their products."

John Haystead

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THE EFFECT OF PARTICLE SIZE ON BIOAVAILABILITY IN CYCLOSPORINE PREPARATIONS BASED ON SUBMICRON DISPERSIONS

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Key words: Cyclosporine A / Bioavailability / Particle Size

The effect of particle size on bioavailability of 9 different formulations with cyclosporine A was studied. A common feature of all the formulations was the ability to form submicron dispersions under dilution. The composition of individual formulations was chosen in such a way that they were based on same or similar excipients. For each formulation, pharmacokinetic study was carried out in beagle dogs. On groups of 10 dogs, the average AUC was evaluated. Particle size of formulations under dilution in water was measured by laser scattering method. According to the results of particle size measurement, the formulations were sorted out into groups of similar particle size distribution by use of two methods of multivariate statistical analysis. The average AUC within groups and between-groups was compared, and the effect of particle size on bioavailability was evaluated.

INTRODUCTION

Cyclosporine A, an immunosuppressive drug, was introduced into the therapeutic practice in 80's. As a poorly water-soluble compound, it was originally formulated into a lipophilic medium providing crude emulsion after dilution with water. Since that time, a lot of effort was paid to the improvement of cyclosporine bioavailability. One of the first improvements, reported either for co-administration of long- and medium-chain triglycerides or reported for sucrose laurate, were associated with formation of mixed micelles in the gut or small intestine (1, 2). Further approaches included formulations based on formation of liposomes (3, 4), nanoparticles, or liquid crystals (5). The common feature of these approaches was to control the creation of some kind of dispersion in either the fluid for administration, or in stomach, or gut or small intestine. Therefore, self-establishing submicron dispersions were generally preferred for this purpose. After microemulsions or microemulsion preconcentrates were introduced in 90's, the size of particles has been considered an important and almost crucial factor affecting the bioavailability of cyclosporine A preparations which are based on the formation of submicron dispersions (6).

To verify such an assumption is not a simple task: once a formulation has a controlled size distribution independent from the conditions of administration (i.e., from dilution, mixing time and speed etc.), it can be changed only by a change of the ratio of individual excipients or by replacement of the excipients. Hence, any change of bioavailability can be attributed to the effect of a particular excipient rather than to the effect of particle size of the formulation. For this reason we

tried to prepare formulations which would differ in the size of particles that the formulations form after dilution by varying only the same or similar excipients. In this way, we obtained 9 different formulations in which the effect of excipients was minimized and the particle size of which ranged from 10 to 500 nm.

Another problem is how to evaluate the particle size. Obviously, the use of one single parameter like the average particle diameter, hydrodynamic diameter or aggregate molecular weight can be misleading not only because of not reflecting the particle shape, but also because of masking the information about particle size distribution. The approach used in this study was to compare the similarity or dissimilarity of particle size distribution by means of statistical methods for multivariate analysis. Two independent methods were used: the principal component analysis (PCA) and cluster analysis (CA). To evaluate the effect of particle size on bioavailability, the average AUC was compared for those formulations which showed significant difference in particle size distribution both by PCA and CA.

METHODS

Materials

All the formulations tested were prepared on laboratory scale equipment in laboratories of Department of Biopharmacy and Pharmacokinetics, IVAX-CR, a.s. Czech Republic. Excipients used in composition of individual formulations were commercially available materials of pharmaceutical grade. The qualitative composition of all 9 formulations is listed in Table 1.

Subjects

Beagle dogs, males aged between 12–36 months of weight 9–15 kg were used in each pharmacokinetic study. The dogs were fed with a standard pellet diet in a quantity 300 g per day with water *ad libitum*.

Pharmacokinetic studies

Each individual formulation was administered with a dosing pipette in a form of pre-diluted dispersion as a single dose of 100 mg cyclosporine A. The administration was preceded by 18 h fasting period. After administration, blood samples were taken in 0, 1, 2, 3, 5, 8, 12, and 24 hour intervals. Samples were analysed for cyclosporine content by non-specific radioimmunoassay method. From the concentration – versus – time curves, area under the curve (0–24) was calculated.

Blood collection

Blood samples were taken from foreleg vein of the dogs into tubes with EDTA K3 (1.5 mg/ml). The samples were immediately frozen at –20 °C and kept in a freezer until analysis.

Cyclosporine A determination

Non-specific RIA assay for cyclosporine A, IMMUNOTECH, Prague, Czech Republic, Cyclosporine RIA and its metabolites, Cat. #1444 was used. 50 µl of blood sample were extracted with 950 µl of methanol. After centrifugation (1600 × g, 5 minutes, 5 °C), 50 µl of extracted samples, controls and standards were transferred into polystyrene tubes. 100 µl of ¹²⁵I-CyA and 50 µl of polyclonal antibody was added. The reaction tubes were incubated 3 hours at 25 °C. 500 µl of separating reagent was added and reaction tubes were incubated 1 hour at 5 °C. After centrifugation (1600 × g, 20 minutes, 5 °C) and decanting the supernatant, the bound radioactivity of calibrators, controls and samples were measured. All calibrators, controls and samples were made in duplicates. The radioactivity was measured using gamma scintillation counter MULTIGAMMA 1261 (LKB, Finland). The results were calculated using WinCalc software (LKB, Finland). The calibration range of RIA (non-specific) method was 8–1680 ng/ml. Functional sensitivity was calculated at about 8 ng/ml. Within assay precision lied at 472 ng/ml – 6.0 %, at 836 ng/ml – 4.2 %. Between assay precision at 347 ng/ml – 5.7 % at 754 ng/ml – 5.6 %. The analysis were performed by Department of Nuclear Medicine at University Hospital in Ostrava. This laboratory participated in international External Quality Assessment (DGKC – Deutsche Gesellschaft für Klinische Chemie, Ringversuch für Cyclosporin).

Particle size determination

Particle size distribution was measured by quasi elastic light scattering method (QELS) using Ar-laser (Lexel Laser Inc., USA, $\lambda = 514.5$ nm, output power 50 mW) as a light source and the BI-9000 AT digital correlator (Brookhaven Instruments, USA) as a detector. The detector and light source arrangement was set up in angle 90° by BI 200 SM goniometer. The samples were prepared by dilution of concentrates with redistilled water at ratio 1:20 followed by standard homogenization in ultrasonic bath (10 mm). All measurements were done at 25 °C.

The autocorrelation curves and the scattered light intensities were processed by Brookhaven software for dynamic light scattering. Particle size distribution spectra obtained were transformed to equal scales. All measurements were done by Department of Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic.

Software and Statistical methods

Pharmacokinetic parameters were calculated with WinNonlin 1.1 (Scientific Consulting Inc., USA). Their Multiple-range analysis, Two-sample analysis and Box-and-Whisker plots were done in Statgraphics, v 7.0. To resolve formulations into groups, principal component analysis method and cluster analysis method in S-Plus 2000 (MathSoft Inc., USA) were used. Bi-directional comparison of bioavailability versus particle size was performed: for pairs of formulations which were identified as substantially different from the particle distribution size point, two-sample comparison of AUC (0–24) was done. Vice versa, formulations identified as significantly different from the bioavailability point of view (having statistically significant difference in AUC found by multiple comparison method) were compared from the point of their particle size distribution.

RESULTS

Pharmacokinetic studies

The results of bioavailability studies in dogs are summarized in Table 2. The graphical analysis of the results is done by means of Box-and-Whisker plot (Figure 1). As can be seen from Figure 1, formulations L261 and L267 appear to be significantly different from the point of their bioavailability in dogs. As possibly different can be identified also the pairs of formulations L267 – L269, L267 – L272, and L267 – L300.

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Table 1. Qualitative and quantitative composition of tested formulations

Components ↓	Formulations →								
	L261	L263	L267	L267.2	L269	L271	L272	L273	L280
Cyclosporine A	10.0 %	10.0 %	10.0 %	10.0 %	10.0 %	10.0 %	10.0 %	10.0 %	10.0 %
Cremophor RH 40	45.0 %	40.0 %			25.5 %	35.0 %	28.2 %	28.0 %	40.0 %
Polymerate Tween 80	13.5 %	20.0 %						22.0 %	
Oleic Acid	31.5 %	10 %		10.0 %					
Dihydroxyyl monolaurate		20%			9.5 %		12.2 %		
Octyl Alcohol			31.5 %	21.0 %	19.9 %	21.0 %	19.0 %	22.0 %	
Polymerate Tween 20			13.0 %			17.0 %			
Carbitol F 1880-2			0.5 %	0.5 %					
Nikol BCD-40			45.0 %	40.0 %					
Dihydroxyyl Monolaurate				8.5 %	14.0 %		18.6 %		
Propylene glycol					20.0 %		12.0 %		10.0 %
Dihydroxyyl Pentadecanoate						17.0 %			
Tocopheryl Sulfate								18.0 %	
Glycerol monolaurate									30.0%
Ethanol									10.0 %
Water				10 %					

) all concentrations listed are w/w concentrations

Table 2. Results of Bioavailability Studies (AUC (0-24)) for 9 Formulations in Dogs

Subjects (Dogs) ↓	Formulations →								
	AUC (0-24) [ng/h]								
	L261	L263	L267	L267.2	L269	L271	L272	L273	L280
1	16747	9823	10198	14835	19806	9384	7131	11171	13442
2	6268	10834	7734	13354	12043	4129	475	13448	896
3	15416	14192	12631	12473	15990	8459	11531	9826	9889
4	17283	12480	11476	13985	12573	9895	10803	13458	11782
5	18322	13741	4145	7266	8854	8488	14725	14516	13485
6	13663	8929	19099	14885	16112	14153	12081	8070	15750
7	11619	12008	5416	8096	9293	10381	13188	11084	13805
8	12623	10308	9893	10768	6193	11518	15900	9121	14814
9	14351	8938	7757	10139	8294	10388	10836	12887	13143
10	18791	16422	11701	8201	14830	12651	13873		12744
Mean AUC (0-24)	14508	11771	9641	11882	12907	11269	12853	11478	12790
Standard Deviation	3563	2339	3195	3195	4349	2302	2649	2857	1892

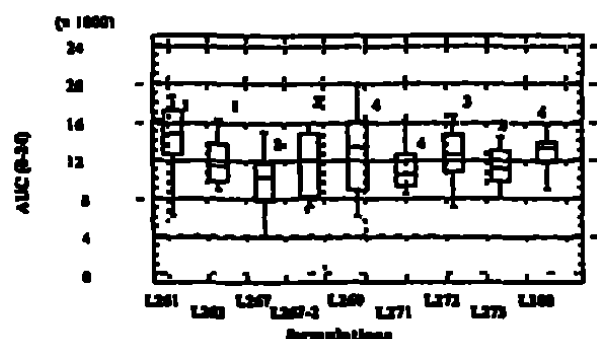


Fig. 1. Box-and-Whisker Plot for AUC(0-24) of Formulations L261-L300

Another statistical method, multiple range analysis, requires suitable extension to be used for specific case. The Least Significant Difference (see Table 3) method provided the most discriminating power in this case and confirmed the significant difference of L261 and L 267 formulations as well as that of formulations L267 - L269, L267 - L272, and L267 - L300. The Tukey HSD and Bonferroni methods identified only the formulations L261 and L 267 as different. The Scheffé method did not found any pair of formulations significantly different from the point of AUC(0-24).

Particle size determination

The distribution of particle sizes of individual formulations is given in Table 4. These data were processed by Principal Component Analysis. As can be seen from Figure 2, more than 54 % of the variability in data can be explained by one principal component and other 26% of variability by the second principal component. Other components 3, 4, 5, 6 and 7 contribute to the description of variability in data by additional 8 %, 5 %, 3 %, 2 % and 1 %, respectively

It can be concluded that the major part of variability in data (> 80 %) can be explained by components 1 and 2.

When the information contained in each particle size distribution spectrum is described by two principal components only, the 9 formulations can be divided into 4 different groups of formulations having similar particle size distribution within group and different particle size distribution between groups. The situation is graphically shown in Figure 3. Group I includes formulations L261 and L263 (see also Fig. 4), Group II consists of one formulation L267 (see Fig. 5), Group III includes formulations L267.2, L272, and L273 (see also Figure 6), and Group IV includes formulations L269, L271 and L300 (see Fig. 7).

Table 3. Multiple Range Analysis of Bioavailability Results of 9 Tested Formulations L261 - L300

Method	Contrasts (pairs of samples compared)	Difference	+/- Limits	Significant Difference
LSD method (Least Significant Difference)	L261 - L267	4867.45	2771.46	*
	L261 - L271	3293.15	2771.46	*
	L267 - L269	-3263.93	2771.46	*
	L267 - L272	-3885.70	2771.46	*
	L267 - L300	-3149.35	2771.46	*
Tukey HSD (Honest Signif- icant Difference)	L261 - L271	4867.45	4439.88	*
Bonferroni	L261 - L271	4867.45	4623.15	*
Scheffé	None	-	-	-

* denotes a statistically significant difference

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Table 4. Distributions of Particle Size of 9 Different Formulations L261 - L300

Particle Size (nm)	Particle count (Relative Intensity Units)									
	L261	L263	L267.2	L272	L273	L271	L269	L270	L268	L266
100	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
110	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
120	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
130	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
140	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
150	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
160	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
170	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
180	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
190	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
200	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
210	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
220	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
230	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
240	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
250	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
260	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
270	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
280	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
290	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
300	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
310	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
320	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
330	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
340	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
350	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
360	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
370	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
380	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
390	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
400	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
410	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
420	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
430	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
440	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
450	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
460	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
470	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
480	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
490	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
500	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
510	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
520	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
530	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
540	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
550	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
560	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
570	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
580	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
590	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
600	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
610	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
620	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
630	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
640	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
650	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
660	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
670	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
680	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
690	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
700	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
710	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
720	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
730	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
740	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
750	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
760	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
770	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
780	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
790	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
800	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
810	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
820	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
830	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
840	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
850	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
860	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
870	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
880	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
890	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
900	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
910	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
920	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
930	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
940	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
950	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
960	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
970	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
980	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
990	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1000	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

classified as related (similar) formulations, as well as the formulations L267.2, L272, and L273. At the same time, these two groups are relatively distant and substantially different from one another. Group IV includes formulations L269 and L271, and also formulation L267 which was evaluated as a self-standing group by PCA method.

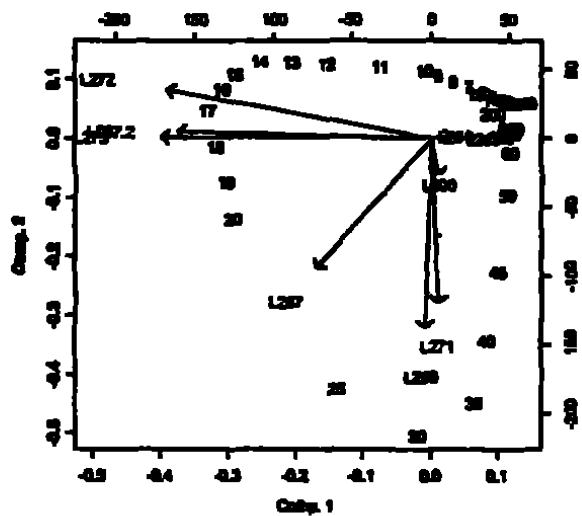


Fig. 3. Principal component analysis of Particle Size Distribution of 9 Different Formulations - Analysis by Two Components

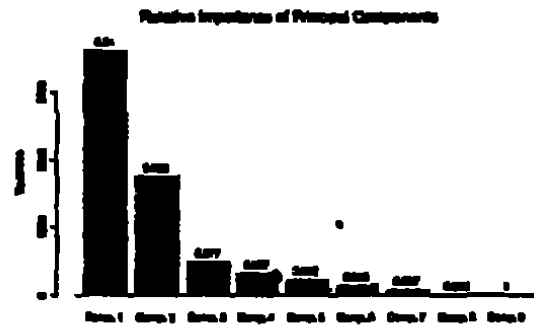


Fig. 2. Principal component analysis of Particle Size Distribution

Groups I, III and IV are substantially different from each other from the point of particle size distribution. On the other hand, formulations being within the same group cannot be considered different but rather similar with respect to the distribution of particle sizes.

Another statistical method which was used for evaluation of the similarity or dissimilarity of particle size distributions is the cluster analysis. As can be seen from Figure 8, the formulations L261, L263 and L300 are

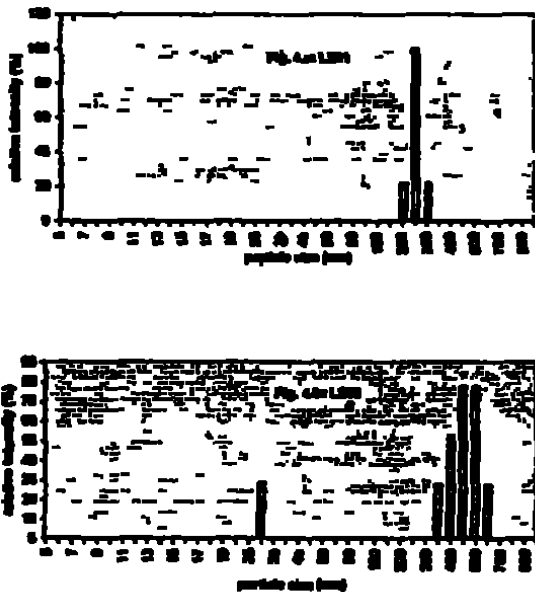


Fig. 4. (a, b) Particle Size Distribution of Formulations L261 and L263 resolved as similar by PCA method - Group I

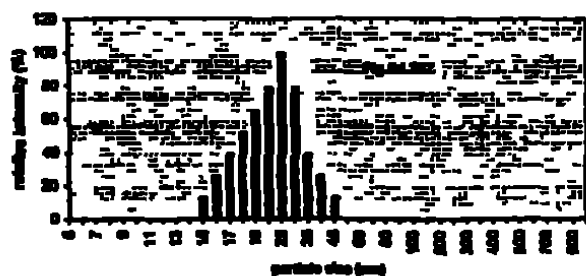


Fig. 5. Particle Size Distribution of Formulation L267 - Group II

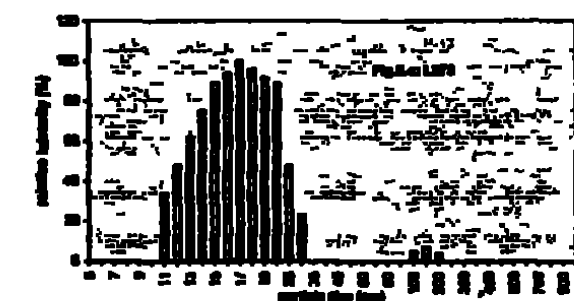
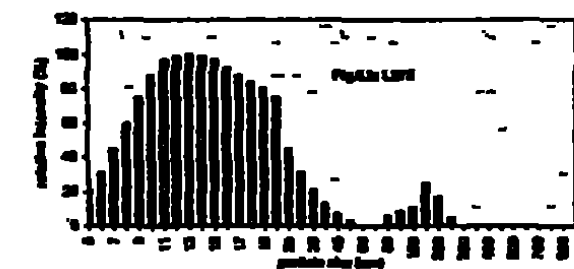
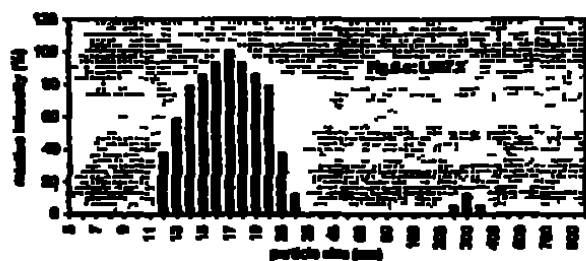


Fig. 6. (a, b, c) Particle Size Distribution of Formulations L267.1, 272 and L273 resolved as similar by PCA method - Group III

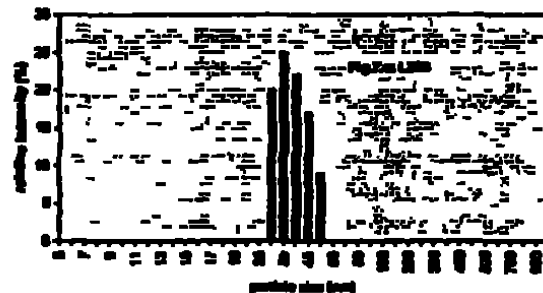
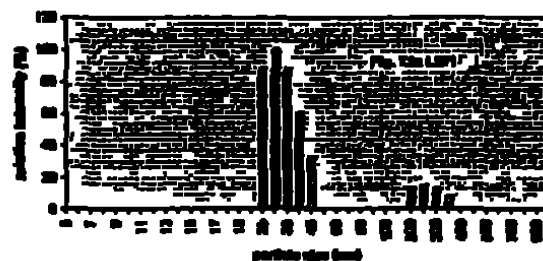
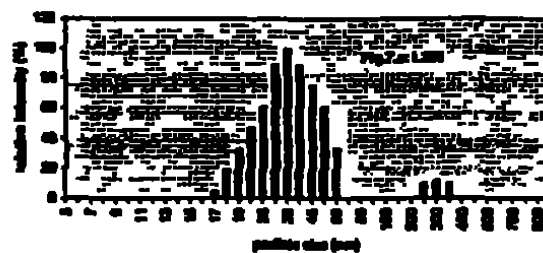


Fig. 7. (a, b, c) Particle Size Distribution of Formulation L268, L271 and L300 resolved as similar by PCA method - Group IV

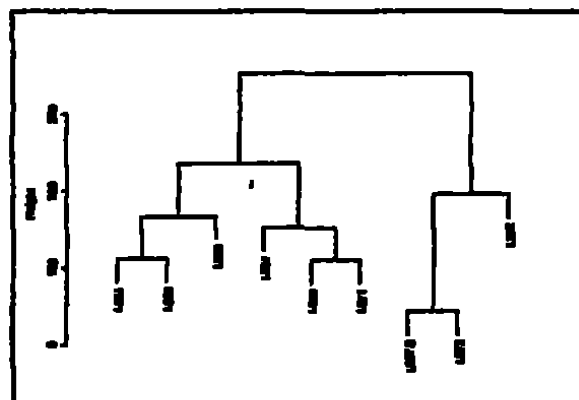


Fig. 8. Cluster Analysis of Particle Size Distribution of 9 Different Formulations

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DISCUSSION

Which is concerning the results of multiple comparisons, the Scheffé method (7) produces the widest interval statements and thus it is the most conservative. For this purpose, the Tukey method (8) seems to be the most suitable. The same result provides the Bonferroni method. Therefore, we consider the bioavailability of formulations L261 and L267 to be significantly different, the bioavailability of L261 to be significantly higher than that of L267. Surprisingly, the formulation L261 forms one of the largest particles (similarly as L263), and the formulation L267 forms very fine particles having maximum particle count around 25 nm.

Formulations L267.2, L 269, L271, L272, L273 and L300 are all highly bioavailable, their average AUC (0-24) lies in the range 10,000–14,000 $\mu\text{g/L.h}$. If we look at their particle size distribution, formulations L267.2, L272, and L273 are classified as different from formulations L269, L271 and L300. However, all of them have maximum particle count for particles in the range from 10 to 50 nm, so from practical point of view, the differences in particle sizes in this range can hardly tell something about their effect on absorption and bioavailability.

Vice versa, the maximum difference in particle size was observed for the formulation L272 on one side (it forms the smallest particles) and formulations L261 and L263 on the other side (they form the largest particles). If we look at their bioavailability, there is no significant difference between these two groups, as the AUC (0-24) of the L272 formulations is in between the formulations L261 and L263. From these data, it seems that particle size is not the key characteristic which affects the bioavailability, and that it is possible to prepare highly bioavailable formulations for cyclosporine active substance which do not necessarily have to form very fine particles, as for example microemulsion (particle size <200 nm).

When particle size is not the key factor, a question arises what other characteristic can explain for the differences in absorption and bioavailability of different cyclosporine A formulations. One of the possible explanations is that the actual contact surface can be the answer to this question. It can explain both for the fact why some experiments showed that the reduction of particle size led to an enhancement of absorption of cyclosporine A, as well as for the fact why some formulations are highly bioavailable even though they form very large particles in solution. In our opinion, the reason for high absorption of some large particles forming formulation lies in the deformation and/or adhesive characteristics of such particles, which are able to produce much larger effective contact surface at the epithelial layer than would correspond to their approximation by ideal spherical shape.

CONCLUSION

We have proved that it is possible to prepare different formulations with cyclosporine A which have different particle size distribution but the same or similar bioavailability in dogs. According to our results, in the submicron region, the particle size distribution of formulations based on self-emulsifying drug-delivery systems does not explain for the differences in bioavailability and is not the key characteristics which has to be observed when formulating the self-emulsifying drug delivery system. It is suggested that a more suitable, bioavailability-related formulation feature has to be found out which can fulfil the role.

ACKNOWLEDGEMENTS

The authors would like to thank to Mr. M. Pidrčík, Department of Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic, for his contribution related to the particle size measurement, and to prof. M. Meloun, Department of Analytical Chemistry, Technical University Pardubice, Czech Republic for his valuable comments on statistical evaluation.

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Glassy Solid Solutions of Poorly Soluble Drugs in Isomalt for a Rapid Bioavailability

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Commonly, the term solid dispersion means the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent, or melting-solvent method. Four types of solid suspensions and two types of solid solutions exist, considering the crystalline or amorphous state of the respective drug and carrier as well as the level of dispersion [1]. Glassy solid solutions are a specific kind of solid dispersions, wherein a drug is dissolved in an amorphous carrier at the molecular level. In order to distinguish between solid suspensions and solid solutions in the case of isomalt as carrier, hot stage microscopy (HSM), dissolution testing and differential scanning calorimetry (DSC) are used.

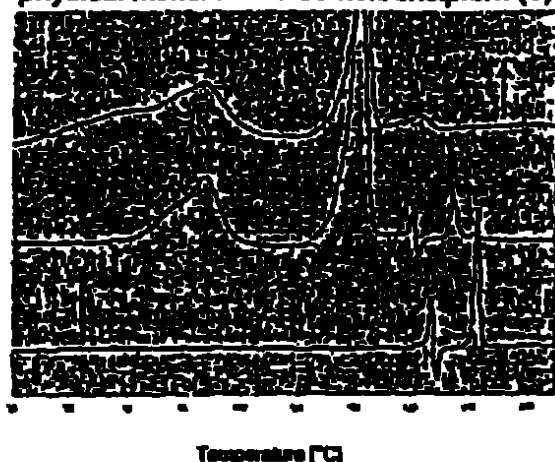
The carrier isomalt (1-O- α -D-glucopyranosyl-D-mannit dihydrate/6-O- α -D-glucopyranosyl-D-sorbit) is registered as sugar substitute and is mainly used for the production of sugar free hard candies. Isomalt can be heated above its melting point without decomposition. By cooling the melt to room temperature it solidifies amorphously with a glass transition at 60°C. Other sugar polyols exhibit lower T_g values, e.g. mannitol and sorbitol have reported values of 10.7°C and 0°C. Thus, glassy systems of isomalt should be more stable than glassy systems of other polyols. Carbamazepine is chosen as model drug, since it is well known that the poor solubility and polymorphism can limitate its bioavailability. Solid dispersions of carbamazepine in isomalt are prepared either by melting the ingredients up to 205°C in a melting pot or by DSC heating scans.

By HSM, 5 % carbamazepine are found to be miscible with isomalt in the liquid or molten state at 190 to 200°C. Nevertheless, when cooling the melt to room temperature, molecular dissolved carbamazepine recrystallizes immediately as can be observed macroscopically. The transparent system changes into an opaque solid suspension. Only the addition of a special excipient leads to a glassy solid solution of carbamazepine in isomalt as can be proved by DSC scans and dissolution profiles of solid dispersions with different compositions. According to the dissolution studies, only 2 % carbamazepine are soluble in glassy isomalt at room temperature whereas 10 to 15 % carbamazepine are dissolvable in the isomalt system containing 25 % of the special excipient. By pounng the ternary melt into 2 g tablet moulds, highly transparent glassy tablets with a light yellow appearance are obtained. All tablets show a significantly enhanced dissolution rate of carbamazepine up to 10 % active ingredient compared with the respective physical mixture.

DSC studies identify the commercially available carbamazepine (scan 1) as polymorph I referring to Kobayashi [2], which is thermodynamically stable at room temperature and melts at 176°C. Polymorph III is preferred above 71 °C and melts at 190°C. In contrast to isomalt alone as carrier (scan 2), form I gradually dissolves in the liquid isomalt/excipient mixture (scan 3).

The solid solution of isomalt and the excipient exhibits a 6°C higher T_g as isomalt and no enthalpy relaxation peak after 15 minutes of storage. Thus, the excipient prevents the system from recrystallization by specific interactions on the molecular level, hereby improving the solubility of carbamazepine in isomalt. With respect to these findings, it seems necessary to use special excipients in order to dissolve reasonable amounts of carbamazepine in glassy isomalt.

DSC scans Carbamazepine alone (1), physical mixture with isomalt (2) and physical mixture with isomalt/excipient (3)



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Abstracts

PHYSICO-CHEMICAL CHARACTERISATION OF GLASS SOLUTIONS PREPARED BY MELT EXTRUSION

Angus Forster

WW Physical Properties, GlaxoSmithKline R & D Stevenage

Melt extrusion has been used as a processing technique since the turn of the century and is employed in the manufacture of the majority of plastic goods. Within the pharmaceutical industry the use of melt extrusion is increasing, particularly in the field of solid dispersions. Solid dispersions are homogeneous mixtures of one or more active ingredients in an inert matrix and are predominately used as a means of increasing the oral bioavailability of poorly water-soluble drugs [1].

During melt extrusion, drug is incorporated into an excipient by melting or plasticising both the drug and excipient. Rapid cooling of this molten mixture favours the formation of glass solutions, where the drug is molecularly dispersed throughout an amorphous excipient [2]. Glass solutions are the ideal type of solid dispersion for increasing drug dissolution and oral bioavailability [3].

One of the most fundamental issues facing the pharmaceutical scientist when working with solid dispersions is how to sufficiently characterise the product. Bym and co-workers have constructed a well-known series of decision trees that describe steps that should be taken for characterisation and subsequent registration of a solid product [4]. None of these decision trees specifically address solid dispersions as their intent is to characterise the solid drug alone; however, many of the questions raised can be extrapolated to include more complex dispersion systems. In this talk a summary decision tree will be constructed detailing the steps that need to be taken to fully understand the melt extruded product. With this in mind, the talk focuses on the following key points:

- Determination of the type of solid dispersion produced
- Detection of the presence of chemical interactions between the drug and excipient
- Measurement of drug dissolution compared to crystalline drug
- Assessment of the physical / chemical stability

To properly address these problems a wide-range of solid-state analytical tests should be considered. Increasingly, the use of spectroscopic techniques is gaining prominence in this area, because of the rich chemical information supplied and the limited amount of sample preparation required. For example, FT-IR with an attenuated total reflectance (ATR) accessory is particularly suited to the analysis of glass solutions, as interactions between the drug and polymer are thought to be of particular importance for increasing or potentially decreasing both physical and chemical stability.

Perhaps, the most problematic question is how to assess or predict physical stability. Modulated temperature DSC can be used to measure the glass transition temperature (T_g) of glass solutions and determine the effect of sorbed water on the T_g . Critical levels of moisture that lower the T_g to below the storage temperature and therefore encourage recrystallisation can also be predicted using various equations [5]. However, determination of the T_g for a range of water contents with MTDSC has shown that significant deviation between the theoretical and measured T_g may occur, which may have a dramatic impact on stability prediction [6].

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InterScience

Properties of rapidly dissolving eutectic mixtures of poly(ethylene glycol) and fenofibrate the eutectic microstructure

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Poly(ethylene glycol) or PEG is an ideal inactive component for preparing simple binary eutectic mixtures because of its low entropy of fusion (approximately 0.0076 J/mol-K), lower melting point (approximately 62 degrees C) compared to most pharmaceuticals, miscibility with drugs at elevated temperatures, and its covalent crystalline lattice. Implication of these physicochemical properties on eutectic crystallization and size reduction of the drug is discussed. Enhancement of the dissolution rate of a poorly soluble compound through the formation of PEG-drug eutectics was investigated using fenofibrate. Solid dispersions of PEG-fenofibrate when characterized, revealed that PEG and fenofibrate form a simple eutectic mixture containing 20-25%(w/w) fenofibrate at the eutectic point. Eutectic crystallization led to the formation of an irregular microstructure in which fenofibrate crystals were found to be less than 10 microm in size. Dissolution rate improvement of fenofibrate correlated with the phase diagram, and the amount of fenofibrate released from the dispersions that contained fenofibrate as a eutectic mixture was at least 10-fold higher compared to untreated fenofibrate. On aging, the dissolution rate of the dispersion containing 15%(w/w) fenofibrate in PEG remained unaltered. The results indicate that PEG-drug eutectic formation is a valuable option for particle size reduction and subsequent dissolution rate improvement. Copyright 2003 Wiley-Liss, Inc. and the American Pharmaceutical Association

SOLID DISPERSIONS OF NIMODIPINE AND POLYOXYETHYLENE -AN ADDITIVE PREVENTS THE DRUG FROM RECRYSTALLIZATION

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Introduction The insufficient solubility of many new drug substances in water as well as in the aqueous gastric fluids cause problems in bioavailability. The development of solid dispersions is an appropriate means to overcome these problems and to guarantee a reasonable bioavailability. Several methods exist to prepare solid dispersions, the melting method being the most convenient. The melting procedure includes the melting of the carrier, the subsequent dissolution of the drug within the melt and finally, the cooling of the obtained solution. During the cooling process the molecular dispersion of the drug within the carrier may be maintained or the drug may recrystallize as a result of the increasing supersaturation due to the lowering of temperature. Moreover, recrystallization can take place during storage as well. The precipitation usually leads to a decrease in the dissolution rate of the drug in the dissolution medium as amorphous materials dissolve faster because of their higher solubility. Therefore, an attempt has been made to prevent the drug from recrystallization.

Materials and methods For the preparation of solid dispersions by the melting method, polyoxyethylene 2000 has been chosen as a carrier due to its low melting point. Nimodipine, a poorly soluble calcium channel antagonist, was used as model drug. The characterization of the products was performed by dissolution testing, differential scanning calorimetry (DSC) and hot stage microscopy (HSM).

Results and discussion Solid dispersions of nimodipine in polyoxyethylene 2000 exhibit a low dissolution rate and lack the capability to supersaturate the dissolution medium. The high tendency of polyoxyethylene 2000 to crystallize during the cooling process or during storage probably leads to an expulsion of the drug from the crystal lattice of the carrier. As a result, the drug first concentrates in areas of lower crystallinity where it subsequently recrystallizes itself when the concentration exceeds the solubility within the carrier. Unexpectedly, investigations by DSC can not prove the existence of crystalline nimodipine in these products. Thermograms only exhibit the melting of polyoxyethylene 2000. In contrast, examinations by HSM reliably allow the detection of fine nimodipine crystals after the melting of polyoxyethylene 2000. Subsequently, as the heating program continues, the gradual dissolution of these crystals can be observed.

The aim of further investigations was to avoid the recrystallization of the drug within the carrier in order to obtain solid dispersions with more favourable dissolution profiles. In contrast to most binary mixtures of polymers where the two components are immiscible, it has been found that one polymeric substance is soluble in polyoxyethylene 2000. The two polymers together form a new homogeneous carrier material. The dispersion of nimodipine in the composed carrier leads to a product with an enhanced dissolution rate and a pronounced supersaturation in the dissolution medium. Investigations by DSC as well as by HSM indicate the absence of nimodipine crystals in these systems. Thus, the new carrier material proves to be suitable for the preparation of solid dispersions with favourable dissolution properties.

Summary The reasonable development of solid dispersions containing nimodipine and polyoxyethylene 2000 with favourable dissolution profiles is based on the proper characterization of the obtained products by thermal analysis. In this context, HSM proves to be an essential tool for the correct interpretation of DSC thermograms. By these means, it is possible to ascribe insufficient dissolution properties of solid dispersions containing only nimodipine and polyoxyethylene 2000 to the presence of crystalline nimodipine within the carrier. Thus, the addition of a substance which prevents the drug from recrystallization successfully leads to products with a high dissolution rate and a pronounced supersaturation in the dissolution medium.

BioAqueous Solubilization Services Technologies for Better Solubilization

Lead Technologies

Controlled Precipitation

A technology that creates crystalline nanostructured drug particles with rapid dissolution rates. With this technology, the drug is dissolved in a water-miscible solvent and dispersed into water. Nanostructured drug particles are formed from the solvent droplets as the solvent dissolves into the water phase.

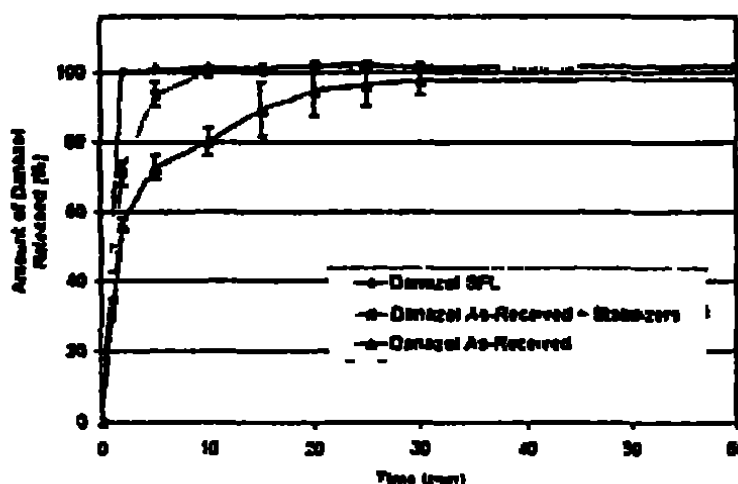
Stabilizers are added to the water and/or solvent to control particle growth and to stabilize the final particles. The stabilized particles are isolated as dry powders by standard techniques.

In this section

[Technologies for Better Solubilization](#)
[Lead Technologies](#)
[Features of Technologies](#)
[Proof of Performance](#)

Template Emulsion

A technology that creates nanostructured drug particles with controlled particle size distribution and rapid dissolution performance. With this technology, an oil-in-water emulsion is prepared, then swelled with a non-aqueous solution of the drug and stabilizers. The particle size distribution of the drug particles is a direct result of the size of the emulsion droplets prior to loading with drug, a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water are removed, and the stabilized nanostructured drug particles are recovered. Various particle morphologies can be achieved by appropriate control of processing conditions.



Spray Freezing into Liquid (SFL)

A novel, cryogenic technology to create nanostructured drug particles with greatly enhanced surface area. This technology consists of an organic or organo-aqueous solution of a drug with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the drug solution freeze at a rate

sufficient to minimize crystallization and particle growth, thus forming nanostructured particles. Depending on the choice of solvent system and processing conditions, these particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under

conditions that avoid agglomeration or ripening of the drug particles.

Evaporative Precipitation into Aqueous Solutions (EPAS)

A technology that creates nanostructured drug particles with rapid dissolution performance. For this technology the drug is dissolved in a water-insoluble solvent and atomized into water at a temperature above the boiling point of the solvent. The rapid expansion and atomization of the solvent in the water phase causes the formation of nanostructured drug particles. The solvent and/or water phase contain the stabilizers for the particles. The evaporated solvent is recovered and the stabilized particles isolated from the aqueous phase by standard techniques.





Setting Specifications for Drug Substance and Drug Product

In August 1996 a major conference on setting drug substance and drug product specifications was held in Washington, DC. This conference was sponsored by PDA, AAPS, USP, FIP, and FDA. The goals were to review the International harmonization document Q6A and to provide feedback to the bodies revising this document. Seven areas were discussed including identification, impurities, dissolution tests, physico-chemical tests, and 3 more. Intense discussion was focused on physico-chemical testing since this area is the least resolved. In this newsletter major issues presented at the conference are reviewed, with particular emphasis on the solid-state chemistry of drugs.

Identification

A specific test is needed for identification of a drug substance. IR seems to be the most popular. However, the section in the USP which allows recrystallization continues to attract interest (<197>). It was pointed out that the identification test is not meant to be a polymorph test.

The single-crystal structure can be very helpful in developing an X-ray diffraction-based identification test. The theoretical powder diffraction pattern of a material can be calculated from the single-crystal data. This pattern is devoid of preferred orientation and shows what lines should be present (and absent). Thus, comparison of the diffraction pattern of the drug substance to the calculated pattern provides a direct method of identification of the substance.

It is important to point out that an identification test is not a limit test. That is, a visual comparison of the spectrum or diffraction pattern of a drug substance to that of a reference merely provides an identification of the substance and does not quantify its polymorphic purity. More sophisticated, validated methods are needed to prove the polymorphic purity (and chemical purity) of a drug substance.

Physico-Chemical Properties – Polymorphs

In recent years, the term polymorphs is frequently used to describe polymorphs, solvates, amorphous forms, and desolvated solvates. Thus when a polymorphism question arises it often involves not strictly polymorphs (different unsolvated crystal forms) but also solvates (forms containing solvent, or water), amorphous forms (noncrystalline forms) and desolvated solvates (forms which can only be made by removing the solvent from a solvate). The flow charts published in our 1995 Pharmaceutical Research Review (*Pharm Res* 1995, 12, 945) and shown in SSCI's Application Note #2 have become a popular way to

approach the major polymorph issues, asking the questions (1) Have polymorphs, hydrates or amorphous forms been discovered, (2) Do they have different physical properties, and (3) What is the drug substance composition?
Discovering Polymorphs and Setting Specifications

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A limit test is often substantiated with studies showing that the contaminating polymorph(s) are bioequivalent to the major polymorph and that the contaminating polymorphs have acceptable stability profiles. Mixtures of polymorphs should be avoided if possible. Mixtures are sometimes indicative of lack of control in the production process. Thus, careful optimization of the production process, in general, and the final crystallization process, in particular, are needed to avoid mixtures. If it is impossible to avoid mixtures, research should be conducted to establish a "best effort" attempt to achieve polymorphic purity.

Specifications on Drug Product

In cases where the polymorph affects bioavailability or chemical stability, there is a developing interest in setting specifications for drug product. Of course, methodology must be available to determine the polymorphs present in the drug product. For relatively high dose drugs, solid-state NMR and X-ray powder diffraction are powerful tools for drug product analysis. Importantly, the detection limit is usually higher in drug products since the excipients often interfere with the assay.

Particle Size

Specifications on particle size are of great interest to regulatory agencies. This is because the particle size can have a significant influence on dissolution rate. In addition, particle size may reflect the polymorph present. Particle size specifications are set for most drug substances.

Particle size specifications are important as a measure of the extent of processing of a drug substance and should be set as soon as possible. Particle size specifications should always be set if a milled or micronized drug is used.

It is difficult to devise a single flow chart to address particle size issues. Instead, four flow chartlets are presented answering the most important questions about particle size: (1) Can the drug substance be manufactured in different particle sizes? (2) Do the different particle sizes have different dissolution rates? And (3) Do the different particle sizes have different processing properties?

A major issue is the method of determination of particle size. At least five methods have been used: (1) sieve analysis, (2) Coulter counter, (3) laser light scattering, (4) microscopic image analysis, and (5) surface area analysis. This latter method is not a direct method for particle size analysis but rather reports a parameter related to particle size. Several ways of reporting particle size are used, including reporting the mean, the maximum, or the distribution. In some cases, a mixture of these parameters are reported.

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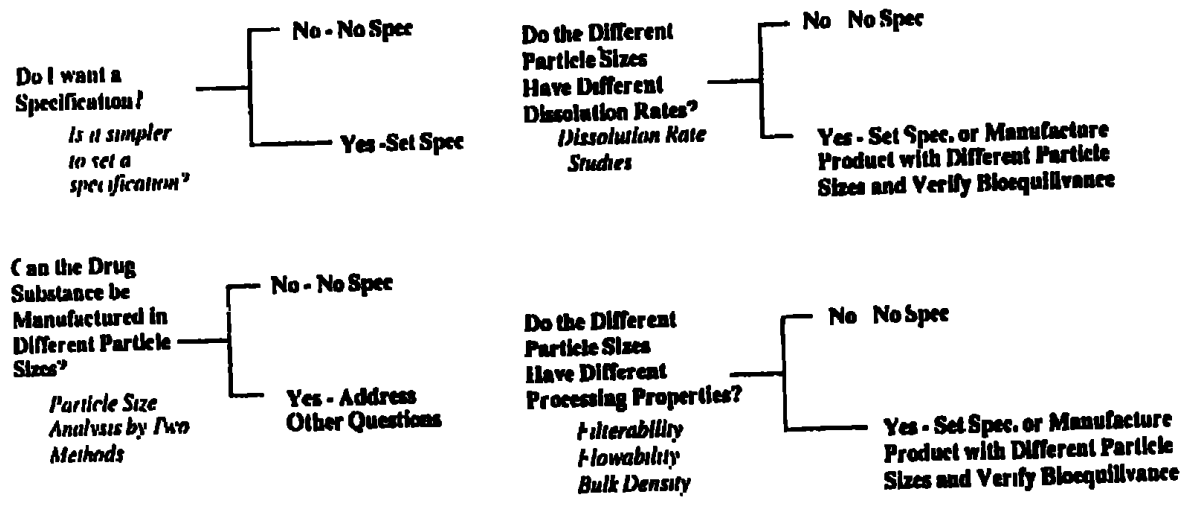


Figure 1 Flow charts for particle size determination

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CAPITULO 5**CONTENIDO .**

- 1 **Patente** **Proceso para generar partículas submicrón
de compuestos insolubles en agua**
2. **Patente** **Proceso de comicronización de Fenofibrato**
- 3 **Patente** **Proceso para reducir tamaño de partícula a
un fármaco**

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Title Processes to generate submicron particles of water-insoluble compounds

United States Patent: 6,177,103

Inventors Pace, Gary W (Raleigh, NC); Vachon, Michael G (Quebec, CA); Mishra, Awadhesh K. (Quebec, CA); Hemikson, Inge B (Stavanger NO); Krukonis, Val (Lexington, MA)

Assignee. RTP Pharma, Inc (Durham, NC)

Appl No. 335735

Filed June 18, 1999

Abstract

Submicron particles of water-insoluble compounds, particularly drugs, are prepared by simultaneously stabilizing microparticulate suspensions of same with surface modifier molecules by rapid expansion into an aqueous medium from a compressed solution of the compound and surface modifiers in a liquefied gas and optionally homogenizing the aqueous suspension thus formed with a high pressure homogenizer

BACKGROUND AND SUMMARY OF INVENTION

A major problem in formulating biologically active compounds is their poor solubility or insolubility in water. For instance, over one third of the drugs listed in the United States Pharmacopoeia are either water-insoluble or poorly water-soluble. Oral formulations of water-insoluble drugs or compounds with biological uses frequently show poor and erratic bioavailability. In addition, drug insolubility is one of the most recalcitrant problems facing medicinal chemists and pharmaceutical scientists developing new drugs. Water-insolubility problems delay or completely block the development of many new drugs and other biologically useful compounds, or prevent the much-needed reformulation of certain currently marketed drugs. Although the water-insoluble compounds may be formulated by solubilization in organic solvents or aqueous-surfactant solutions, in many cases such solubilization may not be a preferred method of delivery of the water-insoluble agent for their intended biological use. For instance, many currently available injectable formulations of water-insoluble drugs carry important adverse warnings on their labels that originate from detergents and other agents used for their solubilization.

An alternative approach for the formulation of water-insoluble biologically active compounds is surface-stabilized particulate preparations. Small particle size formulation of drugs are often needed in order to maximize surface area, bioavailability and, dissolution requirements. Pace et al. ("Novel Injectable Formulations of Insoluble Drugs" in Pharmaceutical Technology, March 1999) have reviewed the usefulness of the microparticulate preparations of water-insoluble or poorly soluble injectable drugs.

In U.S. Pat. Nos. 5,091,187 and 5,091,188 to Haynes describe the use of phospholipids as surface stabilizers to produce aqueous suspension of submicron sized particles of the water-insoluble drugs. These suspensions are believed to be the first applications of the surface modified microparticulate aqueous suspension containing particles made up of a core of pure drug substances and stabilized

cosolvent. Minute additions of a cosolvent can significantly influence the solvent properties. When cosolvents are used in rapid expansion from a supercritical solution, care is required to prevent dissolution of the particles due to solvent condensing in the nozzle. Normally, this is achieved by heating the supercritical fluid, prior to expansion, to a point where no condensate (mist) is visible at the nozzle tip

A similar problem occurs when carbon dioxide is used. During adiabatic expansion (cooling), carbon dioxide will be in two phases unless sufficient heat is provided at the nozzle to maintain a gaseous state. Most investigators recognize this phenomenon and increase the pre-expansion temperature to prevent condensation and freezing in the nozzle. A significant heat input is required (40-50 kcal/kg) to maintain carbon dioxide in the gaseous state. If this energy is supplied by increasing the pre-expansion temperature the density drops and consequently reduces the supercritical fluid's solvating power. This can lead to premature precipitation and clogging of the nozzle.

The solvent properties of liquefied-gas are strongly affected by their fluid density in the vicinity of the fluid's critical point. In rapid expansion from liquefied-gas solutions, a non-volatile solute is dissolved in a liquefied-gas that remains either in the supercritical or sub-critical phase. Nucleation and crystallization are triggered by reducing the solution density through rapid expansion of the liquefied-gas to atmospheric conditions. To achieve this the liquefied-gas is typically sprayed through 10-50 micron (internal diameter) nozzles with aspect ratios (L/D) of 5-100. High levels of supersaturation result in rapid nucleation rates and limited crystal growth. The combination of a rapidly propagating mechanical perturbation and high supersaturation is a distinguishing feature of rapid expansion from a liquefied-gas solution. These conditions lead to the formation of very small particles with a narrow particle size distribution.

There are a number of advantages in utilizing compressed carbon dioxide in the liquid and supercritical fluid states, as a solvent or anti-solvent for the formation of materials with submicron particle features. Diffusion coefficients of organic solvents in supercritical fluid carbon dioxide are typically 1-2 orders of magnitude higher than in conventional liquid solvents. Furthermore, carbon dioxide is a small linear molecule that diffuses more rapidly in liquids than do other antisolvents. In the antisolvent precipitation process, the accelerated mass transfer in both directions can facilitate very rapid phase separation and hence the production of materials with sub-micron features. It is easy to recycle the supercritical fluid solvent at the end of the process by simply reducing pressure. Since supercritical fluids do not have a surface tension, they can be removed without collapse of structure due to capillary forces. Solvent removal from the product is unusually rapid. No carbon dioxide residue is left in the product, and carbon dioxide has a number of other desirable characteristics, for example it is non-toxic, nonflammable, and inexpensive. Furthermore, solvent waste is greatly reduced since a typical ratio of antisolvent to solvent is 30:1.

Exploiting these concepts Henriksen et al. in WO 97/14407, disclosed a process using compressed fluids to produce sub-micron sized particles of water insoluble compounds with biological uses particularly water insoluble drugs by precipitating a compound by rapid expansion from a supercritical solution in which the compound is dissolved or precipitating a compound by spraying a solution in which the compound is soluble into compressed gas, liquid or supercritical fluid which is miscible with the solution but is antisolvent for the compound. In this manner precipitation with a compressed fluid antisolvent (compressed fluid antisolvent) is achieved.

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with natural or synthetic bipolar lipids including phospholipids and cholesterol. Subsequently, similar delivery systems exploiting these principles have been described (G. G. Liversidge et al., U.S. Pat. No. 5,145,684; K. J. Illig et al., U.S. Pat. No. 5,340,564 and H. William Bosch et al., U.S. Pat. No. 5,510,118) emphasizing the usefulness of the drug delivery approach utilizing particulate aqueous suspensions.

In U.S. Pat. No. 5,246,707 Haynes teaches uses of phospholipid-coated microcrystals in the delivery of water-soluble biomolecules such as polypeptides and proteins. The proteins are rendered insoluble by complexation and the resulting material forms the solid core of the phospholipid-coated particle.

These patents and others utilized processes based on the particle size reduction by mechanical means such as attrition, cavitation, high-shear, impactation, etc. achieved by media milling, high pressure homogenization, ultrasonication, and microfluidization of aqueous suspensions. However, these particle size reduction methods suffer from certain disadvantages, such as long process duration (high-pressure homogenization or microfluidization) and contamination (media milling, and ultrasonication). In addition, these methods may not be suitable for aqueous suspensions of compounds with limited stability in aqueous medium at the pH, high temperature and high pressure conditions prevailing in these processes.

Among the alternatives that address these problems is a procedure which uses liquefied gases for the production of microparticulate preparations. In one such method liquefied-gas solutions are sprayed to form aerosols from which fine solid particles precipitate. The phenomenon of solids precipitated from supercritical fluids was observed and documented as early as 1879 by Hannay, J. B. and Hogarth, J. "On the Solubility of Solids in Gases," Proc. Roy. Soc. London 1879 A29, 324.

The first comprehensive study of rapid expansion from a liquefied-gas solution in the supercritical region was reported by Krukons (1984) who formed micro-particles of an array of organic, inorganic, and biological materials. Most particle sizes reported for organic materials, such as lovastatin, polyhydroxyacids, and mevinolin, were in the 5-100 micron range. Nanoparticles of beta-carotene (300 nm) were formed by expansion of ethane into a viscous gelatin solution in order to inhibit post expansion particle aggregation. Mohamed, R. S., et al. (1988), "Solids Formation After the Expansion of Supercritical Mixtures," in Supercritical Fluid Science and Technology, Johnston, K. P. and Penninger, J. M. L., eds., describes the solution of the solids naphthalene and lovastatin in supercritical carbon dioxide and sudden reduction of pressure to achieve fine particles of the solute. The sudden reduction in pressure reduces the solvent power of the supercritical fluid, causing precipitation of the solute as fine particles.

Tom, J. W. and DeBenedetti, P. B. (1991), "Particle Formation with Supercritical Fluids—a Review," J. Aerosol Sci. 22: 555-584, discusses rapid expansion of supercritical solutions techniques and their applications to inorganic, organic, pharmaceutical and polymeric materials. This technique is useful to comminute shock-sensitive solids, to produce intimate mixtures of amorphous materials, to form polymeric microspheres and deposit thin films.

Most studies of rapid expansion from supercritical solution on organic materials utilize supercritical carbon dioxide. However, ethane was preferred to carbon dioxide for beta-carotene because of certain chemical interactions. Carbon dioxide is generally preferred alone or in combination with a

An essential element of this process is the use of phospholipids and other surface modifiers to alter the surface of the drug particles to prevent particle aggregation and thereby improve both their storage stability and pharmacokinetic properties. This process combines or integrates phospholipids or other suitable surface modifiers such as surfactants, as the aqueous solution or dispersion in which the supercritical solution is sprayed. The surfactant is chosen to be active at the compound-water interface, but is not chosen to be active at the carbon dioxide-organic solvent or carbon dioxide-compound interface when carbon dioxide is used as the supercritical solution. The use of surface modifying agents in the aqueous medium allowed making submicron particles by the compressed fluid antisolvent process without particle aggregation or flocculation.

Claim 1 of 15 Claims

What is claimed is

1. A process of preparing a stable suspension of sub-micron particles of a water-insoluble or substantially water-insoluble biologically active compound of up to 2000 nm in size comprising the successive steps of

(a) dissolving a water-insoluble or substantially water-insoluble biologically active compound and first surface modifier in a liquefied compressed gas solvent therefor and forming a solution of greater than 1% w/w of said compound in said solvent and thereafter,

(b) expanding the compressed fluid solution prepared in step (a) into water or aqueous solution containing a second surface modifier and water-soluble agents thereby producing a suspension of microparticles, and thereafter

(c) homogenizing the suspension of step (b) at high pressure.

If you want to learn more about this patent, please go directly to the U.S. Patent and Trademark Office Web site to access the full patent.

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BACKGROUND

Fournier is the assignee of the '726 patent. The '726 patent includes claims directed to a therapeutic fenofibrate composition (claims 1-7), a method for the manufacture of that fenofibrate composition (claims 8 and 9), a method for improving the bioavailability of fenofibrate (claim 10), and a method for treatment of hyperlipidemia or hypercholesterolemia using the claimed fenofibrate composition (claims 11 and 12).

Abbott is Fournier's exclusive licensee under the '726 patent. Abbott also holds a New Drug Application ("NDA") approved by the United States Food and Drug Administration ("FDA") permitting it to market Fournier's fenofibrate capsules in the United States. Abbott sells the capsules under the tradename TRICOR®.

Novopharm filed an Abbreviated New Drug Application ("ANDA") in December 1999 seeking the FDA's approval to market a generic micronized formulation of fenofibrate prior to the expiration of the '726 patent. Along with its ANDA, Novopharm submitted a certification under 21 U.S.C. § 355(j)(2)(A)(vi)(IV) (a "paragraph IV certification") declaring that the manufacture, use, and sale of its proposed fenofibrate formulation would not infringe the '726 patent. Under 21 U.S.C. § 355(j)(2)(B)(i), an ANDA applicant who files a paragraph IV certification is required to include in its application a statement that it will give notice of that filing to the owner of the patent to which the certification pertains, § 355(j)(2)(B)(i)(I), and to the holder of the approved NDA for that drug, § 355(j)(2)(B)(i)(II). Pursuant to those provisions, Novopharm notified Fournier and Abbott respectively that it had filed the ANDA and paragraph IV certification. Also, as required by 21 U.S.C. § 355(j)(2)(B)(II), Novopharm provided in its notice letter a detailed statement of the factual and legal bases for its opinion of noninfringement of the '726 patent.

Fournier and Abbott then filed suit against Novopharm. They alleged that Novopharm's generic version of TRICOR® would infringe one or more claims of the '726 patent and that Novopharm's submission of an ANDA for approval to sell fenofibrate capsules prior to the expiration of the '726 patent constituted an act of infringement under 35 U.S.C. § 271(e)(2). That provision, in pertinent part, provides that

It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food Drug, and Cosmetic Act [codified at 21 U S C § 355(j)] i.e., an ANDA] for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose of such submission is to obtain approval under such Act [i.e., Title 21 of the United States Code] to engage in the commercial manufacture use, or sale of a drug claimed in a patent or the use of which is claimed in a patent before the expiration of such patent

35 U S C § 271(e)(2) (2000) Fournier and Abbott sought, among other things, a judgment that the '726 patent was valid, enforceable, and infringed an order staying the approval of Novopharm's ANDA until the January 19 2009 expiration date of the '726 patent; and an injunction prohibiting Novopharm from commercially manufacturing, selling using or importing infringing fenofibrate compositions

Novopharm amended its ANDA twice both times adding a new dosage form and including a paragraph IV certification for the newly added form Following each of those amendments Fournier and Abbott filed a new complaint against Novopharm The district court eventually consolidated all three actions into a single proceeding ¹⁽¹¹⁾ Novopharm thereafter moved for summary judgment of noninfringement

Claims 1 and 10 which are the '726 patent's only two independent claims define the patented subject matter as follows:

1 A therapeutic composition which is presented in the form of gelatin capsules and which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant wherein the mean particle size of said co-micronized mixture is less than 15 µm

10 A method for improving the bioavailability of fenofibrate in vivo, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 µm

(emphases added)

¹⁽¹¹⁾ Teva Pharmaceutical Industries Ltd ("Teva") was also a named defendant in those three actions in the district court The record reflects that a division of Teva had acquired an equity share in Novopharm prior to the filing of the appellants' first complaint, however, the record also reflects that the parties were negotiating a document releasing Teva from the action as of the time that Novopharm answered the complaint, and Teva is not named as a party to this appeal Fournier and Abbott presently have an additional suit pending against Teva in the United States District Court for the District of Delaware, Abbott Labs v Teva Pharms USA, Inc., No 02-CV-1512 (D Del filed Oct 4 2002)

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Claim 1 of the '726 patent was amended during prosecution, in response to a rejection under 35 U.S.C. § 103. As originally filed, that claim recited the phrase "the said composition containing fenofibrate and a solid surfactant which have been co-micronized." The amendment made during prosecution replaced that phrase with "said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant wherein the mean particle size of the co-micronized mixture is less than 15 μm ." The '726 patent specification includes data showing that the patented composition has improved properties relative to formulations in which (1) a solid surfactant is added to fenofibrate (impliedly without co-micronization) (2) fenofibrate is micronized on its own or (3) fenofibrate and surfactant are separately micronized and then intimately mixed. '726 patent col. 1 ll. 35-43. During prosecution of the application that led to the '726 patent, Fournier also distinguished its composition from prior art formulations in which fenofibrate was granulated in a matrix containing a particle size of between 50 and 500 microns.

The district court found that Fournier had distinguished the claimed invention, as amended, from the cited prior art on the ground that the prior art did not teach or suggest co-micronization of a mixture of fenofibrate and a solid surfactant, which co-micronization resulted in an improvement in bioavailability and dissolution rate not taught or suggested in the prior art. Abbott, slip op. at 2-3. Fournier further distinguished the amended claim on the basis that co-micronization to produce particles having a diameter of less than fifteen microns was not taught or suggested in the prior art. Id. The court also observed that the '726 patent's specification states that:

the "co-micronization of fenofibrate and a solid surfactant (i.e., the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant [to fenofibrate], or by micronizing the fenofibrate on its own or by intimately mixing the separately micronized fenofibrate and surfactant."

Id. at 4 (alteration in original). The court thus concluded that Fournier's claims could not be construed to include "mixtures obtained by adding a surfactant to fenofibrate or micronizing fenofibrate by itself and/or mixing separately micronized fenofibrate and surfactant." Id. at 11.

The district court then found that sodium lauryl sulfate ("SLS") was the only example of a solid surfactant and that a method involving co-micronization of a fenofibrate/SLS mixture prior to the addition of excipients such as lactose or starch was the only detailed example of co-

micronization disclosed in the '726 patent id. at 4-5. Elaborating on that point, the court found further that "[t]he claims description and prosecution history do not indicate that anything other than fenofibrate and a solid surfactant are micronized. No other excipient is identified as part of this mixture." id. at 12. The court concluded on the basis of those findings that the term "co-microniz[ed -ation]" in independent claims 1 and 10 does not encompass co-micronization of excipients other than fenofibrate and a solid surfactant, but instead "is construed to mean that fenofibrate and a solid surfactant have been micronized together in the absence of other excipients." id. The court also concluded that the phrase "fenofibrate/solid surfactant mixture" in claim 10 of the '726 patent must be construed, according to Novopharm's proposal, so as to exclude any ingredients other than fenofibrate and solid surfactant, noting that Fournier and Abbott had not objected to that construction. id. The court applied essentially the same construction to the phrase "mixture of particles of fenofibrate and a solid surfactant" in claim 1, interpreting that phrase to mean a "mixture wholly of fenofibrate and a solid surfactant to the exclusion of any other excipients." id. at 13.

Having so construed the claims, the district court then considered Novopharm's proposed fenofibrate formulations. The court found that, according to the ANDA, Novopharm's process for making its proposed products involves pre-micronizing fenofibrate on its own, i.e., in the absence of solid surfactant. The pre-micronized fenofibrate is then dry mixed with lactose monohydrate, pregelatinized starch, croscarmellose sodium, and croscopolvidone. Separately, a "granulating solution" is prepared by dissolving povidone and SLS in water. The granulating solution is then added to the dry fenofibrate/excipient mixture, and the resulting mixture is then subjected to a "wet granulation" process, which involves mixing with the introduction of additional water, to form a uniform wet mass. The wet mass is then dried to form a dried granulated mixture of fenofibrate, SLS, and excipients. The granulated mixture is dry blended with additional croscarmellose sodium, croscopolvidone, and magnesium stearate to produce granules that can pass through a #16 mesh screen for storage and eventual encapsulation into gelatin capsules. id. at 6.

In Novopharm's motion for summary judgment, it had argued that its process does not include co-micronization of fenofibrate and a solid surfactant, and therefore would not infringe the

726 patent Fournier and Abbott opposed Novopharm's motion alleging that the wet granulation and drying steps used by Novopharm constitute the required co-micronization because the fenofibrate particles are reduced in size during those steps. Nonetheless, finding that there was no dispute among the parties that fenofibrate and a solid surfactant are not "micronized together in the absence of other excipients" in Novopharm's process and having already construed the claims to require just that, the court held that Novopharm's formulations could not literally infringe either independent claim in the patent. Id. at 14.

The court also ruled out infringement under the doctrine of equivalents on the basis of prosecution history estoppel. The court reasoned that Fournier's prosecution arguments, which distinguished the claimed invention from the prior art on the ground that the prior art did not teach or suggest co-micronization of fenofibrate and a solid surfactant such that the co-micronization resulted in improved bioavailability, viewed together with statements in the patent specification and arguments that Fournier made during reexamination of the '726 patent, would reasonably lead a competitor to conclude that Fournier had "relinquished a product and process that involved either adding a surfactant by itself or by micronizing the fenofibrate on its own or by intimately mixing the separately micronized fenofibrate and surfactant." Id. at 14-16. Having concluded that Fournier and Abbott had relinquished coverage of Novopharm's process and thus could not prevail, the district court granted Novopharm's motion for summary judgment of noninfringement.

Fournier and Abbott now appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a district court's grant of summary judgment de novo, reapplying the standard used by the district court. Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp., 149 F.3d 1309, 1315, 47 USPQ2d 1272, 1275 (Fed. Cir. 1998). Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). "The evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in his favor." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 255 (1986).

Determination of patent infringement requires a two-step analysis "First the court determines the scope and meaning of the patent claims asserted [Secondly,] the properly construed claims are compared to the allegedly infringing [product]" Cybor Corp. v. FAS Techs., Inc., 138 F 3d 1448 1454, 46 USPQ2d 1169 1172 (Fed Cir 1998) (en banc) (citations omitted) Step one, claim construction, is an issue of law Markman v. Westview Instruments, Inc., 52 F 3d 967, 970-71 34 USPQ2d 1321, 1322 (Fed Cir 1995) (en banc), aff'd, 517 U S 370 (1996) that we review de novo, Cybor, 138 F 3d at 1456, 46 USPQ2d at 1172 Step two comparison of the claim to the accused product requires a determination that every claim limitation or its equivalent can be found in the accused product Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U S 17 29 (1997) A claim limitation is equivalently present in an accused product "if only 'insubstantial differences' distinguish the missing claim element from the corresponding aspects of the accused [product]" Sage Prods., Inc. v. Devon Indus., Inc., 128 F 3d 1420, 1423 44 USPQ2d 1103 1106 (Fed Cir 1997) (citation omitted) Those determinations are ordinarily questions of fact, Bal v. L & L Wings, Inc., 160 F 3d 1350 1353 48 USPQ2d 1674 1676 (Fed Cir 1998) but summary judgment should be granted "In any case where no reasonable fact finder could find equivalence" Sage Prods., 128 F 3d at 1423 44 USPQ2d at 1106 see also Warner-Jenkinson 520 U S at 39 n 8 ("Where the evidence is such that no reasonable jury could determine two elements to be equivalent, district courts are obliged to grant partial or complete summary judgment")

Fournier and Abbott argue on appeal that the district court erred by construing the claim term "co-micronization" to require micronization of fenofibrate and solid surfactant "in the absence of other excipients" They argue that the court also erred by construing the claim phrase "mixture of" to mean "mixture wholly of," again requiring exclusion of all ingredients other than fenofibrate and solid surfactant in the mixture during co-micronization According to the appellants both misconstructions result from the court's having improperly imported limitations into the claims from the patent's non-limiting examples

We disagree first, with the appellants contention that the district court misconstrued the term "co-micronization" Although courts "must presume that the terms in a claim mean what they say and unless otherwise compelled give full effect to the ordinary and accustomed meaning of

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claim terms " Johnson Worldwide Assocs. Inc. v. Zebco Corp. 175 F 3d 985 989 50 USPQ2d 1607 1610 (Fed Cir 1999), see also Nike Inc. v. Wolverine World Wide, Inc. 43 F 3d 644, 646, 33 USPQ2d 1038 1039 (Fed Cir 1994), E.I. du Pont de Nemours & Co. v. Phillips Petroleum, 849 F 2d 1430 1433 7 USPQ2d 1129 1131 (Fed Cir 1988), we have previously identified limited situations "where a sufficient reason exists to require the entry of a definition of a claim term other than its ordinary and accustomed meaning " Johnson Worldwide 175 F 3d at 990, 50 USPQ2d at 1610 One such situation is when the patentee "has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term " Id.

The district court found that although the term "co-micronization" was not known in the art prior to the filing date of the application that led to the '726 patent both "micronization" and the prefix "co-" had well-known meanings as of that date and one of ordinary skill in the art at that time therefore would have readily understood the meaning of "co-micronization " Had that term not been explicitly defined in the '726 patent specification we might well agree with the appellants that that term could simply mean "micronized with or together" and would not necessarily exclude the presence of ingredients not specifically recited in the claim However the phrase "co-micronization of fenofibrate and a solid surfactant" is in fact explicitly defined at column 1 lines 35-38 of the '726 patent as "micronization of an intimate mixture of fenofibrate and a solid surfactant " Hence this is a case in which the patentee has "chosen to be his own lexicographer " and the district court did not err by reading the patentee's definition from the specification into the claim Moreover, the inclusion of the word "intimate" in the definition together with the fact that fenofibrate and SLS are the only ingredients present in every co-micronized mixture described in the '726 patent's specification makes it abundantly clear that "co-micronization of fenofibrate and a solid surfactant" should be construed as referring to co-micronization of a mixture consisting essentially of fenofibrate and solid surfactant ⁴²¹²¹

Since each of the claims of the '726 patent requires either "a co-micronized mixture of particles of fenofibrate and a solid surfactant" or "co-micronization of the fenofibrate and a solid

⁴²¹²¹ By use of the term "essentially " we do not wish to exclude the possibility of minor impurities being present

surfactant carried out by micronization of a fenofibrate/solid surfactant mixture," each of the claims requires co-micronization of a mixture consisting essentially of only fenofibrate and solid surfactant. Because it is undisputed that fenofibrate and a solid surfactant are not mixed in Novopharm's process without other significant ingredients, viz., excipients and water being present, we conclude that there is no genuine issue of material fact as to literal infringement in this case.

Fournier and Abbott also argue, however, that the district court erred in its analysis of infringement under the doctrine of equivalents by holding that Fournier had relinquished during prosecution coverage of all methods in which fenofibrate is pre-micronized. Fournier and Abbott further contend that the court erred by concluding that no genuine issue of material fact exists with respect to infringement by equivalents, and thus that the court's grant of summary judgment of noninfringement was improper.

In addition to assigning error to the district court's claim construction, the appellants argue that there is substantial un rebutted record evidence that Novopharm's fenofibrate product undergoes a decrease in particle size, to less than fifteen microns, during Novopharm's wet granulation and drying steps. Fenofibrate and SLS are simultaneously present in those steps and the appellants assert the reduction in fenofibrate particle size in the presence of SLS therefore constitutes "co-micronization."

We agree with the appellants that the court erred in its doctrine of equivalents analysis to the extent that it suggested that Fournier had relinquished coverage of all formulations made by methods in which fenofibrate is pre-micronized. Although Fournier distinguished its claimed composition from formulations prepared by combining pre-micronized fenofibrate with a pre-micronized or non-micronized solid surfactant without subsequent co-micronization and is accordingly estopped from asserting coverage of such formulations under the doctrine of equivalents, nothing in the '726 patent's specification, prosecution history, or reexamination record indicates that Fournier gave up coverage of compositions prepared by processes in which pre-micronized fenofibrate is later further micronized in the presence of a solid surfactant (that is, co-micronized with the solid surfactant). However, that error was harmless here.

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The process described in Novopharm's ANDA does not include any step in which fenofibrate and a solid surfactant are in a mixture in the absence of other excipients, and, in view of the above claim construction, there can be no dispute that fenofibrate and solid surfactant are not "co-micronized" as that term is used in the '726 patent. Significantly, Novopharm's process does not involve micronization of any mixture that includes fenofibrate and a solid surfactant, irrespective of the presence or absence of other excipients, as the SLS is dissolved in the aqueous granulating solution prior to mixing with the fenofibrate and remains in solution throughout the wet granulation and drying steps. Dissolved SLS is clearly not a "solid surfactant." Thus, even assuming that Novopharm's wet granulation and drying steps result in some reduction in fenofibrate particle size, those steps nonetheless cannot, as a matter of law, constitute co-micronization of an intimate mixture of fenofibrate and solid surfactant. To hold otherwise would vitiate that limitation altogether in contravention of the all-elements rule. See Warner-Jenkinson, 520 U.S. at 39 n.8.

We have considered Abbott and Fournier's other arguments and find them unpersuasive.

CONCLUSION

The district court did not err in granting summary judgment of noninfringement in favor of Novopharm, for no genuine issue of material fact exists in this case. The court's decision is therefore

AFFIRMED

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SPECIAL PATENT INFRINGEMENT CONCERNS FOR DRUGS

by M. Henry Heines

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The most familiar type of patent infringement is that which arises from the manufacture, use, sale, or offer for sale of a product falling within the scope of a patent. Patent infringement can also occur however by the simple act of submitting an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA). A lawsuit that was recently resolved on appeal demonstrates how this can happen.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Waxman-Hatch Act) contained provisions that amended both the Food and Drugs statute and the patent statute, and the effect of these provisions is seen when an ANDA is filed for a new formulation of a known drug.

The FDA provisions require an ANDA applicant to list all patents that claim the drug in some form and to certify that the new formulation raises no infringement liability under any of those patents. The applicant must also notify the owner of each listed patent and explain why the new formulation is believed to not infringe the patent.

The patent provisions state that if someone submits an ANDA with the intention of manufacturing, selling or using a drug while a patent is in force that covers the manufacture, sale or use, the submission of the ANDA will itself constitute infringement.

Thus, under the FDA statute, the patent owner is notified that a competitor intends to market the drug and is told why the competitor believes it can do so without infringing the patent, while under the patent statute the patent owner can sue the competitor immediately if the patent owner disagrees with the competitor's reasons for noninfringement.

This is exactly what happened with a new drug formulation developed by Mylan Pharmaceuticals Inc. The drug is glyburide, which is known to be effective in reducing the level of glucose in serum and is useful for treating Type II diabetes. The effectiveness of the drug is limited, however, by its low bioavailability (rate of entry into the bloodstream), and various solutions have been proposed. One of these is to prepare the drug in micronized form, i.e., as micronized particles compressed into a tablet, since micronized particles have a high surface area which helps them dissolve faster.

<http://www.townsend.com/news/articles/heines1.html>

08/03/2003

Tabletting drugs contain large amounts of excipients (inert substances that form a vehicle for the active ingredients), however, and particle size of both the drug and the excipients must be carefully controlled so that the tablet will have a uniform consistency and a uniform drug loading

The excipient used with glyburide is lactose. Unfortunately, the formation of lactose particles with sufficient size control for use with micronized glyburide has been a cumbersome and costly process involving wet granulation, drying, and sizing or milling. A cheaper way was the subject of U.S. Patent No. 4,916,163, owned by Pharmacia & Upjohn Company, which was based on the discovery that lactose particles with a high degree of size control can be obtained directly by spray-drying. The patent therefore claims a micronized glyburide composition with "spray-dried lactose as the preponderant excipient."

The lactose in Mylan's glyburide formulation was not spray-dried but instead anhydrous, thereby differing both in its method of preparation and in its absence of the water of hydration present in spray-dried lactose. When Mylan submitted its ANDA, it listed the Pharmacia & Upjohn patent, notified Pharmacia & Upjohn, and explained that the formulation would not infringe the patent since the formulation did not contain spray-dried lactose. Pharmacia & Upjohn did not dispute the distinction but claimed that the two forms of lactose were equivalent and that the Mylan formulation infringed under the "doctrine of equivalents" (Chemical Engineering Progress, Nov. 1997, p. 26).

Patent law states that the doctrine of equivalents will not be applied if applying it would be contrary to positions taken by the inventor or the inventor's attorney while the patent application was pending. Before the '163 patent issued, it had been rejected over earlier patents on lactose-containing glyburide formulations. In response to that rejection, Pharmacia & Upjohn stated that the lactose in the earlier patents was not spray-dried, and that spray-dried lactose was a critical feature of the invention and provided test data showing the manufacturing advantages of the spray-dried form. This was sufficiently convincing that the patent was granted.

The argument and the test data, however, prevented Pharmacia & Upjohn from later extending the scope of the patent to any form of lactose other than spray-dried. The question of whether anhydrous lactose and spray-dried lactose were equivalents in the suit against Mylan was, therefore, never reached, and the patent was deemed un infringed.

U S Current Class
U S Class at Publication
Intern'l Class

424/489, 241/21
424/489, 241/21
A61K 009/14, B02C 023/24

Claims

What is claimed is:

- 1 A process for reducing particle size of a drug, the process comprising (a) dispersing about 10 g or less of the drug in a suitable volume of a liquid dispersion medium to form a suspension, (b) bringing together in a vessel grinding media, magnetically activatable means for stirring and the suspension, (c) magnetically activating the means for stirring to effect milling of the suspension to a weight average particle size not greater than about 1 μ m, and (d) separating the resulting milled suspension from the grinding media and the magnetically activatable means for stirring
- 2 A process for reducing particle size of a drug of low water solubility, the process comprising (a) dispersing about 10 g or less of the drug in a suitable volume of a liquid dispersion medium to form a suspension, (b) bringing together in a vessel grinding media, magnetically activatable means for stirring and the suspension, (c) magnetically activating the means for stirring to effect milling of the suspension to a weight average particle size not greater than about 1 μ m, and (d) separating the resulting milled suspension from the grinding media and the magnetically activatable means for stirring
- 3 The process of claim 1 wherein about 5 g or less of the drug is dispersed in the liquid dispersion medium
- 4 The process of claim 1 wherein about 2.5 g or less of the drug is dispersed in the liquid dispersion medium
- 5 The process of claim 1 wherein the amount of liquid dispersion medium results, after the drug is dispersed therein, in a concentration of the drug in the liquid dispersion medium of about 0.1% to about 90% by weight
- 6 The process of claim 1 wherein the amount of liquid dispersion medium results, after the drug is dispersed therein, in a concentration of the drug in the liquid dispersion medium of about 5% to about 65% by weight

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about 10% to about 50% by weight

- 8 The process of claim 1 wherein the liquid dispersion medium comprises water
- 9 The process of claim 1 wherein the liquid dispersion medium comprises a non-aqueous solvent
- 10 The process of claim 8 wherein the liquid dispersion medium further comprises at least one surface modifying agent
- 11 The process of claim 10 wherein the at least one surface modifying agent is present in a total amount of about 0.1% to about 90% by weight based on the combined weight of the drug and the at least one surface modifying agent
- 12 The process of claim 10 wherein the at least one surface modifying agent is present in a total amount of about 0.1% to about 50% by weight based on the combined weight of the drug and the at least one surface modifying agent
- 13 The process of claim 10 wherein the at least one surface modifying agent is present in a total amount of about 0.1% to about 25% by weight based on the combined weight of the drug and the at least one surface modifying agent
- 14 The process of claim 10 wherein at least one surface modifying agent is selected from the group consisting of sodium dodecyl sulfate, polyvinylpyrrolidone, hydroxypropylmethylcellulose, and hydroxypropylcellulose
- 15 The process of claim 10 wherein the liquid dispersion medium further comprises at least one antifoaming agent
- 16 The process of claim 10 wherein the at least one antifoaming agent is present in the liquid dispersion medium in a total amount of about 0.001% to about 2.5%, by weight
- 17 The process of claim 10 wherein the at least one antifoaming agent is present in the liquid dispersion medium in a total amount of about 0.003% to about 1% by weight
- 18 The process of claim 15 wherein the at least one antifoaming agent comprises a silicon-based polymer
- 19 The process of claim 18 wherein the at least one antifoaming agent is selected from the group consisting of simethicone, Sigma RTM Antifoam A, and equivalents thereto
- 20 The process of claim 1 wherein the grinding media comprise a material selected from the group consisting of glass, lead-free glass, zirconium oxide and latex

- 22 The process of claim 1 wherein at least a substantial portion of said grinding media are in the shape of a sphere
- 23 The process of claim 22 wherein said sphere-shaped grinding media have a weight average diameter of about 0.2 to about 5 mm
- 24 The process of claim 22 wherein said sphere-shaped grinding media have a weight average diameter of about 0.33 to about 1.5 mm
- 25 The process of claim 21 wherein the sphere-shaped grinding media have a weight average diameter of about 0.5 to about 1 mm
- 26 The process of claim 1 wherein the weight ratio of the suspension to all of said grinding media is about 1:10 to about 1:1
- 27 The process of claim 1 wherein the weight ratio of the suspension to all of said grinding media is about 2:10 to about 9:10
- 28 The process of claim 1 wherein the weight ratio of the suspension to all of said grinding media is about 4:10 to about 8:10
- 29 The process of claim 1 wherein the magnetically activatable means for stirring comprises a magnetic stir bar
- 30 The process of claim 1 wherein the magnetically activatable means for stirring comprises a high strength magnetic stir bar
- 31 The process of claim 30 wherein the high strength magnetic stir bar is comprises one to a plurality of magnets comprising neodymium
- 32 The process of claim 30 wherein the high strength magnetic stir bar comprises one to a plurality of NdFeB magnets
- 33 The process of claim 1 wherein said step (c) is performed by placing a rotating magnet near the vessel
- 34 The process of claim 1 wherein said step (c) is performed until substantially all of the drug particles have been reduced to a size not greater than about 1 μ m
- 35 The process of claim 1 wherein said step (c) is performed until the drug particles have been reduced to a weight average particle size of about 10 to about 1000 nm
- 36 The process of claim 1 wherein said step (c) is performed until the drug particles have been reduced to a weight average particle size of about 100 to about 1000 nm
- 37 The process of claim 1 wherein said step (c) is performed until the drug particles have been reduced to a weight average particle size of about 400 to about 900 nm

- 38 The process of claim 1 wherein said step (c) is performed until the drug particles have been reduced to a weight average particle size of about 500 to about 900 nm
- 39 The process of claim 1 wherein said separation step (d) comprises filtration
- 40 The process of claim 1 wherein said filtration step (d) comprises centrifugal filtration
- 41 The process of claim 1 wherein said separation step (d) comprises removal of the suspension from the milling vessel with a pipette
- 42 The process of claim 1 further comprising diluting the milled suspension with at least one pharmaceutically acceptable excipient to form a pharmaceutical suspension
- 43 The process of claim 1 further comprising drying the milled suspension to form a drug powder
- 44 The process of claim 43 wherein the drying step is performed by evaporation, spray drying, rotovapping, lyophilization, or heating in an oven
- 45 The process of claim 43 further comprising mixing the drug powder together with one or more excipients to form a powder blend
- 46 The process of claim 43 further comprising compressing or encapsulating the powder blend to form a solid dosage form
- 47 The process of claim 43 further comprising granulating the powder blend to form a granulate prior to compressing or encapsulating
- 48 The process of claim 47 wherein granulating is performed by wet granulation to form a wet granulate, and wherein the wet granulate is dried prior to compressing or encapsulating
- 49 The process of claim 43 further comprising suspending the drug powder in an inert liquid vehicle to form an imbibable liquid
- 50 The process of claim 49 wherein the inert liquid vehicle is water or fruit juice
- 51 A pharmaceutical suspension prepared according to claim 42
- 52 A powder blend prepared according to claim 45
- 53 A solid dosage form prepared according to claim 46

Description

[0001] This application claims priority of U S provisional application Serial No 60/251,750 filed on Dec 6, 2000

FIELD OF THE INVENTION

[0002] The present invention relates to a process for milling drugs on a small scale and to use of drugs milled by such a process in manufacture of medicaments

BACKGROUND OF THE INVENTION

[0003] The bioavailability of an orally administered drug, as measured by its entry into systemic circulation in the bloodstream, depends on at least two fundamental processes drug dissolution in gastrointestinal fluids (in vivo drug release) and subsequent absorption of the dissolved drug. Several factors influence dissolution of a drug from its carrier, including surface area of the drug presented to the dissolution solvent medium, solubility of the drug substance in the specific solvent medium, and driving forces of the saturation concentration of dissolved materials in the solvent medium. Notwithstanding these factors, a strong correlation has been established between the in vitro dissolution time determined by standard assay procedures for an oral dosage form and the rate of in vivo drug release. This correlation is so firmly established in the art that dissolution time has become generally descriptive of drug release potential for the active component of the particular dosage form.

[0004] When the process of in vivo drug release is slower than the process of absorption, absorption is said to be dissolution rate-limited. Since dissolution precedes absorption in the overall process, any change in the drug release or dissolution process will subsequently influence drug absorption. See for example Lieberman et al (1989), Pharmaceutical Dosage Forms Tablets, Vol 1, pp 34-36 Marcel Dekker, New York. It is clear, therefore, that dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating compositions intended for rapid-onset delivery, particularly where drug absorption is dissolution rate-limited.

[0005] It is well known that one way to improve dissolution of drugs of low water solubility is to reduce drug particle size thereby increasing the specific surface area of the drug. Indeed, patent and other literature relating to nanoparticulate drug compositions teaches that, in general, the smaller the drug particle size, the greater is the advantage in speed of onset of therapeutic effect, or other pharmacodynamic benefit, obtained upon oral administration. For example, at least the following patents propose reduction of particle size to about 400 nm or smaller:

[0006] U S Pat No 5,145,684 to Liversidge et al

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[0007] U S Pat No 5,298,252 to Na & Rajagopalan

[0008] U S Pat No 5,302,401 to Liversidge et al

[0009] U S Pat No 5,336,507 to Na & Rajagopalan

[0010] U S Pat No 5,340,564 to Iilig & Sarpotdar

[0011] U S Pat No 5,346,702 to Na & Rajagopalan

[0012] U S Pat No 5,352,459 to Hollister et al

[0013] U S Pat No 5,429,824 to June

[0014] U S Pat No 5,503,723 to Ruddy et al

[0015] U S Pat No 5,510,118 to Bosch et al

[0016] U S Pat No 5,534,270 to De Castro

[0017] U S Pat No 5,552,160 to Liversidge et al

[0018] U S Pat No 5,573,783 to Desieno & Stetsko

[0019] U S Pat No 5,585,108 to Ruddy et al

[0020] U S Pat No 5,591,456 to Franson et al

[0021] U S Pat No 5,662,883 to Bagchi et al

[0022] U S Pat No 5,665,331 to Bagchi et al

[0023] Mills are among the most commonly used kinds of particle size reduction equipment for preparation of drugs and drug compositions. While there are many different types of mills, most have at least three basic components in common: (1) a structure for feeding material into the mill, (2) a milling chamber with working parts, and (3) a take-off to a receiver or collector in which the milled product is deposited. See Lieberman et al (1989), op cit., Vol 2, p 113. Non-limiting examples of mills commonly used to prepare and process drugs include fluid

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[0024] Although, as described above, dissolution and bioavailability advantages can be realized by milling drugs, particularly drugs of low water solubility, to smaller particle sizes, many difficulties preclude use of known types of mills in certain situations. For example, no practical means of milling small amounts (e.g., less than about 10 grams) of drug material to nanoparticulate dimensions, i.e., to particle sizes smaller than about 1 μ m, have hitherto been available. This has made the entire approach of preparing nanoparticulate drugs (either suspensions or solid compositions), for the purpose of inducing enhancement of dissolution, inaccessible for new drugs in discovery and early development phases, and for cold- or radioactively-labeled drugs—situations in which the quantity of drug available for such studies is usually very limited. Consequently, development of important drug formulations, for example rapid-onset formulations, is often delayed until larger quantities of drug are available.

[0025] Additionally, milling is a very inefficient unit operation with only approximately 0.05% to 2% of the applied energy being utilized in the actual reduction of particle size. Although milling efficiency is dependent upon the type of mill and the characteristic of the material being milled, in general, a large portion (e.g., about 10% to about 50%) of the energy expended during milling is converted to heat. This heat is generated by friction of particles contacting the mill, by plastic deformation of particles that are not fractured, by friction of particles colliding with each other, and/or by friction of mechanical mill parts, etc. In many instances, this heat generation leads to drug degradation. Consequently, common milling processes are suitable only for drugs which are thermally stable. Alternatively, expensive heat removal equipment must be employed to maintain drug stability.

[0026] A further difficulty is that traditional milling equipment suitable for particle size reduction to less than 1 μ m is generally very expensive and as such, is not widely available. Moreover, given the complexity of size reduction processes, few theories of general applicability have been developed. Therefore, most size reduction problems in the pharmaceutical industry must be solved empirically rather than theoretically. See Lieberman et al (1989), op cit, Vol 2, pp 107-112. Even when available, traditional milling equipment designed for heavy industry or large scale use is often not amenable to small scale empirical problem solving.

[0027] A yet further difficulty with traditional milling is that steel or some similar grinding media are typically employed. Use of metals in milling a suspension introduces the risk of metal contamination and consequent chemical decomposition.

[0028] Therefore, if an inexpensive, widely available, energy-efficient, laboratory-scale process for milling drugs of low water solubility to a nanoparticulate size range could be developed, a significant advance would be realized in preparation of drugs and drug compositions used in the treatment of a wide variety of disorders, particularly disorders where rapid onset of therapeutic action is desired.

SUMMARY OF THE INVENTION

[0029] Accordingly, the present invention provides a process for reducing particle size of a drug, the process comprising (a) a step of dispersing about 10 g or less of the drug in a suitable volume of a liquid dispersion medium to form a suspension, (b) a step of bringing together in a vessel grinding media, magnetically activatable means for stirring and the suspension, (c) a step of magnetically activating the

separating the resulting milled suspension from the grinding media and the magnetically activatable means for stirring

[0030] In one embodiment of the invention, the process further comprises (e) a step of drying the milled suspension resulting from step (c) to form a drug powder. In this embodiment, the drying step (e) can occur prior to or after step (d). Drug powders prepared according to this process can be further formulated to provide a pharmaceutical composition.

[0031] Other features of the invention will be in part apparent and in part laid out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] FIG. 1 shows in diagrammatic form an apparatus suitable for the process of the invention.

[0033] FIG. 2 shows a perspective representation of a high strength magnetic stir bar suitable for the process of the invention.

[0034] FIG. 3 shows a cross section view of a high strength magnetic stir bar suitable for the process of the invention.

[0035] FIG. 4 shows a side view of a high strength magnetic stir bar suitable for the process of the invention.

[0036] FIG. 5 presents particle size data for milled suspensions D1-D4 prepared as described in Example 1, as measured by Fraunhofer diffraction.

[0037] FIG. 6 shows optical micrographs of samples taken from milled suspensions D1-D4 under non-polarized (left) and polarized (right) light.

DETAILED DESCRIPTION OF THE INVENTION

[0038] The process of the invention is especially suitable for reducing particle size of a drug of low water solubility. The process comprises (a) a step of dispersing about 10 g or less, preferably about 5 g or less, and more preferably about 2.5 g or less, of the drug in a suitable volume of a liquid dispersion medium to form a suspension, (b) a step of bringing together in a vessel grinding media, magnetically activatable means for stirring, and the suspension, (c) a step of magnetically activating the means for stirring to effect milling of the suspension to a D₅₀ particle size not greater than about 1 μ m, and (d) a step of separating the resulting milled suspension from the grinding media and the magnetically activatable means for stirring.

[0039] Drugs of Low Water Solubility

[0040] Any suitable drug may be utilized in methods, processes and compositions of the invention. Preferably, the drug is one having low

water solubility, for example a solubility in water, measured at 37 degree C, not greater than about 10 mg of drug per ml of water, and preferably not greater than about 1 mg of drug per ml of water. Solubility in water for many drugs can be readily determined from standard pharmaceutical reference books, for example The Merck Index, 11th ed, 1989 (published by Merck & Co, Inc, Rahway, NJ), the United States Pharmacopoeia, 24th ed (USP 24), 2000, The Extra Pharmacopoeia, 29th ed, 1989 (published by Pharmaceutical Press, London), and the Physicians Desk Reference (PDR), 2000 ed (published by Medical Economics Co, Montvale, NJ), each of which is individually incorporated herein by reference

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[0041] For example, individual drugs of low solubility as defined herein include those drugs categorized as "slightly soluble", "very slightly soluble", "practically insoluble" and "insoluble" in USP 24, pp 2254-2298, and those drugs categorized as requiring 100 ml or more of water to dissolve 1 g of the drug, as listed in USP 24, pp 2299-2304. Processes of the invention are particularly suitable for drugs the absorption of which is dissolution-rate limited.

[0042] Illustratively, suitable drugs of low water solubility include, without limitation, drugs from the following classes: abortifacients, ACE inhibitors, alpha- and beta-adrenergic agonists, alpha- and beta-adrenergic blockers, adrenocortical suppressants, adrenocorticotrophic hormones, alcohol deterrents, aldose reductase inhibitors, aldosterone antagonists, anabolics, analgesics (including narcotic and non-narcotic analgesics), androgens, angiotensin II receptor antagonists, anorexics, antacids, anthelmintics, antiacne agents, antiallergics, antialopecia agents, antiamebias, antiandrogens, antianginal agents, antiarrhythmics, antiarteriosclerotics, antiarthritic/antirheumatic agents (including selective COX-2 inhibitors), antasthmatics, antibacterials, antibacterial adjuncts, anticholinergics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antidiarrheal agents, antidiuretics, antidotes to poison, antidyskinetics, antieczemata, antiemetics, antiestrogens, antifibrotics, antiflatulents, antifungals, antiglaucoma agents, antigonadotropins, antigout agents, antihistaminics, antihyperactives, antihyperlipoproteinemics, antihyperphosphatemics, antihypertensives, antihyperthyroid agents, antihypotensives, antihypothyroid agents, anti-inflammatories, antimalarials, antimanics, antimethemoglobinemics, antimigraine agents, antimuscarinics, antimycobacterials, antineoplastic agents and adjuncts, antineutropenics, antiosteoporotics, antipagetics, antiparkinsonian agents, antipheochromocytoma agents, antipneumocystis agents, antiprostatic hypertrophy agents, antiprotozoals, antipruritics, antipsoriasis, antipsychotics, antipyretics, antirickettsials, antiseborrheics, antiseptics/disinfectants, antispasmodics, antisiphylitics, antithrombocytopenics, antithrombotics, antitussives, antiulceratives, antiurolithics, antivenins, antiviral agents, anxiolytics, aromatase inhibitors, astringents, benzodiazepine antagonists, bone resorption inhibitors, bradycardic agents, bradykinin antagonists, bronchodilators, calcium channel blockers, calcium regulators, carbonic anhydrase inhibitors, cardiotonics, CCK antagonists, chelating agents, cholelitholytic agents, choleretics, cholinergics, cholinesterase inhibitors, cholinesterase reactivators, CNS stimulants, contraceptives, debriding agents, decongestants, depigmentors, dermatitis herpetiformis suppressants, digestive aids, diuretics, dopamine receptor agonists, dopamine receptor antagonists, ectoparasiticides, emetics, enkephalinase inhibitors, enzymes, enzyme cofactors, estrogens, expectorants, fibrinogen receptor antagonists, fluoride supplements, gastric and pancreatic secretion stimulants, gastric cytoprotectants, gastric proton pump inhibitors, gastric secretion inhibitors, gastropromotors, glucocorticoids, alpha-glucosidase inhibitors, gonad-stimulating principles, growth hormone inhibitors, growth hormone releasing factors, growth stimulants, hematinics, hematopoietics, hemolytics, hemostatics, heparin antagonists, hepatic enzyme inducers, hepatoprotectants, histamine H sub 2 receptor antagonists, HIV protease inhibitors, HMG CoA reductase inhibitors, immunomodulators, immunosuppressants, insulin sensitizers, ion exchange resins, keratolytics, lactation stimulating hormones, laxatives/cathartics, leukotriene antagonists, LH-RH agonists, lipotropics, 5-lipoxygenase inhibitors, lupus erythematosus suppressants,

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narcotic antagonists, neuroprotectives, nootropics, ovarian hormones, oxytocics, pepsin inhibitors, pigmentation agents, plasma volume expanders, potassium channel activators/openers, progestogens, prolactin inhibitors, prostaglandins, protease inhibitors, radio-pharmaceuticals, 5 alpha -reductase inhibitors, respiratory stimulants, reverse transcriptase inhibitors, sedatives/hypnotics, serotonins, serotonin noradrenaline reuptake inhibitors, serotonin receptor agonists, serotonin receptor antagonists, serotonin uptake inhibitors, somatostatin analogs, thrombolytics, thromboxane A sub 2 receptor antagonists, thyroid hormones, thyrotropic hormones, tocolytics, topoisomerase I and II inhibitors, uricosurics, vasodilators, vasoprotectants, xanthine oxidase inhibitors, and combinations thereof

[0043] Non-limiting illustrative examples of suitable drugs of low water solubility include acetohexamide, acetylsalicylic acid, alclufenac, allopurinol, atropine, benzthiazide, carbamazepine, carprofen, celecoxib, chlorthalidone, chlorpromazine, clonidine, codeine phosphate, codeine sulfate, codeine, dexacoxib, diclofenac, diltiazem, enolic acids, estradiol, etodolac, etoposide, fenbufen, fenclofenac, fenpropfen, fentiazac, flurbiprofen, gaseofulvin, haloperidol, ibuprofen, indomethacin, indomethacin, indoprofen, ketoprofen, linezolid, lorazepam, medroxyprogesterone acetate, megestrol, methoxsalen, methylprednisone, morphine sulfate, morphine, naproxen, nicergoline, nifedipine, niflumic, oxaprozin, oxazepam, oxyphenbutazone, parecoxib, phenindione, phenobarbital, phenytoin, piroxicam, pirprofen, prednisolone, prednisone, procaine, progesterone, pyrimethamine, rofecoxib, sulfadiazine, sulfamerazine, sulfisoxazole, sulindac, suprofen, temazepam, tiaprofenic acid, tiludisole, tolmetec, valdecoxib, etc

[0044] Where the drug being milled is not of low water solubility, the liquid dispersion medium is preferably substantially free of water

[0045] Energy Efficiency

[0046] A presently contemplated advantage of the process of the invention, in addition to its unique suitability where only small quantities of drug are available, is that it requires less energy and/or produces less heat than conventional milling processes. Consequently the process of the invention results in substantially less or no drug degradation (and/or conversion of crystalline to amorphous state) compared to conventional milling processes, particularly where moderately stable or unstable drugs are used. Heat production can be measured by standard means, for example, by using a thermometer. Drug degradation and conversion to an amorphous state can be measured by any method known in the art, for example, by high performance liquid chromatography (HPLC), high pressure liquid chromatography, thin-layer chromatography (TLC), paper chromatography, gas chromatography, differential scanning calorimetry (DSC), X-ray crystallography, etc

[0047] Chemical Stability

[0048] Another presently contemplated advantage of the process of the invention is that it employs chemically inert grinding media which are substantially resistant to chipping or cracking. Consequently, risk of chemical degradation of drug particles due to milling is greatly reduced or eliminated

[0049] Drug Particle Size

[0050] As used herein, the term "D sub 50" refers to a linear measure of diameter having a value such that 50% by volume of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter. For practical purposes a determination of D sub 50 based on 50% by weight rather than by volume is generally suitable. As used herein, therefore, D sub 50 particle size is essentially synonymous with weight average particle size. 47

[0051] Particle size can also be characterized, for example, by D sub 10, which refers to a linear measure of diameter having a value such that 10% by volume of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter, or by D sub 90, which refers to a linear measure of diameter having a value such that 90% by volume of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter.

[0052] Drugs prepared according to the process of the invention have a D sub 50 particle size not greater than about 1000 nm, preferably about 10 nm to about 1000 nm, more preferably about 100 nm to about 1000 nm, still more preferably about 400 nm to about 900 nm and most preferably about 500 nm to about 800 nm.

[0053] In a further preferred embodiment, about 50% to 100%, more preferably about 75% to 100%, and still more preferably about 90% to 100% by weight of drug particles prepared according to the process of the invention have a linear diameter not greater than about 1000 nm. In a particularly preferred embodiment, substantially all of the drug particles prepared by the process of the invention have a linear diameter not greater than about 1000 nm.

[0054] Any suitable detection method can be used to determine particle size of drugs prepared according to the process of the invention. Illustrative processes include appropriate microscopy (e.g. visible light microscopy, ultraviolet microscopy, or electron microscopy), dynamic light scattering (DLS), turbidimetry, etc. In general, one of ordinary skill in the art will be able to select an appropriate size detection method for the particle size range being detected.

[0055] Liquid Dispersion Medium

[0056] The invention can be practiced with any liquid dispersion medium in which the particular drug selected is substantially insoluble (i.e., less than about 10 and preferably less than about 1 mg of drug per ml of liquid dispersion medium). A presently preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid dispersion media in which the particular drug selected is substantially insoluble, for example, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane and glycols. Alternatively, the liquid dispersion medium can comprise molten material, for example molten polyethylene glycol or a gelucire, which can be heated and maintained in liquid form during milling and then allowed to cool and solidify after milling.

[0057] A suitable liquid dispersion medium preferably comprises at least one surface modifying agent(s). Surface modifying agent(s) can be added to the liquid dispersion medium at any step of the process, for example, before and/or after the milling step (c). Preferably, surface modifying agent(s) are added prior to the milling step (c). Suitable surface modifying agents can be selected from known organic and inorganic pharmaceutically acceptable excipients. Such excipients include various polymers, low molecular weight oligomers, natural 48

products, surfactants, etc. Non-limiting, representative examples of excipients that can be used as surface modifying agents include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetamacrogol emulsifying wax, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene castor oil derivatives, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecyl sulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone, preferably polyvinylpyrrolidone having a molecular weight of about 30,000. Most of these excipients are described in detail in *The Handbook of Pharmaceutical Excipients*, The Pharmaceutical Press (1986). Surface modifying agents are commercially available and/or can be prepared by processes known in the art.

[0058] Particularly preferred surface modifying agents are sodium dodecyl sulfate, polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose. If present in a liquid dispersion medium, at least one surface modifying agent is preferably present in a total amount of about 0.1% to about 90%, preferably about 0.1% to about 50%, and more preferably about 0.1% to about 25%, by weight based on the combined weight of drug and the at least one surface modifying agent.

[0059] For some drugs, particles will tend to agglomerate during the milling process of the invention. Without being bound by theory, it is believed that drug particle agglomeration during milling prevents reduction of drug particles to small sub-micron sizes. Where such small sub-micron particle sizes are desired, one or more surface modifying agents are preferably selected (by type and amount) so as to minimize, reduce and/or inhibit drug particle agglomeration during and/or after milling.

[0060] One of ordinary skill in the art will, through routine optimization, be able to determine which surface modifying agents (and ideal concentrations) are effective for minimizing, inhibiting, and/or reducing agglomeration of particles of a particular drug during milling and/or storage of the suspension. Illustratively, if particle agglomeration occurs during milling of a particular drug, a miniaturized screening assay can be performed to optimize liquid dispersion medium components. An exemplary miniaturized screening assay is a 96-well plate screen. Visual detection or automated absorbance can be used to measure drug particle agglomeration. Such an assay can also be used to optimize liquids used to rinse and/or dilute milled suspensions and to test drug particle agglomeration under stressed conditions such as freeze-thaw or elevated temperatures.

[0061] Conversely, where a lower limit on drug particle size reduction is desired (i.e. drug particles below a specific size are not desired) one of ordinary skill in the art will readily be able to control the use of surface modifying agents during milling so as to not limit drug particle agglomeration and, consequently, limit drug particle size reduction to the desired range.

[0062] Preferably, one or more antifoaming agents are added to the liquid dispersion medium. If present in a liquid dispersion medium, one or more antifoaming agents are typically present in a total amount of about 0.001% to about 2.5%, and preferably about 0.003% to about 1%, by weight of the liquid dispersion medium. Silicon-based polymers are preferred antifoaming agents. Polydimethylsiloxane (e.g. dimethicone USP) and Sigma Antifoam A Concentrate or an equivalent thereof are particularly preferred antifoaming agents.

[0063] Preferably, the apparent viscosity of a liquid dispersion medium used to prepare nanoparticulate drug particles according to the invention is about 1 to about 1000 cP, and preferably about 1 to about 500 cP

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[0064] In the process of the invention, about 10 g or less of a drug is placed in a suitable amount of the liquid dispersion medium. What constitutes a "suitable amount" in the present context depends, among other factors, on the amount of drug used, the particular drug being used, the size of the vessel, the amount of grinding media used, and the particular components of the liquid dispersion medium. In general, a suitable amount of liquid dispersion medium is an amount which, after the drug is dispersed therein, results in a concentration of drug in the liquid dispersion medium of about 0.1% to about 90%, preferably about 5% to about 65%, and more preferably about 10% to about 50%, by weight. Concentrations can be readily optimized by one skilled in the art depending on the particular drug and the particular liquid dispersion medium used. Without being bound by theory, higher drug concentrations are generally desired and tend to result in a more efficient milling process and in more flexibility in transferring a suspension after milling. This in turn allows for increased recovery of milled drug particles.

[0065] Grinding Media

[0066] Grinding media of any suitable shape (e.g., balls, banded balls, cubes, cylinders, beads, etc.), size, size distribution, density and/or material can be used in the milling step. The grinding media should be chemically inert and resistant to chipping or cracking during the process of the invention. Preferred grinding media comprise glass, lead-free glass, latex and/or zirconium oxide and are in the shape of spherical beads. Preferably, such beads have a weight average diameter of about 0.2 to about 5 mm, more preferably about 0.33 to about 1.5 mm, and still more preferably about 0.5 to about 1 mm. More preferably, substantially all of the spherical beads have a diameter of about 0.2 to about 5 mm, more preferably about 0.33 to about 1.5 mm, and still more preferably about 0.5 to about 1 mm. Without being bound by theory, it is generally believed that smaller grinding media are more efficient in the milling process of the invention since more bead-bead contact results.

[0067] The amount, by weight, of grinding media used to prepare nanoparticulate drug particles according to the process of the invention depends on the particular volume of liquid dispersion medium used, the drug used, the size, density and shape of the grinding media, and the size of the vessel in which the grinding takes place. The amount of grinding media can be readily optimized by one skilled in the art taking into account the above factors. Generally, a suitable suspension grinding media weight ratio is about 1:10 to about 1:1, preferably about 2:10 to about 9:10 and more preferably about 4:10 to about 8:10. The suspension in this context includes all components of the liquid dispersion medium as well as the drug.

[0068] Milling Apparatus

[0069] A suitable milling apparatus for use in the process of the invention is illustrated diagrammatically in FIG. 1.

[0070] A vessel 11 is adapted to receive a suspension comprising the liquid dispersion medium 12 for the drug, grinding media 13 and magnetically activatable means 14 for stirring the dispersion medium with grinding media therein.

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[0071] The vessel 11 is illustratively a vessel having a capacity of about 100 ml to 1000 ml during milling. The vessel is held in place by suitable support means such as a clamp 16

[0072] The grinding media 13 are illustratively spherical beads, about 0.2 mm to about 5 mm in diameter, and are illustratively of latex, glass or zirconium oxide.

[0073] The magnetically activatable means for stirring illustratively comprises a magnetic stir bar 14 which preferably comprises a high strength magnetic material, for example neodymium. An activating device 17, illustratively a magnetic stir plate, preferably with the cover plate removed to increase field strength, is placed near, preferably immediately under, the stirring means.

[0074] The term "magnetically activatable" as used herein with respect to the means for stirring describes a means for stirring which is capable of being set into motion by magnetic forces. To "magnetically activate" a means for stirring, as the phrase is used herein, describes use of a magnetic force to cause motion, preferably rotation, of the means for stirring.

[0075] Any suitable magnetically activatable means for stirring can be used in the process of the invention. A preferred magnetically activatable means for stirring is a magnetic stir bar or a rotating magnet. Magnetic stir bars and/or rotating magnets used as magnetically activatable means for stirring in processes of the invention can be of any suitable size and/or shape (e.g., oblong, oval, rectangular, cylindrical, egg-shaped, etc.) and can be uncoated or coated with any suitable material, for example rubber, plastic, metal, fluoropolymer, etc. Preferably, the magnetically activatable means for stirring is of sufficient magnetic strength so as to resist decoupling during the milling process. A sufficient strength of a magnetically activatable means for stirring will be determined based on, inter alia, viscosity of the liquid dispersion medium, amount of grinding media being used, desired milling speed, and vessel size. One or more magnetically activatable means for stirring can be used.

[0076] One illustrative commercially available stir bar suitable as a magnetically activatable means for stirring is a samarium-cobalt stir bar (Mastco). Such stir bars are available in egg-shape having longitudinal lengths of 10 mm, 15 mm, 25 mm, and larger.

[0077] In a particularly preferred embodiment, the stir bar is a high strength magnetic stir bar comprising (i) a non-reactive, abrasion-resistant case having a longitudinal axis, and (ii) a magnetic assembly comprising one to a plurality of lanthanide magnets completely enclosed in and substantially filling the case. Preferably the assembly has a coercive force and/or a maximum energy product substantially greater than that of a samarium-cobalt magnet, and has a polarity substantially aligned with the longitudinal axis of the case.

[0078] In a particularly preferred embodiment, the magnetic assembly comprises a plurality of lanthanide magnets linearly and contiguously arranged, each magnet having a first face in the orientation of a north pole and an opposing face in the orientation of a south pole. Adjoining faces of adjacent magnets have opposite polarity, and the first and second faces are substantially perpendicular to the longitudinal axis of the case.

[0079] Suitable lanthanide magnets can be of any desired shape, for example box-, doughnut-, triangular-, bar- or disk-shape. Preferably the

magnets are of disk- or doughnut-shape most preferably the magnets are of disk-shape Where the magnets are of disk- or doughnut shape, they preferably have a diameter of about 2 to about 25 mm and a thickness of about 0.5 to about 20 mm Where the stir bar comprises more than one magnet, it is preferred that all of the magnets have substantially the same shape and preferably, the individual faces present on each magnet are of substantially the same cross-sectional area. Preferably, each magnet has cross-sectional faces of substantially the same surface area as the other magnets

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[0080] Lanthanide magnets herein are magnets composed of a material comprising at least one lanthanide element. Preferably such magnets have a coercive force and/or a maximum energy product substantially greater than that of a samarium cobalt magnet. Particularly preferred lanthanide magnets comprise neodymium. Such magnets can comprise additional materials, for example iron and boron. An exemplary lanthanide magnet comprises neodymium/iron/boron, also referred herein as an NdFeB magnet.

[0081] A non-reactive, abrasion-resistant case herein can comprise any suitable material. Preferably, the material is water-impermeable, resistant to cracking or leaking during use in the process of the invention, and is chemically inert. The case can be a single-piece case or a multi-piece case. Non-limiting illustrative examples of suitable materials for use in such a case include rubber, metals, epoxy, plastics and other polymers, and combinations thereof. Illustrative polymers include RheFlex RTM tubing (Rheodyne), polypropylene, polymethylmethacrylate, fluoropolymers such as polytetrafluoroethylene (PTFE, available commercially as Teflon RTM), ethylene-tetrafluoroethylene fluoropolymer (e.g. Tefzel RTM), perfluoroalkoxy copolymer resin (Teflon RTM PFA), fluorinated ethylene propylene polychlorotrifluoroethylene, polyvinylidene fluoride fluoroplastic (e.g. Kynar), etc. A particularly preferred case comprises PTFE tubing whereby the ends of the tube are fitted with PTFE discs and sealed with epoxy cement.

[0082] An exemplary high strength magnetic stir bar 20 for use in a process of the invention is illustrated in FIG. 2 (perspective representation), FIG. 3 (section view), and FIG. 4 (side view). In this example, disc-shaped NdFeB magnets 1 are linearly stacked to a desired length and press fit into a piece of PTFE tubing 2 which is of slightly greater length than the stacked magnets. The ends of the tubing are then sealed by placing epoxy cement 3 in the end of the tube, press fitting a PTFE disk 4 thereon, and placing another layer of epoxy cement 5 on the outside of the PTFE disk. Alternatively, the ends of the sleeve can be sealed with epoxy cement and no PTFE disk. To reduce rotational friction, a piece of external tubing 6, for example Tygon tubing, can be slipped over the tube so that the bar balances evenly when placed on a flat, horizontal surface. Preferably such external tubing is of lesser length than the stir bar and is fixably located around the midsection of the stir bar, for example as illustrated in FIG. 2.

[0083] This high strength stir bar has at least two important advantages over conventional commercially available stir bars. First, the bar is very difficult to decouple during milling, thus allowing for greater milling speeds and consequent reduced processing time. Second, the wide size range of available NdFeB magnets allows for preparation of stir bars of any length (typically to a resolution of 1 mm). Such stir bars are useful in processes of the invention and in any other process which would benefit from use of a high strength, sturdy, inexpensive, and custom-sized stir bar.

[0084] Any suitable device can be used to magnetically activate the means for stirring. A preferred device is a rotating magnet, preferably a high strength rotating magnet. The step of magnetically activating the means for stirring is performed by placing the device (in the active or

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on position) not greater than that from which the particular magnetically activatable means for stirring can be set in motion by the particular device used, such a distance will be determined both by characteristics of the particular means for stirring and by characteristics of the device used to activate the means for stirring. Generally, such a distance is not greater than about 2 meters, preferably not greater than about 1 meter, more preferably not greater than about 0.5 meter, and still more preferably not greater than about 0.33 meter. In practice, the distance will be as short as can conveniently be arranged, for example about 0.01 to about 0.1 meter. If the device used to magnetically activate the means for stirring is a stir plate, for example a Magne stir, removal of the cover plate will enhance performance by increasing the available magnetic field.

[0085] Any suitable size and/or type of vessel, for example a scintillation vial, a cryogenic tube, a beaker, a flask, a conical tube, a cylinder, etc., can be used in the process of the invention. Preferably, the vessel is made of glass or Pyrex R™ and has a flat bottom. As will be discussed below, when milling at the microgram scale, the vessel is preferably made of hard plastic or latex which can be punctured using moderate force. Preferably, prior to milling, the vessel is about 20% to about 85%, more preferably about 25% to about 80%, and still more preferably about 30% to about 75% full, by total volume. Such a volume includes the grinding media, magnetically activatable means for stirring, drug, and liquid dispersion medium.

[0086] Stirring Time and Rate

[0087] All other factors being equal (e.g., bead size, bead amount, bead material, vessel size etc.), size of drug particles prepared according to a process of the invention is inversely related to stirring time (i.e., the longer the stirring time, the smaller will be the drug particles) and stirring rate (i.e., the faster the stirring rate over a given period of time, the smaller will be the drug particles). Any desired stirring rate and/or amount of stirring time can be employed. In practice, however, a sufficient milling time will be about 0.15 to about 72 hours, preferably about 0.15 to about 48 hours, and more preferably about 0.15 to about 24 hours. Generally, a suitable stirring rate will be about 10 to about 4000 rpm, and preferably about 100 to about 3500 rpm. Typically, where milling speeds greater than about 1500 rpm are desired, a high strength stir bar as described herein above will be needed in order to resist decoupling. In performing the process of the invention, one of ordinary skill can readily optimize stirring time and rate as well as other factors described herein above in order to prepare drug particles to a desired size range.

[0088] Separation of Grinding Media and Suspension

[0089] Grinding media and/or magnetically activatable means for stirring can be separated from a milled suspension prepared according to the process of the invention by any suitable means. Non-limiting examples of illustrative separation means include filtration, suction filtration, centrifugal filtration, extraction with a syringe or pipette, pouring off, physical removal (e.g., with tongs or a net), etc. Illustratively, the separation means can comprise removing the milled suspension from a milling vessel using a transfer pipette, for example a 1.5 ml Samco. Preferably the transfer pipette has an aperture small enough so grinding media present in the vessel will not be entrained by the pipette. Optionally, the grinding media can be washed/rinsed with fresh liquid dispersion medium to aid in recovery of drug particles. For enhanced drug recovery, multiple small volume washes are generally preferred to one large volume wash. Filtration and pipetting are

[0091] In such cases, centrifugal filtration may be used to remove suspension from grinding media. Where centrifugal filtration is used to remove suspension from the milling vessel, the milling vessel should comprise a penetratable hard plastic as opposed to glass. Centrifugal filtration is performed by using a small gauge needle or similar object to pierce one to a small plurality of holes in the bottom of the milling vessel. Without being bound by theory, no suspension typically drains out of such holes by gravity because of the surface tension effects as noted above. The pierced vessel is then suspended over a receiver vessel and the two vessels are placed in a centrifuge. The vessels are then centrifuged for about 10 to about 60 seconds at about 100 to about 1000 rpm during which time the suspension is transferred from the milling vessel to the receiver vessel, the grinding media remain in the milling vessel. Preferably, the minimum amount centrifugation time and speed necessary to transfer suspension from the milling vessel to the receiver vessel should be used. Suspensions having high concentrations or viscosities may necessitate longer or faster spinning or the use of more holes. One of ordinary skill in the art will readily optimize centrifugation filtration conditions based on size and characteristics of the milled suspension.

[0093] In one embodiment of the invention, a milled suspension resulting from step (c) or (d) of the above process is further diluted to form a pharmaceutical suspension. The milled suspension is preferably diluted with a liquid dispersion medium selected to minimize drug particle aggregation upon storage, for example as is described hereinabove. Any additional pharmaceutically acceptable excipients may also be added to the pharmaceutical suspension.

[0095] In a particularly preferred embodiment of the invention, a milled suspension resulting from step (c) or (d) of the above process is dried to form a drug powder. The drying step can comprise any suitable method of drying, for example evaporation, rotovapping (rotary evaporation), spray drying, lyophilization, conventional heating, for example in an oven, etc. Spray drying and rotovapping are preferred methods of drying. Any suitable spray drying method known in the art can be employed. Generally, spray drying is a process by which a solution or suspension comprising dissolved or dispersed drug is rapidly sprayed over a current of warm air, resulting in formation of a dry powder.

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[0097] Formulation

[0098] A drug powder prepared as provided herein can be further formulated together with one or more pharmaceutically acceptable excipients to produce a pharmaceutical composition, for example by direct compression or granulation. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling, storage, disintegration, dispersion, dissolution, release or organoleptic properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, glidants, crystallization inhibitors, surface modifying agents, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition.

[0099] Excipients employed in preparing compositions according to the invention can be solids, semi-solids, liquids or combinations thereof. Formulation can occur by any known technique of pharmacy that comprises admixing an excipient with the drug powder. A composition prepared by the process of the invention contains a desired amount of drug per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispersible powder, granules, a suspension, an elixir, a liquid, or any other form reasonably adapted for such administration. If intended as an imbibable liquid, for example a suspension, elixir or a liquid, drug powder prepared according to the invention can be suspended in one or more inert carriers, for example water or fruit juice. If intended for parenteral administration, it can be in the form, for example, of a suspension. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of drug, such as tablets or capsules.

EXAMPLES

[0100] The following examples illustrate aspects of the present invention but should not be construed as limitations.

Example 1

[0101] Dispersions D1-D4 containing 5% by weight celecoxib were prepared by the process described below. The dispersions differed only in the particle size range of the celecoxib.

[0102] 1 Celecoxib was micronized in an air jet mill to form a drug powder.

[0103] 2 The drug powder was added to an aqueous solution containing 2.5% low viscosity hydroxypropylcellulose (HPC-SL) and 0.12% sodium dodecyl sulfate, to form a suspension.

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[0104] The suspension was wet milled to form a milled suspension according to the following protocol. A sample amount of 6.0 ml of the suspension (containing 20% celecoxib), a 19 mm magnetic stir bar made by VWR, 8 ml of lead-free glass beads, and 50 μ l of antifoaming agent (Sigma Antifoam A Concentrate) were added to a 20 ml scintillation vial. To provide a milled suspension having a target particle size range of 6-7 μ m (i.e., the size range achieved in the micronizing step, used to provide a comparative composition), the vial was shaken for two minutes. To provide a milled suspension having smaller target particle size ranges, the vial was suspended over a high-strength rotating magnet so that milling occurred by agitation of the glass beads by rotation of the magnetic stir bar. Target particle size ranges were varied by controlling magnet rotation rate, milling time and/or bead size, as shown in Table 1. Small aliquots were removed at intervals in order to monitor progress of particle size reduction.

[0105] 4. The resulting milled suspension in each case was transferred to a larger vial and diluted with fresh vehicle to form a final milled suspension. Nominal celecoxib concentration in final suspensions was 5% by weight.

TABLE 1 Milling conditions used to produce milled suspensions D1-D4

Suspension	range (μ m)	(mm)	(min)	(rpm)	Milled Target size (μ m)	Bead size (μ m)	Milling time (min)	Milling speed (rpm)
D1	6-7	3	3	6	—	—	—	—
D2	1-3	3	3	3	6	26	900	—
D3	0.5-0.9	1	25	1	55	25	900	—
D4	0.2-0.4	0.5	52	1250	—	—	—	—

Example 2

[0106] Celecoxib particle size in milled suspensions D1-D4 as prepared in Example 1 was determined by laser (Fraunhofer) diffraction and by optical microscopy.

[0107] Fraunhofer scattering was measured on static suspensions samples using a Sympatec spectrometer. Samples were diluted with water into a static cell at a concentration that maintained a reduction in laser intensity of approximately 20%. The choice of collection lens was determined by the population of large material present in suspension, and thus was different for each sample. However, the smallest focal length optic appropriate was used in each case. No Mie scattering corrections were applied. The results, presented in FIG. 5, show a D_{sub 50} particle size consistent with the target size range. D_{sub 50} and other particle size parameters shown in FIG. 5 are believed to be overestimated for the 0.2-0.4 μ m celecoxib dispersion, since this size range is at the very limit of detection by this technique.

[0108] In order to visually confirm particle sizes, optical microscopy was used. Observations were carried out using an Olympus BH-2 microscope with attached video camera. Images were then digitized (Snappy 4.0, Play Inc., Rancho Cordova, Calif.) and manipulated (Paint Shop Pro 6.02, JASC, Eden Prairie, Minn.) as appropriate. FIG. 6 shows micrographs of samples taken from celecoxib dispersions D1-D4 with non-polarized (left) and polarized (right) light. The bar represents 10 μ m. Significant Brownian motion was observed in suspensions D3 and D4, an observation consistent with presence of very small nanoparticles. In contrast, only slight Brownian motion was noted in dispersion D2 and none at all in suspension D1.

Example 3

[0109] Samples of milled suspensions prepared in Example 1 were dried individually by rotovapping according to the following procedure. 3

RE11 Rotovapor) The flask was suspended in water at a temperature of 40 degree C and rotated at approximately 100 rpm. A gentle vacuum was pulled on the flask for 0.5-1 hour to avoid bubbling of the suspension. After this time, a full house vacuum was employed and the evaporation proceeded for not less than 48 hours.

Example 4

[0110] Samples of milled suspensions prepared in Example 1 are spray dried individually at room temperature using a Yamato GB-21 spray dryer to form drug powders DP1, DP2, DP3 and DP4, respectively, under the following conditions: (a) liquid flow rate of 5 ml/min, (b) inlet air temperature of 110-130 degree C, (c) outlet air temperature of 60-70 degree C, and (d) drying airflow of about 30% to about 50% of the capacity of the spray dryer.

Example 5

[0111] Valdecoxib, linezolid, phenytoin, griseofulvin and carbamazepine were milled according to the general procedure described for celecoxib in Example 1. Milling parameters are shown in Table 2.

2TABLE 2 Milling parameters for various drugs		Valdecoxib	Linezolid	Phenytoin	Solution Components	2% PVP- 2% PVP- 3 75% PVP- K30
and K30	and K30	0 5% 0 15% SDS	0 15% SDS	SDS, 10 mM	in H sub 20	in H sub 20 Na citrate pH 3
Anti-foam (mu l)	3 30 40	Drug				
Concentration (%)	0 25 20 10	Suspension volume (ml)	0 5 g 3 g 7 5 ml	or weight (g)	Stir bar type	NdFeB bar NdFeB bar NdFeB bar
Stir bar length (mm)	5 3 19	Grinding media size (mm)	0 50-0 75 0 50-0 75 0 50-0 75	Grinding media volume (ml)	0 75 g 4 7 g 8 0 ml	or weight (g)
Milling time (h)	15 18 11	Milling Speed (rpm)	3000 3000 1500	D sub 50 (nm)	460 sup 1 1900 sup 1 200 sup 1	1000 sup 2 130 sup 3
Griseofulvin Carbamazepine		Solution Components	3 75% PVP-K30, 3 75% PVP-K30, 0 5% SDS, 0 5% SDS, 10 mM Na citrate	10 mM Na citrate	pH 3 pH 3	Anti-foam (mu l) 40 40
Drug	Concentration (%)	10 10	Suspension volume (ml)	7 5 ml 7 5 ml	or weight (g)	Stir bar type
NdFeB bar NdFeB bar	Stir bar length (mm)	19 19	Grinding media size (mm)	0 50-0 75 0 50-0 75	Grinding media volume (ml)	8 0 ml 8 0 ml
or weight (g)	Milling time (h)	11 11	Milling Speed (rpm)	1500 1500	D sub 50 (nm)	250 sup 1 2500 sup 1 160 sup 3 2600 sup 3
Size		Detection Method	sup 1Turbidimetry, sup 2Optical Microscopy, sup 3X-Ray Diffraction			

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Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S A , reúne los requisitos formales exigidos por la ley al momento de su presentación

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha,

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