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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Señor
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E. S. D.



No. 07-028925-00019-0000

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Ref.:	Expediente No.:	07-028925
	Trámite:	2
	Evento:	1
	Actuación:	430
	Oficio No.:	14145
	Título:	"Nuevas Composiciones Farmacéuticas que comprenden ácido 4-(4-(3-(4-cloro-3- trifluorometil-fenil)-ureido)-3- fluoro-fenoxi)-piridin-2-carboxílico para el tratamiento de trastornos hiperproliferativos"
	Solicitante:	BAYER PHARMACEUTICALS CORPORATION

MAURICIO JARAMILLO CAMPUZANO, abogado en ejercicio, identificado con la cédula de ciudadanía número 80.421.942 de Usaquén y la Tarjeta Profesional No. 74.555 del Consejo Superior de la Judicatura, actuando en mi carácter de apoderado de la solicitante, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, como resultado del examen de fondo realizado con fundamento al artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito presentar respuesta al Oficio No. 14145, de conformidad con los siguientes argumentos:

1. Descripción – Título

En atención a lo manifestado por el Sr. Examinador, atentamente se propone el siguiente título el cuál en cumplimiento con las normas respectivas, no hace mención del uso o aplicación para la cual va dirigida la invención:

**COMPOSICIÓN QUE COMPRENDE UNA DISPERSIÓN SÓLIDA
COMPRENDIENDO METILAMIDA DEL ÁCIDO 4{4-[3-(4-CLORO-3-
TRIFLUOROMETILFENIL)-UREIDO]-3-FLUORO-FENOXI}-PIRIDIN-2-
CARBOXÍLICO Y LA MATRIZ Y PROCESO PARA SU PREPARACIÓN**

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1
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2. Reivindicaciones

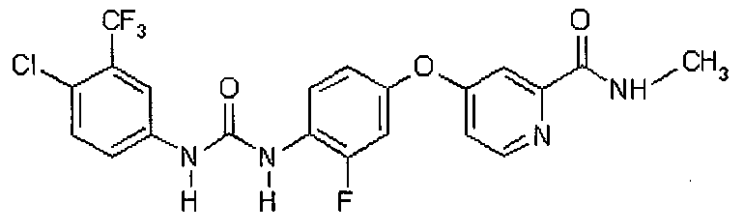
- 2.1. Se acompaña un nuevo pliego de 22 reivindicaciones, basado en una parte del anterior de 35 reivindicaciones con limitaciones y modificaciones a fin de satisfacer las observaciones recibidas y mejorar la claridad.
- 2.2. En el presente pliego se han cancelado las reivindicaciones 31 a 35 observadas respecto de excepciones de patentabilidad (métodos de tratamiento) y la reivindicación 30 por causas formales.
- 2.3. En la reivindicación 1 se han suprimido o reemplazado las expresiones observadas: "al menos", "excipientes poliméricos o no poliméricos", "polímeros solubles en agua", matriz aceptable" y "substancialmente".
- 2.4. Respecto de la expresión "comprende", la solicitante propone respetuosamente que se reconsidere la actual redacción donde dicha expresión se encuentra en una forma aceptable, indicando los componentes de la composición o los pasos del proceso que se pasan a definir. Sin embargo, si el Sr. Examinador señalase la enmienda a realizar, el solicitante prestará la debida atención para su cumplimiento.
- 2.5. Las actuales reivindicaciones 17 a 22, basadas en las anteriores reivindicaciones 23 a 29, se encuentran correctamente definidas por los pasos o etapas del proceso de preparación, indicando las variables esenciales correspondientes.

3. Excepciones de Patentabilidad

- 3.1. Respecto de la actividad o nivel inventivo de la presente solicitud en vista de los documentos D1: WO 00/42012, D2: WO 00/41698 y D3: WO 03/068228, se informa que pertenecen al mismo solicitante y no contienen materia que anticipe o sugiera el alcance de la presente solicitud, tal como se ha reconocido en el informe del Examen Internacional. Estos documentos se refieren a ω -carboxiaril difenil-ureas substituidas pero no revelan ni sugieren los compuestos de metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluoro-fenoxi}-piridin-2-carboxílico de Formula (I) de esta solicitud:

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Además, D1, D2 y D3 no mencionan ni sugieren las dispersiones sólidas ni la matriz de esta solicitud. No hay nada en los documentos citados que pueda inducir a un experto en la materia a obtener las composiciones de dispersión sólida de esta solicitud.

- 3.2. Debe notarse que esta solicitud define una particular matriz, que permite la solubilidad de un específico componente activo, otorgándole características novedosas y no deducibles a partir del arte previo.
- 3.3. Esta dispersión sólida es totalmente diferente de las mezclas físicas convencionales.
- 3.4. Existe una fuerte evidencia que las composiciones y su proceso de preparación no son anticipados ni pueden deducirse del arte previo. Dicho arte previo no anticipa ni sugiere: (i) que las presentes dispersiones sólidas se puedan formar, (ii) que puedan conducir a sistemas efectivos de suministro del compuesto activo, y (iii) que presenten ventajas respecto de composiciones conocidas, como en la presente invención.
- 3.5. Como puede observarse en la Figura 1 de esta solicitud, estas dispersiones sólidas muestran un aumento de la velocidad de disolución de la composición comparada con las mezclas físicas convencionales.
- 3.6. Además, en la Tabla 1 de esta solicitud se muestran las significativas mejoras en la biodisponibilidad en animales de las dispersiones sólidas de esta solicitud comparada con formulaciones de la base libre del compuesto de fórmula (I) (que difiere del compuesto definido en la actual reivindicación 1, pero que podría considerarse como el más cercano). Dichas mejoras también se discuten en las páginas siguientes a la Tabla 1 de esta solicitud.
- 3.7. Se señala, además, que los resultados no esperables resultan más claros en esta solicitud, ya que la velocidad se expresa correctamente en horas, salvando un aspecto dificultoso que existía en la solicitud internacional original.

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- 3.8. La formación de las dispersiones sólidas depende de la favorable compatibilidad entre este compuesto y esta matriz, sobre lo cual no hay revelación, sugerencia, pautas, modelos o teorías de utilidad en el arte previo. Aún más, no es posible predecir si una dispersión sólida puede ser un medio eficaz de suministro de un principio activo.
- 3.9. Por empezar, si la solubilidad del principio activo en la matriz fuese baja, el producto terminado (tableta, etc.) puede ser demasiado voluminoso para poder ser ingerido. Además, no es conocido ni predecible si la dispersión sólida puede presentar ventajas en su suministro en relación con la biodisponibilidad resultante. Por el contrario, en la Tabla 1 de esta solicitud se muestran resultados que son 2 a 3 veces superiores a los de formas convencionales de suministro, lo cual es evidentemente novedoso y no predecible.
- 3.10. En apoyo de lo antedicho, se acompañan copias de documentos que aportan información útil adicional para apreciar el complejo campo de estas composiciones de dispersión sólida.
- 3.10.1. El documento de Leuner et al. (2000) discute la solubilidad de una droga en dispersiones sólidas, indicando la ausencia de pautas o modelos que permiten predecir su factibilidad y eficacia. Este documento indica que es necesaria una actividad inventiva de investigación experimental para establecerlo. Por ejemplo, se enuncia que "aunque las dispersiones sólidas podrían tener un potencial para mejorar la solubilidad de drogas, en 40 años de investigación sólo se encontraron unos pocos casos de productos útiles."

Además, Leuner et al. señalan la importancia de establecer la solubilidad mutua al intentar formar una dispersión sólida (p. 49, líneas 9 a 13). En la página 58, líneas 1 a 3, indican otras condiciones cuantitativas que deben cumplirse.

Leuner et al. muestran que no puede predecirse la solubilidad y demás condiciones indispensables en estas composiciones.

Leuner et al. también informan que los métodos convencionales requieren condiciones que no satisfacen todos los compuestos farmacéuticos y matrices.

Por ejemplo, la fusión en caliente (p. 51, líneas 3 a 5 y 17 a 19) exige estabilidad térmica y la evaporación de solventes exige una suficiente solubilidad de todos los componentes en un mismo solvente (p. 51, líneas 25 a 27).

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Otra información de utilidad para reconocer la necesidad de actividad inventiva se encuentra en Leuner et al. en la p. 50, líneas 46 a 48, donde se demuestra la significación de los resultados de la Tabla 1 de esta solicitud.

- 3.10.2. Con similar información adicional se acompaña copia de un trabajo de Craig (Int. J. of Pharm., 321 (2002), p. 131 a 144). Por ejemplo, en la p. 132, Craig manifiesta que los productos de dispersión sólida han dado resultados desfavorables, a pesar de unos 500 trabajos publicados en la materia, debido a la pobre predictibilidad de las dispersiones sólidas.
- 3.10.3. Otra publicación de utilidad que se adjunta pertenece a Serajuddin (J. Pharm. Sciences, vol. 88, nº 10, Oct 1999, p. 1058-1066). Por ejemplo, en la p. 1059, Serajuddin manifiesta que la aplicación de dispersiones sólidas es muy limitada respecto de la especificación de formas de dosis adecuadas y cita sólo 2 productos de interés (diferentes de los de esta solicitud).
- 3.10.4. También se adjuntan las publicaciones de Stavchansky et al. (J. Pharm. Sciences, vol. 73, nº 6, p. 733-736) y de Wald et al. (Pharm. Res. 1995, 127, Supl. 6090) con similar información.
- 3.10.5. Estos documentos adjuntos facilitan el reconocimiento de que las actuales reivindicaciones 1 a 22, sustentadas por la Tabla 1 de esta solicitud, son novedosas y no obvias a partir del arte previo.
- 3.11. En conclusión, los documentos D1, D2 y D3 u otros del arte previo no afectan la novedad y/o el nivel inventivo de esta solicitud.

4. Fundamentos de Derecho

Fundamento la presente solicitud, en las siguientes normas legales:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 45 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. Las demás normas concordantes.

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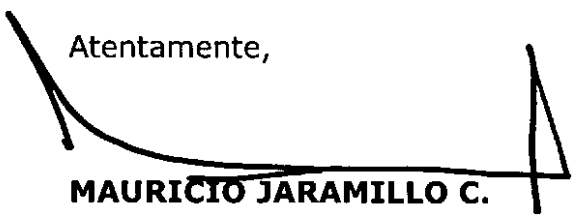
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5. Notificaciones

Informo que mi representada y el suscrito recibiremos notificaciones en la secretaría de su Despacho o en mi oficina de abogado, situada en la Calle 67 # 7-35, Of. 1204 de Bogotá D.C., teléfono 3192900.

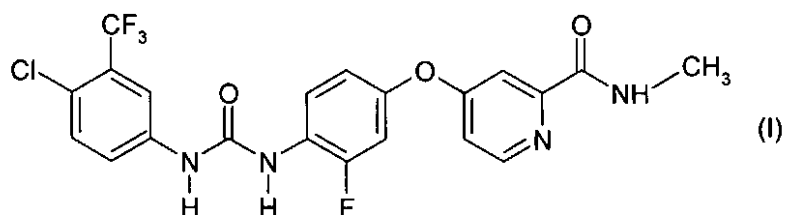
Atentamente,


MAURICIO JARAMILLO C.
C.C. No. 80'421,942 de Usaquén
T.P. No. 74,555 del C.S.J.
JBS

Adjunto: Lo anunciado.

REIVINDICACIONES

1. Una composición que comprende una dispersión sólida comprendiendo el compuesto metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluoro-fenoxi}-piridin-2-carboxílico de la fórmula I:



o una sal, hidrato o solvato del mismo y una matriz aceptable para uso farmacéutico que comprende un compuesto seleccionado del grupo que consiste en polivinilpirrolidona, hidroxialquilcelulosa, celulosa microcristalina, carboximetil celulosa sódica y polímeros reticulados de la misma, almidón y derivados de almidón.

2. La composición de acuerdo con la reivindicación 1, en la cual dicha hidroxialquilcelulosa es hidroxipropilcelulosa o hidroxipropilmetilcelulosa, el polímero reticulado de carboximetil celulosa sódica es croscarmelosa sódica y el derivado de almidón es almidón glicolado sódico.

3. La composición de acuerdo con la reivindicación 1, en la cual dicha matriz comprende un polímero seleccionado del grupo formado por polivinilpirrolidona, hidroxipropilcelulosa e hidroxipropilmetilcelulosa.

4. La composición de acuerdo con la reivindicación 1, en la cual polivinilpirrolidona es un agente de matriz.

5. La composición de acuerdo con la reivindicación 4, en la cual la relación ponderal del compuesto de la fórmula I calculado como base libre de solvente respecto de la polivinilpirrolidona está entre 1:0,5 y 1:20.

6. La composición de acuerdo con la reivindicación 1, en la cual hidroxipropilcelulosa es un agente de matriz.

7. La composición de acuerdo con la reivindicación 6, en la cual la relación ponderal del compuesto de la fórmula I calculado como la base libre de solvente respecto de hidroxipropilcelulosa está entre 1:0,5 y 1:20.

8. La composición de acuerdo con la reivindicación 1, la cual comprende adicionalmente croscarmelosa sódica, almidón glicolado sódico, hidroxipropilcelulosa poco sustituida, almidón, celulosa microcristalina o una combinación de los mismos.

9. La composición de acuerdo con la reivindicación 1, en la cual la dispersión sólida comprende polivinilpirrolidona y croscarmelosa sódica.

10. La composición de acuerdo con la reivindicación 1, en la cual la dispersión sólida comprende polivinilpirrolidona y almidón glicolado

sódico.

11. La composición de acuerdo con la reivindicación 1, en la cual la dispersión sólida comprende polivinilpirrolidona, croscarmelosa sódica y celulosa microcristalina.

12. La composición de acuerdo con la reivindicación 1, en la cual la dispersión sólida comprende hidroxipropilcelulosa y croscarmelosa sódica.

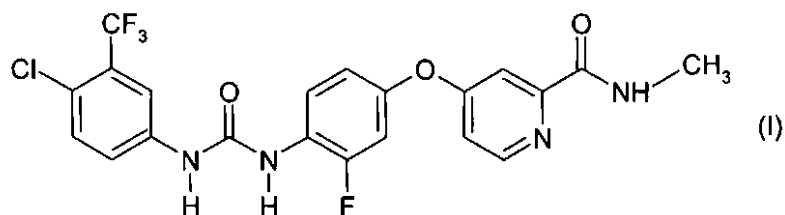
13. La composición de acuerdo con la reivindicación 1, en la cual la dispersión sólida comprende hidroxipropilcelulosa y azúcar, alcohol de azúcar o ciclodextrina seleccionada del grupo que consiste en sucrosa, lactosa, fructuosa, maltosa, rafinosa, sorbitol, lactilol, manitol, eritritol, treitol, adonitol, arabitol, xilitol, dulcitol, inositol, trehalosa, isomaltosa, inulina, maltodextrina, β -ciclodextrina, hidroxipropil- β -ciclodextrina, sulfobutil éter de ciclodextrina, o combinaciones de los mismos.

14. La composición de acuerdo con la reivindicación 1, en la cual la dispersión sólida es homogénea.

15. La composición de acuerdo con la reivindicación 1, que contiene el compuesto de la fórmula I en forma amorfa.

16. La composición de acuerdo con la reivindicación 1, que está en la forma de una tableta, cápsula, polvo, granulado o sachet.

17. Un proceso para la preparación de una composición de acuerdo con cualquiera de las reivindicaciones precedentes, que comprende someter simultáneamente el compuesto de la fórmula I:



y un agente de matriz a cualquiera de los pasos de:

extrusión del material fundido en caliente, donde ambos se extruden en un extrusor a una temperatura de 160 °C a 200 °C, o

técnicas de evaporación de solventes donde ambos se disuelven en un solvente seleccionado del grupo que consiste en metanol, etanol, n-propanol, isopropanol y acetona y mezclas de los mismos, hasta que todos estén en solución y se evapora el solvente bajo vacío hasta sequedad.

18. El proceso de acuerdo con la reivindicación 17, en el cual la dispersión sólida se prepara por extrusión de fusión en caliente.

19. El proceso de acuerdo con la reivindicación 17, en el cual la dispersión sólida se prepara por técnicas de evaporación de solventes.

20. El proceso de acuerdo con la reivindicación 17, en el cual el solvente es una mezcla de etanol y acetona.

21. El proceso reivindicado en las reivindicaciones 17 a 20, en el

cual la composición se trata además en un paso de procesamiento adicional, que comprende molienda, tamizado, compactación con rodillos, trituración, selección, mezclado, o una combinación de los mismos.

22. El proceso reivindicado en las reivindicaciones 17 a 21, que comprende el paso adicional de conformar la composición para darle forma a la mezcla como tabletas, cápsulas rellenas o sachets.

Review article

Improving drug solubility for oral delivery using solid dispersions

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Abstract

The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has dramatically increased. Although solid solutions have tremendous potential for improving drug solubility, 40 years of research have resulted in only a few marketed products using this approach. With the introduction of new manufacturing technologies such as hot melt extrusion, it should be possible to overcome problems in scale-up and for this reason solid solutions are enjoying a renaissance. This article begins with an overview of the historical background and definitions of the various systems including eutectic mixtures, solid dispersions and solid solutions. The remainder of the article is devoted to the production, the different carriers and the methods used for the characterization of solid dispersions. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Solid solution; Solid dispersion; Eutectic mixture; Amorphous state; Bioavailability; Solubility; Dissolution

1. Introduction

Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Consideration of the modified Noyes–Whitney equation [1,2] provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the

compound, C_s is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the luminal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution: the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media [3]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches.

Table 1 summarizes the various formulation and chemi-

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FORMA DE INFORMACION BASICA

Nombre del producto: Paquete Variado Gourmet #4

País de origen: USA

Nombre de la compañía: Daniele, Inc.

Nombre y Dirección del fabricante: 105 Davis Drive, Pascoag, R.I 02859

Número de teléfono: 401-568-6228

Número de fax: 401-568-4788

Correo electrónico: info@danieleinfo.com

Tipo de producto: Una combinación de un paquete de 3 carnes gourmet frías: picoso, seco-curado, salchicha seca de Puerco, salami seco curado de Puerco con pimienta, y picoso, seco-curado Puerco capollo.

Presentación: Las 3 carnes frías gourmet pre-rebanadas son empacadas al vacío en plástico transparente.

Número de unidades por paquete: 1

Contenido neto (Volumen y/o peso): 16 oz peso exacto

Table 1

Approaches to improve the solubility or to increase the available surface area for dissolution

I. Physical modifications

Particle size

- Micronization
- Nanosuspensions

Modifications of the crystal habit

Polymorphs

Pseudopolymorphs (including solvates)

Complexation/solubilization

- Use of surfactants
- Use of cyclodextrines

Drug dispersion in carriers

- Eutectic mixtures
- Solid dispersions (non-molecular)
- Solid solutions

II. Chemical modification

Soluble prodrugs

Salts

cal approaches that can be taken to improve the solubility or to increase the available surface area for dissolution.

Of the physical approaches, review articles have already been published on the use of polymorphs [4], the amorphous form of the drug [5] and complexation [6,7]. Decreasing the particle size of the compound by milling the drug powder theoretically results in an increase in the available area for dissolution, but in some cases the micronized powder tends to agglomerate, thereby at least partly negating the milling procedure. Presenting the compound as a molecular dispersion combines the benefits of a local increase in the solubility (within the solid solution) and maximizing the surface area of the compound that comes in contact with the dissolution medium as the carrier dissolves. This review is therefore devoted to a discussion of the use of molecular and near-molecular dispersions for the optimization of oral delivery of poorly soluble drugs.

2. Definitions

2.1. Simple eutectic mixtures

No review of solid dispersions would be complete without a brief description of eutectic mixtures, which are the cornerstone of this approach to improving bioavailability of poorly soluble compounds. A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state (Fig. 1). When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components.

When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug [9,10]. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

2.2. Solid solutions

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions [11] and the dissolution rate is determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude.

Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solventum (substitutional, interstitial or amorphous).

2.2.1. Continuous and discontinuous solid solutions

2.2.1.1. Continuous solid solutions In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2.2.1.2. Discontinuous solid solutions In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical

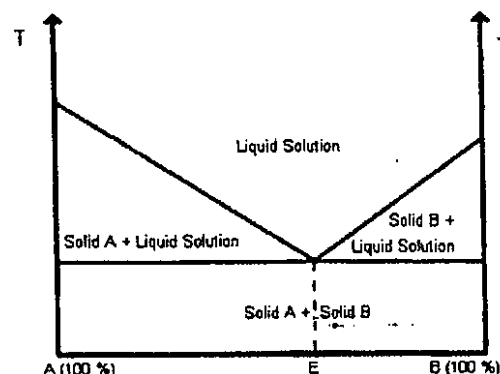


Fig. 1. Phase diagram for a eutectic system (reproduced with modifications from Ref. [8]).

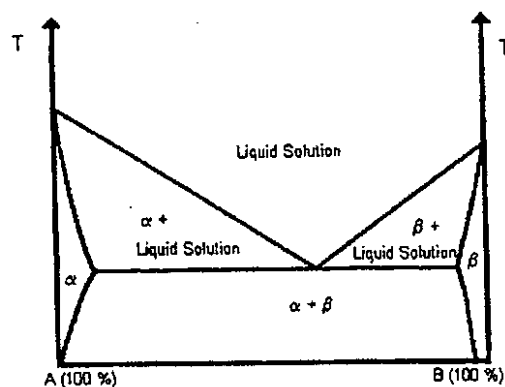


Fig. 2. Phase diagram for a discontinuous solid solution (reproduced with modifications from Ref. [8]).

phase diagram is shown in Fig. 2. α and β show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg et al. [11] that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

2.2.2. Substitutional crystalline, interstitial crystalline and amorphous solid solutions

2.2.2.1. Substitutional crystalline solid solutions Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig. 3. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [12].

2.2.2.2. Interstitial crystalline solid solutions In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Figs. 4 and 5). As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the

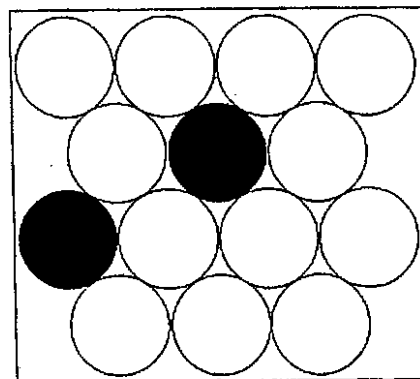


Fig. 3. Substitutional crystalline solid solution (reproduced with modifications from Ref. [13]).

solvent molecule's molecular diameter [14]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

2.2.2.3. Amorphous solid solutions In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig. 6). Using griseofulvin in citric acid, Chiou and Riegelman [16] were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

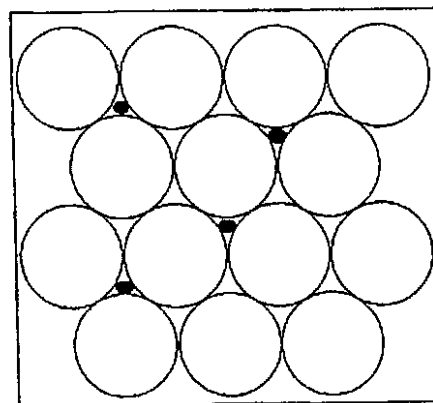


Fig. 4. Interstitial crystalline solid solution (reproduced with modifications from Ref. [13]).

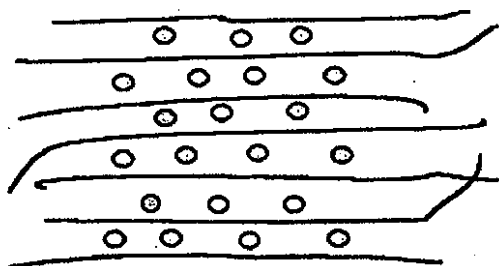


Fig. 5. Interstitial solid solutions of small molecules in the crystalline parts of a polymer (reproduced with modifications from Ref. [15]).

3. Formulation of solid solutions

In the early 1960s, Sekiguchi et al. reported that formulation of eutectic mixtures could lead to an improvement in the release rate and thereby the bioavailability of poorly soluble drugs. Eutectic combinations such as sulphathiazole/urea [9] and chloramphenicol/urea [17] served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier. Both preparations exhibited faster release and better bioavailability than conventional formulations. The explanation offered for this behaviour was that, after dissolution of the urea, a fine suspension of drug particles was exposed to the dissolution medium (or GI fluids) and that both the smaller particle size and better wettability of the drug particles in this suspension contributed to a faster dissolution rate.

The next development was the preparation of solid solutions by Levy [18] and Kanig [19]. In contrast to a eutectic mixture, the dispersed component in a solid solution is molecularly dispersed. In a very informative series of publications, Goldberg [10,11,20,21] discussed the theoretical and practical advantages of solid solutions over eutectic mixtures. The improvement in dissolution characteristics was at first attributed 100% to the reduction in particle size. Molecular dispersion represents the ultimate in particle size reduction [21], and after the carrier has dissolved, the

drug is molecularly dispersed in the dissolution medium, i.e. is present in solution form. A further reason for the improvement in the dissolution rate is that the drug has no crystal structure in the solid solution [22]. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolve is not a limitation to the release of the drug from a solid solution. After the solid solution has dissolved, the drug is present as a supersaturated solution. In some cases, the carrier may serve to inhibit precipitation of the drug from the supersaturated solution [23–25]. It has also been speculated that, if the drug does precipitate, it will precipitate out as a metastable polymorph with a high solubility compared to that of the most stable form [24,26]. A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug [13]. Even carriers that are not surface active, e.g. urea and citric acid, can improve wetting characteristics. Of course, if carriers with surface activity such as cholic acid, bile salts [27], cholesterol esters [28] and lecithin [29] are used, the improvements in wetting can be much greater. Another way in which the carrier can influence the drug's dissolution properties is via direct solubilization or a cosolvent effect.

The relationship between the release characteristics of the solid solution and a physical mixture of the two components varies with the drug/carrier combination. For example, the release rate from a solid solution of prednisolone in Cremophore® is almost identical with the release rate from a simple mixture of the two components [30]. A physical mixture of glyburide and PEG 6000 exhibited better solubility and faster dissolution than that of the pure drug [31]. The solubility of paracetamol is greater in urea than alone [10]. However, the solubility of sulfathiazole is adversely affected by mixing with urea [9]. In general, dissolution rates are compared among the pure drug, a physical mixture and the solid solution to assess the benefits of preparing a solid solution.

3.1. Methods for preparing solid solutions

3.1.1. Hot melt method

Sekiguchi and Obi [9] used a hot melt method to prepare simple eutectic mixtures. Sulphathiazole and urea were melted together at a temperature above the eutectic point and then cooled in an ice bath. The resultant solid eutectic was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. Whether or not a molecular dispersion can be achieved depends on the degree of supersaturation and rate of cooling attained in the process. In other words, the process has an effect on the resultant dispersion and can be varied to optimize the product. Sekiguchi et al. [17] and Chiou and Riegelman [16] accelerated the cooling rate by snap-cooling on stainless steel plates. Kanig [19] introduced the variation of spraying the hot melt onto a cold surface. A further

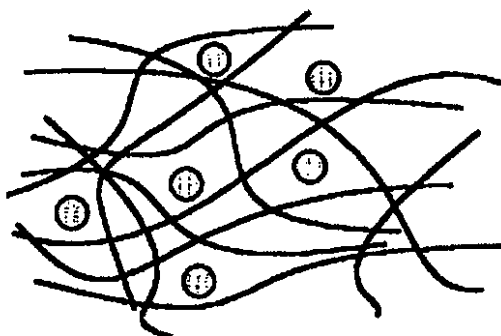


Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

approach is to prepare the solid dispersion by injection molding, as demonstrated by Wacker et al. [32].

An important prerequisite to the manufacture of solid solutions by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important limitation to the hot melt method is the thermostability of the drug and the carrier. If too high a temperature is required, the drug may decompose or evaporate. Of course, oxidative reactions can be avoided by processing in an inert atmosphere or under vacuum, while evaporation can be avoided by processing in a closed system.

Because of these limitations, the solvent method became more popular in the 1970s and 1980s. In recent years, however, the hot melt method has enjoyed a renaissance in the form of hot melt extrusion. Extrusion of moistened powders has been well known in the pharmaceutical sciences for many years [33]. Hot melt extrusion is a very common way of processing plastics in the polymer industry, but Speiser [34,35] and Hüttenrath [36] were the first to adapt the process for pharmaceutical purposes. In recent years, this method has been applied to the manufacture of solid solutions. A scheme of a hot melt extruder is shown in Fig. 7. The drug/carrier mix is typically processed with a twin-screw extruder of the same type used in the polymer industry. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed.

A further alternative for processing thermolabile substances is by hot-spin-melting. Here, the drug and carrier are melted together over an extremely short time in a high speed mixer and, in the same apparatus, dispersed in air or an inert gas in a cooling tower. Some drugs that have been processed into solid dispersions using hot-spin-melting to

date include testosterone [38], progesterone [39] and dienogest [40].

3.1.2. Solvent method

Until the advent of the solvent method, solid solutions were prepared exclusively by the melting method. Tachibani and Nakumara [41] were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β -carotene in the highly water soluble carrier polyvinylpyrrolidone (PVP). The evaporation method was then taken up by Mayersohn and Gibaldi [42]. By dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent, they were able to achieve a solid dispersion. The release rate of griseofulvin from the solid dispersion was five to 11 times higher than that of micronized drug, depending on the drug/carrier ratio. Bates [43] introduced the term coprecipitates to describe solid dispersions that are manufactured by the solvent evaporation method. Although the term coprecipitate is strictly speaking inaccurate in this case, it is still widely used in this sense today. Simonelli et al. [44] used the term coprecipitate more correctly to describe a solid dispersion of sulphathiazole and PVP that had been precipitated from a solution in sodium chloride by the addition of hydrochloric acid. Solid dispersions and solutions that are manufactured by the solvent evaporation method should really be called coevaporates and not coprecipitates.

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. Temperatures used for solvent evaporation usually lie in the range 23–65°C [45,46]. The solvent can also be removed by freeze-drying [31] or by spray-drying [47]. It must be remembered that when an organic solvent is to be removed, small variations in the conditions used can lead to quite large changes in product performance. Another point to consider is the importance of thoroughly removing all of the solvent, since most of the organic solvents used have toxicity issues.

With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermolabile substances. Likewise, many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities. As a result, for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions.

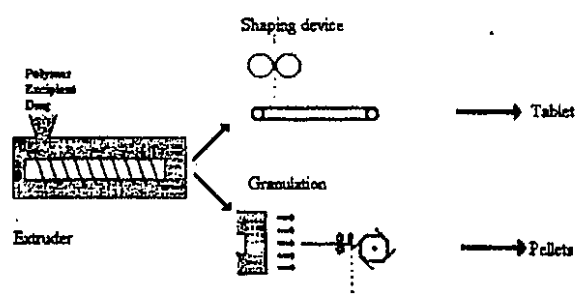


Fig. 7. Scheme of a hot melt extruder (reproduced with modifications from Ref. [37]).

3.2. Carriers

3.2.1. Polyethylene glycol (PEG)

3.2.1.1. General characteristics of PEGs Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200–300 000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500–20 000 are usually employed. As the MW increases, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800–1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20 000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g. the m.p. of PEG 1000 is 30–40°C, the m.p. of PEG 4000 is 50–58°C and the m.p. of PEG 20 000 is 60–63°C) [48]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds [31] and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000 [49].

3.2.1.2. Influence of the PEG chain length PEGs of MW 4000–6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50°C. If a PEG with too low a MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [50]. PEGs with higher MW have also been used with success: products containing PEG 8000 [51] and 10 000 [52] showed enhanced dissolution rates compared to the pure drug.

The importance of the carrier to performance of the solid dispersion was illustrated in a study of 14 different drugs formulated as solid dispersions in PEG 6000 [53]. In this study, Dubois and Ford showed that, when the drug is present in a low drug/carrier ratio (<2% in the case of phenylbutazone, up to 15% in the case of paracetamol), the release rate is dependent only on the carrier and not on the drug properties. Results with indomethacin showed similar behaviour. Further studies indicated that the release rate is inversely proportional to the chain length of the PEG [54]. Similar results were obtained with etoposide [50] and griseofulvin [16]. However, other studies revealed contradictory behaviour. For example, glyburide release from a solid dispersion in PEG 6000 was faster than from a similar dispersion in PEG 4000 [31]. Possible

reasons for the better release from PEG 6000 are that the PEG 6000 was able to dissolve more of the drug than the PEG 4000, leading to a greater percentage drug in the molecularly dispersed form, and that the higher viscosity of the PEG 6000 hindered precipitation of the drug following dissolution of the carrier.

A comprehensive study of phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW [54]. When the percentage of drug used was low (0.5–2%), the release followed the rank order PEG 1500 > 4000 > 6000 > 20 000, at percentages of 3 and 4% the rank order was PEG 1500 > 4000 > 20 000 > 6000 and at a 5% loading the order was 20 000 > 4000 > 1500 > 6000. Since the rank order could be clearly correlated with the crystallinity of the solid dispersion, the authors concluded that the release is dependent on the extent to which a molecular dispersion can be formed. On the other hand, contradictory results were obtained with chloramphenicol/PEG solid dispersions, for which the rank order of release was PEG 6000 > 4000 > 12 000 > 20 000 [55]. In yet other cases, the MW of the PEG had no influence at all on the release rate. For example, Mura et al. [56] showed that 10% dispersions of naproxen in PEG 4000, 6000 and 20 000 all exhibited similar release.

3.2.1.3. Influence of the drug/PEG ratio The drug/carrier ratio in a solid dispersion is one of the main influences on the performance of a solid dispersion. If the percentage of the drug is too high, it will form small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug. Lin and Cham [57] showed that solid dispersions of naproxen in PEG 6000 released drug faster when a 5 or 10% naproxen loading was used than when a 20, 30 or 50% loading was used. These results could be explained on the basis of X-ray diffraction results, which indicated that dispersions with low loading levels of naproxen were amorphous whereas those with high loadings were partly crystalline. However, the upper limit to the percentage carrier that can be employed is governed by the ability to subsequently formulate the solid dispersion into a dosage form of administrable size.

3.2.1.4. Drug/PEG systems Griseofulvin is probably the most studied drug with respect to dispersion in PEGs. Chiou and Riegelman [16] were able to achieve a noticeable increase in the release rate of griseofulvin from solid dispersions in PEG 4000, 6000 and 20 000. The fruit of research with PEG/griseofulvin combinations is the marketed product, Gris-PEG®. More recent studies with griseofulvin and PEGs have focussed on mixtures with various emulsifying agents. Sjökvist et al. [58] introduced small quantities of polysorbate 80, polyethylenedodecylether (Brij® 35), sodium dodecylsulphate (SLS) and dodecylammonium bromide into 10% w/w dispersions

of griseofulvin in PEG 3000 and by doing so were able to achieve substantial increases in both the rate and extent of dissolution. Best results were obtained with SLS. Other combination systems, such as a griseofulvin/PEG 6000/talc system [47] could only achieve similar results to that of the two-component dispersion. However, the talc system had the advantages of being easier to process and being less tacky.

An increase in the release rate by formulation as a solid dispersion in PEG 4000 has been observed for many drugs, including oxazepam [59], piroxicam [60], zolpidem [61] and glyburide [31]. In some cases, in vivo data have verified the importance of the increase in release rate to the bioavailability of the drug in question. Arias et al. [62] were able to show that a doubling of the release rate in vitro could be translated into an increase in the diuretic effect of triamterene in rats. A good correlation between release data from solid dispersions of nifedipine in PEG 6000 and the elimination of the drug in urine was documented in human studies [63]. Similarly, a two-fold increase in the release rate of carbamazepine achieved by formulation as a solid dispersion in PEG 4000 and 6000 was translated into an increase in the bioavailability relative to a suspension of the drug and the marketed product, Tegretol® [46]. However, even better results could be achieved with a hydroxypropyl- β -cyclodextrin complex. Norfloxacin/PEG 6000 solid dispersions also produce a moderate increase in bioavailability [64]. Further drugs which exhibit elevated release rates when formulated as PEG solid dispersions include Sr33557, a new calcium antagonist [65], ketoprofen [66], oxazepam [67], nifedipine [68], phenytoin [69], ursodeoxycholic acid [70], fenofibrate [71] and prednisolone [30].

There have also been several studies with PEGs of higher MW. Perng et al. [51] achieved a ten-fold increase in the release rate of an experimental 5-lipoxygenase inhibitor with PEG 8000 using a hot melt method. Studies of coevaporates of ibuprofen with PEG 10 000, with the talc system and with mixtures of the two indicated that the mixture of the PEG with talc produced the best results [52].

3.2.1.5. Problems with PEGs In general, there are few toxicity concerns associated with the PEGs and they are approved for many purposes as excipients. The low molecular weight PEGs do, however, tend to show slightly greater toxicity than those of higher molecular weight [48]. In addition, a great number of drugs are compatible with the PEGs. A few cases have been observed in which the PEG proved to have stability problems during manufacture by the hot melt method. A reduction in the PEG chain length was observed for combinations with disulfiram, furosemide, chlorothiazide and chlorpropamide [53]. Another difficulty can lie in the subsequent formulation of the solid dispersion into an acceptable dosage form. If the dispersion is too soft it can be difficult if not impossible to manufacture a tablet dosage form. This is most likely to occur if a PEG with too low a

MW is used or if the drug has a plasticizing effect on the PEG [50].

3.2.2. Polyvinylpyrrolidone (PVP)

3.2.2.1. General characteristics of PVP Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3 000 000. These can be classified according to the *K* value, which is calculated using Fikentscher's equation [72]. Table 2 provides an overview of the relationship between the *K* value and the approximate molecular weight of PVP.

The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (T_g) is high; for example, PVP K25 has a T_g of 155°C [73]. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid [74].

3.2.2.2. Influence of the PVP chain length The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration [72]. Studies with coevaporates of chloramphenicol and PVP revealed that the dissolution of chloramphenicol was slower when PVPs of higher MW were used as the carrier [55]. Similarly, the slower dissolution of indomethacin from PVP K90 compared to PVP K12 was attributed to the higher viscosity generated by PVP K90 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion [24]. Other drugs for which release is known to be slower when incorporated in PVPs of higher MW include sulphathiazole [44] and phenytoin [69]. In the case of probucol, however, a somewhat different relationship was seen: here the rank order of release rate was PVP K30 > K25 > K90 [75]. In

Table 2
K values of PVP and the corresponding molecular weights [72]

<i>K</i> value	Approximate molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

general, though, the dependency of the release rate on MW is clearer for the PVPs than in the case of solid dispersions prepared with PEGs.

3.2.2.3. Drug/PVP ratio Similarly to PEG, solid dispersions prepared with high proportions of PVP tend to exhibit a higher drug solubility and release rate than those with high proportions of drug. For albendazole, for example, it has been shown that an increase in the %PVP in the dispersion leads to an increase in the release rate [76]. Doherty and York [77] studied the release behaviour of furosemide/PVP dispersions as a function of the degree of crystallinity of the preparation. When solid dispersions comprising 50% furosemide were prepared, crystalline regions could be detected by X-ray diffraction. In contrast, when the drug/carrier ratio was 2:3, the dispersion was amorphous. Dispersions containing crystalline areas exhibited biphasic release profiles, with the amorphous areas dissolving quickly and the crystalline areas more slowly. Similar behaviour was reported by Keamey et al. [45] for the experimental anti-inflammatory compound CI-987. When the carrier comprised 81% of the dispersion, no crystalline areas could be detected and the release rate of the compound was rapid. Interestingly, when the %carrier was further increased, the release rate became slower. In the case of piroxicam/PVP solid dispersions [78], the release rate increased with the %PVP up till a ratio of drug/carrier of 1:4, after which it fell again (at ratios of 1:5 and 1:6). These results were clarified with X-ray diffraction studies. Only the dispersion containing a 1:4 ratio was amorphous; at all other ratios semi-crystalline areas could be detected. In this case, the 1:4 ratio proved to be optimal for the formulation of piroxicam in PVP K30.

3.2.2.4. Drug/PVP systems Most studies of PVP solid dispersions reported in the literature have used PVPs of MW 2500–50 000 (K12 to K30). As in the case of PEGs, griseofulvin has been one of the most widely studied compounds. The first solid dispersions of griseofulvin in PVP were reported in 1966 by Mayersohn and Gibaldi [42]. Improved dissolution of the test compound from solid dispersions prepared with PVP K17 have been reported variously for sulphathiazole [44], hydrochlorothiazide [79], and piroxicam [80]. For a series of non-steroidal anti-inflammatory drugs (NSAIDs) including mefenamic acid, azapropazone, glafenin and flufenin, it was shown that coevaporates prepared with PVP K25 improved the release and bioavailability of the drug more than those prepared with PEG 6000 [81]. Furthermore, it was shown in the same studies that the NSAIDs were less likely to cause ulceration in the GI tract when administered as a solid dispersion. In another study, the release rates from solid dispersions of etoposide in PEGs and PVPs were compared [50]. PVP K25 produced faster release than PEG 3400, 6000 or 8000. On the other hand, the release rate from PEG 3400 and 6000 was higher than from PVP K17. Using PVP K30 as the carrier, the release

rate of the 5-lipoxygenase inhibitor SB 210661 [51], a weakly basic experimental compound, RS 8359 [82] and benidipine HCl [83] could all be improved. In the case of atenolol, the improvement in release rate using PVP K30 proved to be better than the release rate from other carriers tested [84].

3.2.2.5. Toxicity profile of PVP Polyvinylpyrrolidones found their first pharmaceutical application as plasma expanders in the 1940s. This role became less important with the advent of dextrans. However, PVPs are still widely used in the pharmaceutical sector as excipients. When given orally, they are regarded as not being toxic, partly because they have too high a MW to be absorbed from the GI tract. Reports of side effects are restricted to the formation of granulomas after intramuscular injection [72].

3.2.3. Polyvinylalcohol (PVA), crospovidone (PVP-CL), polyvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA)

All three polymers belong to the polyvinyl group. Whereas polyvinylalcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. When solid dispersions of nifedipine were prepared with carrier mixtures consisting of nicotinamide and PVP, hydroxypropylmethylcellulose (HPMC) or PVA in a drug/nicotinamide/polymer ratio of 1:3:1, those prepared with PVA dissolved 20 times as fast as the drug alone [85]. However, the other carriers, HPMC and PVP, yielded even better results. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in beagles by a factor of 3.5 [86]. Moneghini et al. [84] reported that in the case of atenolol, too high a PVA/PVP content could lead to a decrease in the release rate of the drug. This observation was attributed to high viscosity in the diffusion boundary layer adjacent to the dissolving surface. Similar results were subsequently reported for PVA/PVP coevaporates of carbamazepine [87]. In this case the optimal drug/carrier ratio was 1:4; when the proportion of carrier was either lower or higher, the increase in the release rate was not as dramatic. The fall-off at higher carrier ratios could be attributed to gel formation in this case. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.8 [88] in comparison with either the drug powder or a physical mixture of furosemide with crospovidone. The mechanism of the increase in the release rate of furosemide proved to be the presentation of the drug in the amorphous form in the dispersion, as shown by X-ray diffraction studies.

3.2.4. Cellulose derivatives

3.2.4.1. General characteristics of cellulose derivatives

Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β -1,4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl- (HPC), hydroxypropylmethyl- (HPMC) and many other semi-synthetic celluloses. Since each glucose unit has three hydroxyl groups that can be derivatized, the average substitution grade (SG) cannot exceed three, unless of course the hydroxyl groups on the substituents themselves (e.g. in the case of HPMC) are also derivatized. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP).

3.2.4.2. Hydroxypropylmethylcellulose (HPMC) HPMCs are mixed ethers of cellulose, in which 16.5–30% of the hydroxyl groups are methylated and 4–32% are derivatized with hydroxypropyl groups. For example, Type 2910 has an average methoxy content of 29% and an hydroxypropyl content of 10%. The molecular weight of the HPMCs ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane [89].

Studies with albendazole, a poorly soluble weak base with incomplete bioavailability, showed that the release rate and the bioavailability in beagles could be improved through preparation of a solid dispersion in HPMC [90]. It was further demonstrated that HPMC was able to inhibit the recrystallization of the albendazole, and that a further improvement in release characteristics could be achieved when a carrier mixture consisting of HPMC and HPMCP was employed. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nifedipine [91] and benidipine [83]. In combination with nicotinamide as the carrier system, HPMCs produced the best increase in the release of nifedipine of the series PVP, PVA and HPMC [85].

3.2.4.3. Hydroxypropylcellulose (HPC) Hydroxypropylmethylcellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 40°C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H) [92]. Yuasa et al. [93] carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

3.2.4.4. Carboxymethylcellulose (CMEC) CMEC also belongs to the cellulose ethers, but unlike many of the others

it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5–6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8 [94]. Likewise, the bioavailability of the test substance MFB-1041 could be substantially improved in beagles [95].

3.2.4.5. Hydroxypropylmethylcellulose phthalate (HPMCP)

HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). Their solubility in organic solvents is also type-dependent. Their MWs range from 20 000 to 2 000 000 [96]. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a coevaporate of HPMCP [94]. In this case it was shown that griseofulvin was present in the dispersion in the amorphous form. Using a spray-drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug [95]. Furthermore, the oral bioavailability in beagles was almost 17 times better following administration of the drug in solid dispersion form. In studies of coevaporates of the poorly water soluble cytostatic drug HO-221, it was shown that, while at pH 1.2 the dispersion in HPMCP did not release the drug, at pH 6.5 it released the drug as well as dispersions in the pH-independent polymers PVP and PVP/PVA [86]. In this set of studies, the bioavailability of the various dispersions of HO-221 was assessed in beagles. The coevaporate in PVP/PVA led to an increase in bioavailability of 30–60%, whereas the coevaporate in HPMCP led to almost complete absorption of the drug. Since the intraduodenal application of the PVP/PVA coevaporate also led to virtually complete absorption, it was concluded that the incomplete absorption from PVP/PVA coevaporate after oral administration was due to precipitation of the drug following rapid dissolution and formation of a supersaturated solution in the gastric juice. These studies demonstrated the potential advantage of using a gastric juice resistant polymer as carriers for poorly soluble drugs.

3.2.5. Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mostly used as coatings to modify the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit® [97]. Among the Eudragits,

Eudragit® E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pHs, while Eudragit® L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as a coevaporate with Eudragit® E, the rate of dissolution was much higher than from the pure drug powder [83]. On the other hand, Eudragit® L has been successfully used to increase the dissolution of griseofulvin and spirinolactone at a pH value of 6.8 [94].

3.2.6. Urea

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 1 and it also exhibits good solubility in many common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea [9]. Similarly, Goldberg et al. [21] reported faster dissolution rates of chloramphenicol when prepared with urea as the carrier. Although urea is not often used as a carrier these days, it has been recently shown that the dissolution rate of the poorly soluble compound ofloxacin can be improved by more than three-fold by incorporating it in a coevaporate with urea [98]. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 [70]. A two-fold increase in the dissolution rate of phenytoin has also been achieved with urea; however, in this case PEG 6000 was far more efficient [69].

3.2.7. Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare coevaporates. Despite these drawbacks, several attempts to prepare solid dispersions using sugars and their derivatives have been reported. Mannitol, which has a melting point of 165–168°C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method. Improved release characteristics have been reported for sorbitol dispersions of several compounds, including nitrofurantoin [63], prednisolone [30], ofloxacin [98] and ursodeoxycholic acid [70]. In most of these cases, other carriers produced better results. Interestingly, nitrofurantoin showed better release from sorbitol than mannitol dispersions (the two sugars are isomers) [63]. Indeed, a dispersion of prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol [30]. Chitosan, a derivative of the polysaccharide chitin which is formed by deacetylation at the N position, has also been used as a carrier in solid dispersions. Both chit-

osan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder [99]. In these studies, the performance of the coevaporates was compared to that of physical dispersions prepared by co-grinding. The coevaporates produced faster release rates than co-ground mixtures.

3.2.8. Emulsifiers

The release behaviour of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are usually used in combination with another carrier. For example, the release of naproxen from solid dispersions in PEG 4000, 6000 and 20 000 could be further enhanced when either sodium lauryl sulphate (SLS) or Tween® 80 (a polyethylene sorbitan fatty acid ester) was added to the system [56]. Inclusion of alkali dodecylsulphate surfactants in carrier systems can lead to conversion of a solid dispersion to a solid solution. Melts of griseofulvin and PEG 6000 normally contain crystalline areas; in the presence of SLS a solid solution is formed [100].

Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [27] demonstrated the ability of bile salts such as cholic acid, deoxycholic acid and lithocholic acid to improve not only the release but also the sedative effects of reserpine when given as a coevaporate. Likewise, the release of hydrocortisone can be enhanced by formulation as a solid dispersion in cholesterol and various cholesterol esters [28]. In recent times, however, there has been little activity in this area.

3.2.9. Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin [16,20]. In more recent years, no further studies with these two acids have been published. Melts of nifedipine with nicotinamide, the amide of nicotinic acid, exhibited about a six-fold increase in the dissolution rate compared to the drug powder but even better results were obtained with PEG 6000 as the carrier [68]. By combining the nicotinamide with a polymeric carrier such as HPMC or PVP, the release of nifedipine could be further greatly improved [85]. The best results, a 20-fold increase, were obtained with a dispersion of nifedipine, nicotinamide and HPMC in a ratio of 1:3:1.

3.2.10. Other carriers

Many other substances have been tested as carriers for solid dispersions. A hydrolysis product of collagen, Gelita®

Collagel, was reported to improve the release rate of oxazepam by a factor of six when prepared as a solid dispersion by spray drying [67]. Even after tableting, the solid dispersion displayed better release characteristics than the physical mixture or the drug powder alone [101]. Other materials tested include pentaerythritol [16] and phospholipids [46].

3.3. Characterization of solid dispersions

The methods that have been used to characterize solid dispersions are summarized in Table 3. Among these, the most important methods are thermoanalytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the solid dispersion, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. Due to the complex composition of these preparations, it is often difficult to delineate precisely between molecularly dispersed and not molecularly dispersed systems and different analytical methods may yield disparate results. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions.

Thermoanalytical methods include all that examine a characteristic of the system as a function of temperature. Of these, differential scanning calorimetry (DSC) is the most highly regarded method. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for

systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of under 2% cannot generally be detected with DSC [15].

The principle behind X-ray diffraction is that when an X-ray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5–10% cannot generally be detected with X-ray diffraction.

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not [22].

Release rate experiments cannot be used on a stand-alone basis to determine whether a solid solution has been formed or not. However, in conjunction with other physicochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve the dissolution characteristics of the drug in question, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. A well-designed release experiment will show whether the solubility of the drug and its dissolution rate has been enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixtures of the drug and carrier can help to indicate the mechanism by which the carrier improves dissolution: via solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a solid dispersion/solution.

Table 3
Methods for the characterization of solid dispersions

Dissolution testing
Thermoanalytical methods: differential thermoanalysis and hot stage microscopy
Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change
X-Ray diffraction
Spectroscopic methods, e.g. IR spectroscopy
Microscopic methods including polarization microscopy and scanning electron microscopy

4. Summary and future perspectives

Experience with solid dispersions over the last 20–30 years indicates that this is a very fruitful approach to improving the release rate and oral bioavailability of poorly soluble drugs. The most frequent concerns with solid dispersions have been the ability to scale-up the manufacturing method, the physical stability of the dispersion, and the amount of carrier needed to facilitate the required increase in the release rate. When a high carrier/drug ratio must be

used, the amount of dispersion required to administer the usual dose of the drug may be too high to produce a tablet or capsule that can be easily swallowed. The higher the unit dose of the drug, the more likely this problem is to occur. Another aspect that must be considered is the correlation between in vitro and in vivo results. Dispersions with a rapid in vitro release rate may fail to improve the oral bioavailability if the in vitro test conditions do not adequately simulate the gastrointestinal conditions, or if there is some specific interaction between the carrier and a component of the GI fluids or a co-ingested foodstuff. Despite these concerns, several products containing solid dispersions are already on the market and the number is expected to increase dramatically in the next years.

Two trends strongly favour an increasing role for solid dispersions in pharmaceutical development: the increasing number of drug candidates which are poorly soluble, and the substantial improvements in the manufacturing methods for solid dispersions that have been made in the last few years. The application of hot melt extrusion to the production of solid dispersions is a particularly important breakthrough for scale-up of solid dispersion manufacture. Another advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation. Yet another advantage of solid dispersions over other approaches is that the increases in solubility and release rate that can be achieved are often much, much greater (up to orders of magnitude). This could potentially lead to an increase in bioavailability that is so great that the dose administered could be lowered.

Aspects that still need to be addressed in the next years include further improvements in manufacturing on a large scale, and better predictions of whether a particular drug/carrier combination will lead to a true solid solution or to a partly crystalline dispersion as well as whether the dispersion will remain physically stable during further processing and storage. Last but not least, although this article has been devoted to the use of solid dispersions for the improvement of the release rate and oral bioavailability, by judicious choice of the carrier it is also possible to delay or slow down the release pattern of a drug by formulating it as a solid dispersion. The availability of a wide variety of polymers that are themselves poorly soluble or which swell under aqueous conditions suggests that solid dispersions have tremendous potential in the area of controlled release dosage forms.

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Review

The mechanisms of drug release from solid dispersions in water-soluble polymers

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Abstract

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability, of a range of hydrophobic drugs. However, despite the publication of numerous original papers and reviews on the subject, the mechanisms underpinning the observed improvements in dissolution rate are not yet understood. In this review the current consensus with regard to the solid-state structure and dissolution properties of solid dispersions is critically assessed. In particular the theories of carrier- and drug-controlled dissolution are highlighted. A model is proposed whereby the release behaviour from the dispersions may be understood in terms of the dissolution or otherwise of the drug into the concentrated aqueous polymer layer adjacent to the solid surface, including a derivation of an expression to describe the release of intact particles from the dispersions. The implications of a deeper understanding of the dissolution mechanisms are discussed, with particular emphasis on optimising the choice of carrier and manufacturing method and the prediction of stability problems. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Dissolution; Eutectic; Particle size; Polyethylene glycol; Solid dispersion; Stability

1. Introduction

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. More specifically, Chiou and Riegelman (1971), in their classic review, defined these sys-

tems as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method', while Corrigan (1985) suggested the definition as being a 'product formed by converting a fluid drug-carrier combination to the solid state'. In practice, these dosage forms have been traditionally regarded as being synonymous with systems whereby the *in vitro* release of the drug is enhanced compared to conventional dosage forms, with concomitant implications for

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in vivo release. Furthermore, the carrier used has, again traditionally, been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars. However, the proliferation of publications in the area since the first solid dispersions were described (Sekiguchi and Obi, 1961) has led to a broadening of these definitions to include water insoluble matrices such as Gelucires and Eudragits that may yield either slow or rapid release and absorption. Numerous reviews have appeared in the literature (Chiou and Riegelman, 1971; Ford, 1986; Craig, 1990; Serajuddin, 1999), attempting to bring together the various publications and ideas associated with these dosage forms. The latest of these (Serajuddin, 1999) gives details of some more recent approaches such as the use of surface active carriers and the use of melt-extrusion of PVP dispersions as a means of manufacturing viable dosage forms using this technology.

One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Indeed, the sheer simplicity of the manufacturing method, the fact that in general only the drug and carrier are required and the frequently reported improvements in both the dissolution rate and bioavailability would lead one to expect that the transfer to the market place would be rapid and widespread. This has not been the case, despite approximately 500 papers having been published on the subject. While this is to a large extent associated with manufacturing and stability considerations, it is also arguable that a primary reason is poor predictability of solid dispersion behaviour due to the lack of a basic understanding of their properties. In particular we believe there are four key problem areas in this respect:

1. *The solid state structure.* It is still not clear how the drug is dispersed within the matrix in the majority of cases. Methods such as DSC, XRD and hot stage microscopy have been widely employed but the question as to whether the drug is present as a molecular, a crystalline particulate or an amorphous particulate dispersion is far from clear in the major-

ity of cases. Fortunately, this issue has been studied in more detail in recent years, with techniques such FTIR, Raman spectroscopy and solid state NMR being employed in addition to the aforementioned methods, particularly to study the nature of the molecular interactions between the drug and the carrier in amorphous systems (e.g. Matsumoto and Zografi, 1999; Forster et al., 2001).

2. *The mechanism by which dissolution enhancement occurs.* While a number of theories have been proposed (outlined below) the mechanism by which the dissolution rate is improved in relation to conventional dosage forms is again not fully understood.
3. *The stability of the dispersions on storage.* Numerous studies have observed changes to the dissolution rate on storage. However, again the mechanism responsible is not yet clear. This is arguably a direct result of the poor understanding of the dissolution rate mechanism or mechanisms; it is by definition difficult to understand why a dissolution profile changes with time if the factors determining the initial dissolution behaviour are not known. Clearly, such instability, though not universal, renders the dispersions unsuitable as products when it does occur.
4. *Poor understanding of the in vitro/in vivo correlation.* While numerous studies have reported enhanced dissolution rates and absorption rates from solid dispersions the correlation between the two is not straightforward. It should also be born in mind that the literature tends to be success led, hence examples of poor absorption improvement are less likely to be brought to the scientific community's attention.

The above difficulties are all functions of the fundamental understanding of the behaviour of the systems, with the first three being related to the physical behaviour of the dispersions. Consequently, while developments in manufacturing methods and the use of alternative carriers are undoubtedly welcome there remains a need to consider what has been learned over the past forty years in terms of the mechanisms by which dissolution enhancement occurs. The function of the

current discussion is therefore not to review the field of solid dispersions as a whole but instead to examine the current state of knowledge with regard to the dissolution mechanisms.

2. Proposed structures of solid dispersions

Before discussing the dissolution properties of the dispersions, it is clearly essential to have some consideration of the solid-state properties of these systems. The dispersions have traditionally been formed by heating mixes of the drug and carrier to the molten state (although whether this molten mix is a suspension or solution is usually not defined) followed by resolidification via cooling. Alternative methods involve dissolving the components in a mutual volatile solvent followed by evaporation or dissolving the drug in a solvent such as propylene glycol and adding that to the molten carrier. Other approaches include melt-extrusion methods (Sprokel et al., 1997; Zhang and McGinity, 2000; Forster et al., 2001) that appear to offer a number of interesting opportunities.

Irrespective of the methodology used, the question as to the physical nature of the dispersion remains unanswered in many cases. Classically, Chiou and Riegelman (1971) defined a number of possibilities. These include eutectic systems, whereby on cooling the molten mix the system forms a microfine dispersion of the two components with a concomitant decrease in melting point. This has been a favoured explanation for several systems, particularly in the light of DSC studies that have frequently been reported to show a eutectic melting point and a lowering of the melting points of the principle components. However, some caution is required in this interpretation for a number of reasons. In the first instance, it is essential to bear in mind that unless one is exactly at the eutectic composition, the system will contain a mixture of the microfine

dispersion and one or other component as a separate phase, as indicated in Fig. 1a. Indeed, as one cools from the melt of any composition other than that corresponding to the eutectic, one component will progressively solidify, thereby rendering the remaining liquor richer in the other component until the eutectic composition is reached, at which point the remaining liquid will solidify as a fine dispersion. Consequently, if the reported systems are indeed eutectics it is necessary to appreciate the complex nature of the mixes used in practice. The second issue is that the polyethylene glycols used for the majority of solid dispersion studies (molecular weight 4000–20,000) may exist in more than one crystal form, exhibiting multiple melting points in the region of 55–65 °C (Beech et al., 1972; Buckley and Kovacs, 1976). It has been suggested that many of the dual melting points described in the literature ascribed to eutectic behaviour may in fact be chain folded forms of the PEG itself (Craig, 1990). Thirdly, it is arguably essential to compare the melting behaviour of the solid dispersion to that of a physical mix of the drug and carrier, as many studies have indicated that the phase diagrams of the two systems may be extremely similar (Sekiguchi et al., 1963; Chiou and Niazi, 1971, 1973). Indeed, the presence of the carrier in the molten state may itself lower the melting point of the drug. Consequently, the detection of melting point lowering and, in the case of PEGs, the appearance of a lower temperature melting peak, does not necessarily indicate the presence of a eutectic. While some systems must inevitably form eutectics, the number of studies that have demonstrated unequivocally that a eutectic is present is in fact very limited.

The second common explanation is that of a solid solution, whereby the drug is present as a molecular dispersion within the carrier. This is a fully feasible explanation but again caution is required in terms of the detection of such systems.

Fig. 1. (a) Schematic eutectic phase diagram, showing effect of cooling at the eutectic point (A to B) whereby only the eutectic solidifies. This is compared to cooling at an alternative composition (C to D) whereby component X solidifies during cooling, leaving the remaining liquor richer in Y until the eutectic temperature/composition is reached. (b) Schematic solid solution phase diagram (partial miscibility), showing regions of solid solubility at the extremes of composition. (c) Schematic monotectic phase diagram, showing convergence of the liquidus with the melting point of one component.

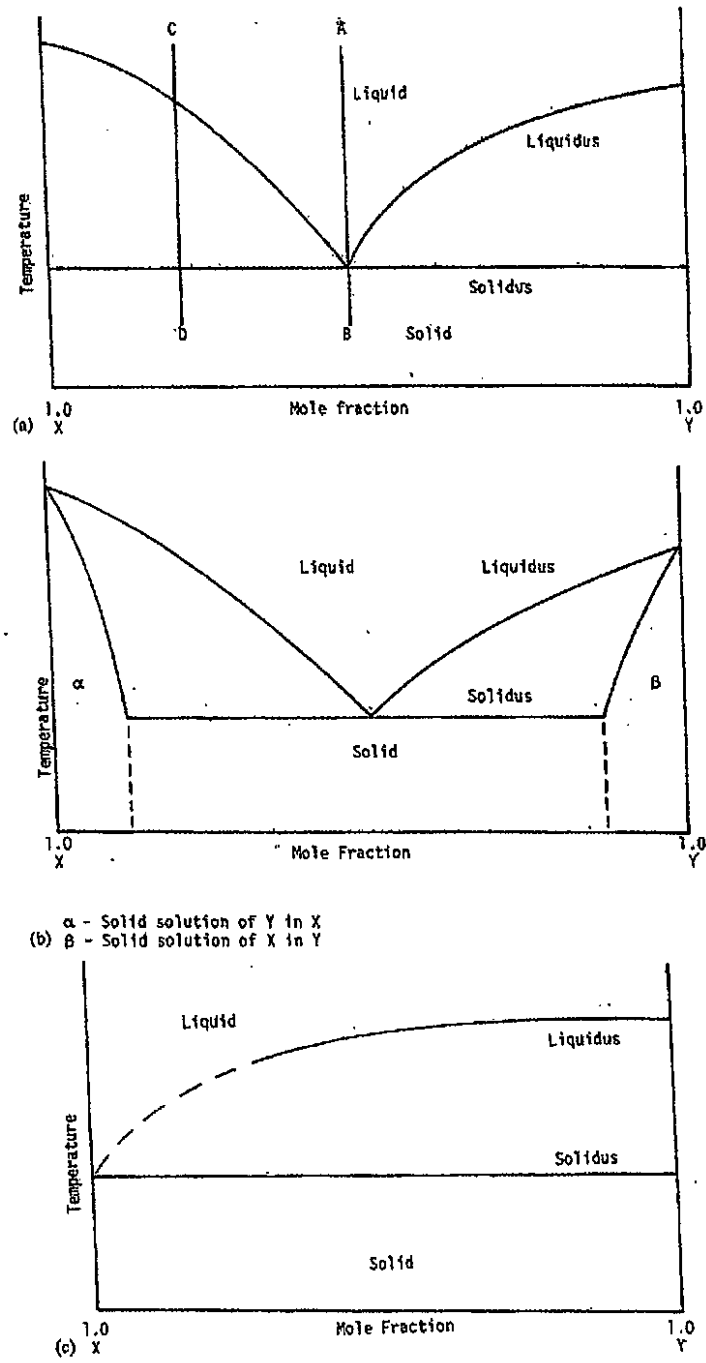


Fig. 1.

In practice the majority of such systems are likely to show only partial miscibility, hence the drug may only be in 'solution' at low concentrations (Fig. 1b), although it is appreciated that partial miscibility could in theory involve quite extensive drug incorporation at a molecular level. Nevertheless unequivocal demonstration of solid solubility is not as simple as one may imagine. For the reasons outlined above the melting point of a drug may be lowered and broadened so as to make it undetectable using DSC (Lloyd et al., 1997a). Similarly, XRD analysis needs to be conducted in comparison to physical mixes of identical composition to ascertain whether the lack of appearance of drug peaks is due to solid solution formation or is simply a function of the sensitivity of the instrument.

Thirdly, the drug may be present as a dispersion in a glassy matrix. This is certainly the case with amorphous polymers such as PVP and is probably also of relevance in many cases to semicrystalline materials such as PEGs (e.g. Anguiano-Igea et al., 1995; Tantoshaiyakul et al., 1996). Again, questions still remain as to whether the drug is dispersed on a molecular basis, is present as a separate amorphous phase or is present as a separate crystalline phase (or some combination of these). In some respects this is perhaps the area in which the most progress has been made, as the work by the group of Zografi (e.g. Matsumoto and Zografi, 1999) and others over the last decade has provided a more thorough basis by which to study and understand amorphous systems. This is arguably ironic as such systems may be expected to be more complex than crystalline dispersions. Finally, complex formation has been suggested as a further possibility. Clearly this is applicable to materials such as cyclodextrins and may also be of relevance to PVP and other carriers.

A further category that has been suggested since the review of Chiou and Riegelman (1971) has been that of monotectic systems (e.g. Kaur and Grant, 1979; Najib and Suleiman, 1989). These systems were suggested on the basis of the frequent observation that many reported eutectics had eutectic points that appeared to be convergent with the melting point of the pure material,

as indicated in Fig. 1c. Such systems have been reported in the alloy literature but later studies have indicated that, rather than indicating specific equilibrium phase behaviour, such diagrams may be simply a reflection of a completely non-interacting system, whereby the drug is simply present as a separate phase within the carrier. This was exemplified by a study by Lloyd et al. (1997b) whereby the model drug (paracetamol) was found to simply crystallise as a separate phase on cooling, as demonstrated by hot stage microscopy, the lowering of drug melting point being a simple reflection of the presence of molten carrier.

Overall, therefore, there still remain numerous questions regarding the physical nature of solid dispersions, despite the chemical simplicity of these systems. There is an argument that, at least in the case of PEGs and other largely crystalline carriers, the system may be simpler than has been assumed, with the two components simply existing as separate phases (Craig, 1990; Lloyd et al., 1997a,b). Similarly it could also be argued that hot stage microscopy observations during cooling is one of the most reliable methods for ascertaining the solid state structure, especially given the propensity of DSC to demonstrate effects that are a function of the temperature programme rather than being a direct reflection of the solid state structure at room temperature.

3. Drug release from solid dispersions

While a number of potential and realised advantages of solid dispersions have been described in the literature, the single most widely cited consideration is the improvement in dissolution rate, with concomitant implications for improving the bioavailability of poorly water-soluble drugs. Such improvements in dissolution rate are often considerable, with increases of up to four hundred fold having been reported (Said et al., 1974). It is therefore all the more remarkable that the mechanism underpinning these increases is so poorly understood. This may be largely because there are comparatively few papers available whereby elucidation of the mechanism (or mechanisms) involved is a specific objective. In this article,

therefore, emphasis is placed on discussing some of the ideas associated with the release process with a view to developing the argument that a more fundamental understanding of the process will facilitate rational design of the associated dosage forms.

The currently accepted range of possible mechanisms of enhanced dissolution effectively stems from the seminal review by Chion and Riegelman (1971). These include the following:

3.1. Particle size reduction and reduced agglomeration

These may be usefully considered together as both are related to increases in the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties, hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area.

3.2. Increased solubility or dissolution rate of the drug

Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in vitro experiments the carriers often elicit minimal solubility increases. This does, however, work on the assumption that the concentration of the carrier after complete dissolution in the water bath (e.g. 0.5 g/l) may be used as a model of the behaviour at the dissolving surface. Similarly, the carrier and drug may form a soluble complex, as is well established for cyclodextrins, although the evidence for this occurring with other carriers is weaker. Finally, changes to the physical properties of the drug such as degree of crystallinity and

polymorphic form may also be considered under this category.

In parallel with these considerations, there has also been an alternative line of thinking that has attempted to consider the processes that may be involved during dissolution in more detail. It may be argued that this type of approach has arisen as a result of seminal papers by the groups of Corrigan, Ford and Nystrom in the 1980s but has not yet been fully incorporated into the common parlance within the field, despite the possibilities for dissolution prediction that it appears to offer. However, the strands of these arguments have not yet been weaved together in a single article and it is this deficiency that the present communication is attempting to address.

There have been two apparently conflicting lines of research along these lines. In the first instance, Corrigan (1985, 1986) provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. The author found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases. This again implies that it is the dissolution rate of the carrier and not the drug that may dominate the process. Similarly, a study by Craig and Newton (1992) indicated that a log-linear relationship existed between the (measured as opposed to nominal) molecular weight of the PEG carrier and the dissolution rate, again implying that the properties of the polymer were dominating the dissolution process.

Corrigan (1985) has suggested that carrier-controlled dissolution may be modelled in terms of the approach outlined by Higuchi et al. (1965) and Higuchi (1967), whereby the dissolution of two-component systems is considered. Upon exposure to the solvent both components dissolve at rates proportional to their solubilities (C_s) and

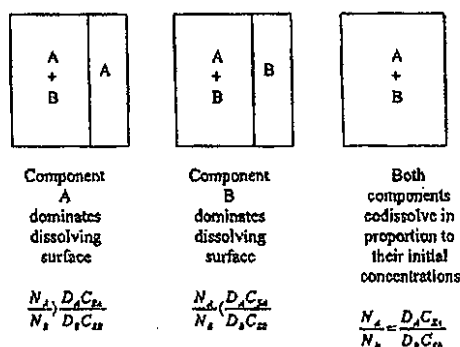


Fig. 2. Schematic representation of the dissolution model for a two component system (after Higuchi et al., 1965). See text for explanation of symbols.

diffusion coefficients (D) in the dissolving medium, as predicted for single component systems by the well-known Noyes–Whitney equation. However this model predicts that the interfacial layer between the dissolving front and the solvent will become depleted in the more rapidly dissolving component, leading to the creation of a surface layer rich in one component through which the other must diffuse prior to release into the bulk phase (Fig. 2). More specifically the model predicts that one component (for example A) will form such a surface layer when

$$\frac{N_A}{N_B} > \frac{D_A C_{SA}}{D_B C_{SB}} \quad (1)$$

where N is the proportion of each component and the subscripts A and B refer to the two components, respectively. Under these circumstances the dissolution rates will be given by

$$G_A = \frac{D_A C_{SA}}{h} \quad (2)$$

and

$$G_B = \frac{N_B}{N_A} G_A \quad (3)$$

where G is the dissolution rate/unit area and h is the diffusion layer thickness. In other words the model predicts that the dissolution rate of the minor component will be determined by that of the component in excess (although it should be

noted that 'minor' is more precisely defined in terms of Eq. (1) rather than simply the weight fraction present). This may in turn be applied to solid disperse systems by arguing that when the drug is present as a 'minor' component (which is almost invariably the case) the dissolution of that drug will be dominated by the dissolution behaviour of the carrier, as is indeed seen in practice (Corrigan, 1986). Interestingly, the predicted component ratio at which dominance changes between the two components is given by

$$\frac{N_A}{N_B} = \frac{D_A C_{SA}}{D_B C_{SB}} \quad (4)$$

This therefore predicts that if a drug (B) has a very low solubility in relation to that of the polymer (A) then the drug loading up to which carrier-controlled dissolution will apply will be similarly low, while a more soluble drug will show carrier-controlled dissolution up to a higher drug loading (assuming similar diffusion coefficients). This would appear to contradict the observations of Dubois and Ford (1985), who noted that phenacetin (0.77 mg/ml solubility) showed a more limited range of carrier-controlled dissolution (up to 5% loading) than did the less soluble (0.04 mg/ml) indomethacin (up to 10% drug loading). This could be due to diffusion coefficient effects or else to differences in the dispersion profiles of the two drugs within the polymer.

Leading on from these studies, Lloyd et al. (1999) argued that if dissolution was dominated by the properties of the carrier and not the drug (at least in some cases) then the physical form of the drug should be irrelevant to the release rate. These authors examined the release of paracetamol from PEG 6000 dispersions, using different drug size fractions in the initial preparation process and different manufacturing methods which were known to alter the physical properties of the drug (Lloyd et al., 1997b). First inspection of the dissolution data indicated a higher release from the larger size fraction systems. However, these authors also measured the concentration of drug at the dissolving surface, finding that settling had occurred during the solidification process on cooling from the melt. Once this had been corrected for (see Eq. (3)), the dissolution rates were found

to be independent of manufacturing conditions or initial particle size. This therefore confirmed that for these systems the physical form of the drug was unimportant as far as the release rate was concerned but also highlighted the danger of settling leading to higher effective concentrations of drug being present at the dissolving surface than may be anticipated from the total drug content.

However, while these studies, described together, give the impression of there being a common unifying mechanism underpinning release, there have been a number of papers suggesting that other mechanisms may be of relevance. For example, Sjökvist and Nyström (1991) measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles. In an attempt to reconcile these contradictions Sjökvist-Saers and Craig (1992) used an homologous series of drugs (*para*-aminobenzoates) in PEG 6000 in an attempt to interrelate the solid state structure, drug solubility and dissolution rate. These authors noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behaviour as drug-controlled dissolution as opposed to carrier-controlled dissolution. It was also noted that as the concentration of the drug increased the dissolution rate became effectively independent of composition and very similar to the drug alone (Fig. 3); in this respect therefore the behaviour corresponds to the Higuchi model when the drug is the dominant component. However the interrelationship between the dissolution rate and the solubilities of the drugs at high polymer contents runs contrary to what one would expect from the Higuchi model; if the dissolution was carrier controlled the drug properties should make no difference to the dissolution rate.

Overall, therefore, there appear to be two sets of observations with regard to the mechanism of drug release from solid dispersions. In the first instance, some systems appear to show carrier-

controlled release whereby, at least at low drug loadings, the rate of release is controlled by that of the carrier and is independent of drug properties. Secondly some systems show release behaviour that is dependent on the properties of the drug rather the polymer, even at low drug loadings. The following questions therefore arise; what is happening to the drug during either of these processes, which factors determine whether the dissolution is carrier- or drug- controlled and what are the implications of understanding the mechanism for dosage form design?

4. Possible mechanism of dissolution from solid dispersions and implications for manufacture

Given the above considerations, there does appear to be more than one mechanism by which drugs may be released from solid dispersions. Probably the simplest scenario is that found at high drug loadings, where authors appear to agree that the formation of the drug-rich layer suggested by Higuchi et al. (1965) and applied to solid dispersions by Corrigan (1985) provides a satisfactory explanation. This leaves the dual observations for low drug loadings regarding drug-controlled and carrier-controlled dissolution. We believe that both may be facets of essentially the

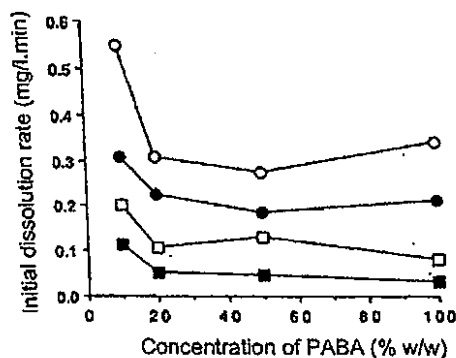


Fig. 3. Relationship between initial intrinsic dissolution rate and concentration of *para*-aminobenzoic acid (PABA) in PEG 4000 solid dispersions. (○) Methyl PABA; (●) ethyl PABA; (□) propyl PABA; (■) butyl PABA (reproduced with permission from Sjökvist-Saers and Craig, 1992).

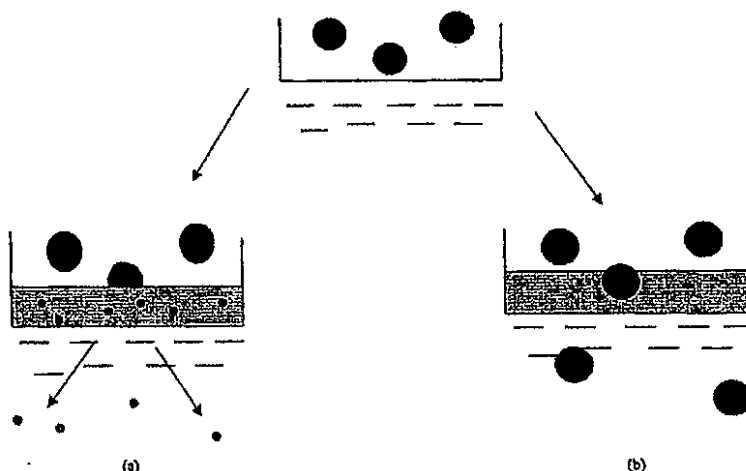


Fig. 4. Schematic diagram showing the fate of drug particles during the dissolution process. (a) Carrier-controlled dissolution, whereby the drug dissolves into the concentrated carrier layer prior to release and (b) drug-controlled dissolution whereby the drug is released effectively intact into the dissolution medium. Large spheres represent undissolved drug particles, small spheres partially dissolved drug particles, shaded regions correspond to hydrated material.

same process and propose a model, outlined in Fig. 4, that attempts to explain how the drug particles may be behaving during the dissolution process. The model works on the premise of there being a highly concentrated polymer layer at the dissolving surface (at least at low drug loadings) through which the drug must pass prior to release into the bulk phase.

In Fig. 4a, the process associated with carrier-controlled dissolution is described. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer. However, the viscosity of the layer is such that drug diffusion is very slow as predicted by the well-known Stokes–Einstein equation

$$D = \frac{kT}{6\pi\eta r} \quad (5)$$

where k is Boltzmann's constant, η is the viscosity and r is the radius of the diffusing molecule. Consequently the rate-limiting step to dissolution of the drug becomes the release of the polymer

itself and hence Eq. (3) becomes applicable to describe the release of the drug. It should be noted that the dissolution of a water soluble polymer may not be modelled by simple diffusion equations with complete confidence as such polymers do not show saturation solubility as such but rather will swell and sorb water to produce a continuum of concentrations between the solid surface and the bulk medium; these and related issues have been addressed in communications by Ueberreiter (1968). However, the principle outlined above is nevertheless still applicable.

The second scenario, that of drug-controlled dissolution, is outlined in Fig. 4b. In this case dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself. This may still lead to considerable improvements in dissolution compared to conventional dosage forms due to the higher surface area associated the particles and the possibility of improved wetting and decreased agglomeration.

The question therefore arises as to why some drugs will follow the scenario shown in Fig. 4a and others 4b. The most likely explanation must be the tendency of the drug to dissolve into the concentrated polymer diffusion layer. As stated previously, the solubility of drugs in low concentrations of carrier solutions does not tend to be significantly enhanced compared to that in water alone. However, several studies have demonstrated that the drug solubility increases disproportionately in higher concentration solutions. More specifically, a log-linear relationship has been described for several systems as predicted by the expression given by Yalkowsky et al. (1972) for cosolvent systems

$$\log S = \log S_w + \sigma f \quad (6)$$

where S is the solubility of the solvent under investigations, S_w is the solubility in water, σ is a constant and f is the proportion of cosolvent present in the system. It is therefore feasible that for many drug-carrier combinations the drug solubility in the concentrated layer is sufficiently high so as to allow dissolution to occur prior to the dissolving front of the composite solid reaching the particles. Once in solution in the diffusion layer, the viscosity is sufficiently high so as to render diffusion through the concentrated layer slow and the rate-limiting step to release becomes the diffusion of the carrier molecules into the bulk phase, as predicted by the Higuchi model. In the case of drugs whereby the solubilisation is low, however, the particles may be simply released partially or completely intact from the matrix, whereupon dissolution occurs from the free particle surface.

Overall, therefore, the release mechanism will depend on whether the drug dissolves in the polymer diffusion layer rapidly or not which will in turn be dependent largely on the solubility of the drug in this layer. However, other considerations must also be borne in mind. For example, the hydrodynamics of the dissolution process may also play a role in determining the mechanism in that more rapid stirring speeds may favour drug-controlled dissolution by enhancing the rate of polymer dissolution into the bulk in relation to drug dissolution into the diffusion layer. Similarly

by changing the physical form of the drug (e.g. size reduction), one could conceivably change the mechanism by altering the dissolution kinetics into the diffusion layer. Furthermore, while the process has been described above as one of two extremes it is possible that in many cases elements of both are present, e.g. the particles may partially dissolve in the diffusion layer before being released intact, thereby providing two simultaneous mechanisms of dissolution. However, the model does serve to provide an explanation for the differences in behaviour of various drugs and also suggests that the measurement of drug solubility in carrier solutions may, with refinement, provide a means of predicting the dissolution mechanism.

5. Mathematical modelling of drug-controlled dissolution

As there are already effective expressions available to model carrier-controlled drug dissolution (Eqs. (1)–(4)), it would clearly be desirable to derive an expression whereby the intact particle release mechanism could be described. Outlined below is a suggested basis for such an analysis. This approach has been developed on the idea of the solid polymer receding to a distance such that a single particle is released, as indicated in Fig. 5. Two of the main assumptions of the model become immediately apparent. Firstly it is assumed that the drug is released only when the solid front has receded a distance equivalent to the diameter of that particle and secondly that the particle does not undergo significant dissolution prior to release. A third assumption concerns the equivalence of the densities of the drug and polymer; this may be easily corrected for but it is felt that the error arising from this assumption will be small in relation to the other approximations involved. Fig. 5 presents a representation of the salient features of the solid dispersion structure relevant to the proposed model.

The overall dissolution rate at time t ($G_T(t)$) may be considered to be essentially a function of the mean dissolution rate from each individual particle ($G_P(t)$) and the number of particles available $N(t)$, i.e.

$$G_T(t) = \sum_{i=1}^N G_p(t) \approx G_p(t)N(t) \quad (7)$$

where G_p is the dissolution rate at time t of the individual particles. In the first instance it is necessary to calculate the time dependence of the particle release process by considering the time required for sufficient polymer to dissolve in order to release a particle. This is achieved by considering the intrinsic polymer dissolution rate P_A (wt/ $A \cdot t$ where A is area of dissolving surface). The dissolution rate (P_T) may also be expressed in terms of the volume of polymer dissolved in unit time from a disk of diameter $2R$

$$P_T = \frac{P_A}{\rho} \pi R^2 \quad (8)$$

where ρ is the density of the polymer. The volume of dispersion (V_p) that needs to dissolve for a particle of diameter r to be released is given by

$$V_p = 2\pi r R^2 \quad (9)$$

hence the time (t_p) required to release such a particle is given by

$$t_p = \frac{V_p}{P_T} = \frac{2r\rho}{P_A} \quad (10)$$

Note that equivalence of matrix dissolution and polymer dissolution can be reasonably assumed

from the Higuchi model (Higuchi et al., 1965) if the polymer is present in large excess. The above may be modified for situations where this does not apply but for the present purposes this assumption is satisfactory.

To calculate the number of particles released in time t_p (N_p) it is merely necessary to calculate the number of particles present in V_p by multiplying by the weight fraction x (here we assume density equivalence of the two components) and dividing by the volume of a single particle

$$N_p = \frac{3R^2 x}{2r^2} \quad (11)$$

Consequently from Eqs. (10) and (11)

$$\frac{\partial N}{\partial t} = \frac{3R^2 x P_A}{4r^2 \rho} \quad (12)$$

Integrating between $t = 0$ and $t = t$ gives

$$N(t) = \frac{3R^2 x t}{4r^2 \rho} \int_{t=0}^{t=t} P_A dt \quad (13)$$

It is then possible to combine the above with an expression describing the dissolution of a single particle. Numerous such models are available with varying degrees of sophistication but for the present purposes one may use the simple expression derived by Goyan (1965)

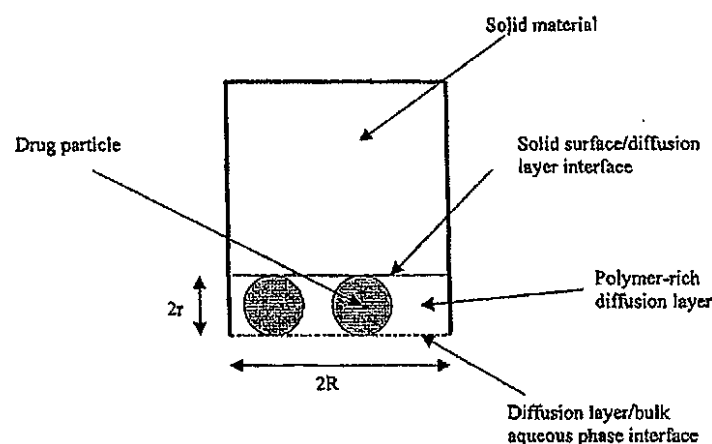


Fig. 5. Schematic representation of the structure of solid dispersions with reference to the model derived for drug-controlled dissolution.

$$G_p = \frac{D}{r}(C_s - C) \quad (14)$$

where C_s and C represent the solubility and bulk concentration. Overall therefore the dissolution rate of the system is given by

$$G_T = \frac{3D(C_s - C)R^2\alpha}{r^4\rho} \int_0^{t-t'} P_A dt \quad (15)$$

The integral term is simply the intrinsic dissolution rate constant of the polymer. Clearly this model may be further refined and many of the assumptions accounted for. However, it does provide a basis for further work and also, interestingly, predicts that the dissolution rate will be highly dependent on the initial particle size. It also predicts non-linearity of the dissolution profiles, even from a constant surface area disk. This was indeed observed in the study by Sjökvist-Saers and Craig (1992) for systems showing drug-controlled dissolution.

6. Implications of understanding the dissolution mechanism for the practical use of solid dispersions

The obvious question to arise at this stage is what are the implications of such knowledge for dosage form design? The primary issue must be the prediction and control of dissolution rate. If a system is undergoing carrier-controlled dissolution then the physical properties of the drug should be largely irrelevant (given the proviso stated above regarding changing the mechanism). This then means that the initial particle size and the physical form of the drug are of minimal importance. This in turn implies that, provided the physical form of the carrier is not greatly changed, the manufacturing process variables such as maximum temperature used is irrelevant. This specific factor is an interesting case in point as it has not yet been fully established whether the drug needs to be dissolved in the molten polymer during preparation or not; indeed it has been largely assumed that both components need to be fully liquefied during manufacture. Studies by Lloyd et al. (1999) for a carrier-controlled system have shown this not to be the case, with the

manufacturing temperature used having no effect on paracetamol release. In fact the drug recrystallizes as a separate phase anyway on cooling hence the maximum fusion temperature, with concomitant costs and safety issues, may not need to be as high as has been assumed. If, on the other hand, the dissolution process is drug-controlled then the properties of the drug become crucial.

This distinction also has implications for the choice of carrier. If the system is carrier controlled, then changing the molecular weight of the carrier, incorporating a proportion of lower molecular weight material or adding surfactants may all have a beneficial effect. Indeed, if a carrier-controlled system is desirable then screening could be performed to determine which carriers or mixtures of carriers provide ample solubilisation of the drug prior to extensive experimentation. However, perhaps the most important implication of such knowledge concerns the understanding of a perennial problem associated with these systems, namely stability issues. Despite the plethora of reports describing changes in dissolution rate on storage, a universal explanation for this phenomenon has not yet been established. In the light of the above, one can see why this has been the case, simply because the mechanism of ageing must be intimately linked to the mechanism of dissolution. More specifically, if the system is carrier-controlled then, in the absence of a change of mechanism, the ageing effects must be due to changes in the properties of the polymer. This is a large and well studied field within the polymer sciences, particularly for amorphous or semicrystalline polymers, and it is likely that means of predicting and preventing such effects may be found in this literature. If, on the other hand, the system is drug controlled then it is the properties of the drug itself that must be considered such as slow recrystallisation from unstable solid solutions, changes in polymorphic form, particle size increases or recrystallisation from the amorphous state. However, the key issue is that unless the basic mechanism of release is understood it does seem unlikely that prediction of ageing effects will be possible.

7. Conclusions

This article has outlined some of the current thinking with regard to the mechanisms by which drugs may be released from solid dispersions, focussing on the solid state properties of the dispersions and the possible fates of drug particles within a solid disperse matrix. It is proposed that two mechanisms may be of relevance, involving either carrier or drug controlled release, the predominance depending on the solubility of the drug in concentrated solutions of the carrier. The implications for this model have been outlined, with particular emphasis on understanding stability issues. Overall, solid dispersions present the industry with some extremely exciting possibilities with regard to the formulation of poorly soluble drugs, yet until the fundamental behaviour of these systems is understood the utility of this approach will inevitably remain limited or at best empirical.

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Attachment C

Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs

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Abstract □ Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and self-emulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts. Solid plugs are formed inside the capsules when the melts are cooled to room temperature. Because of surface activity of carriers used, complete dissolution of drug from such solid dispersions can be obtained without the need for pulverization, sieving, mixing with excipients, etc. Equipment is available for large-scale manufacturing of such capsules. Some practical limitations of dosage form development might be the inadequate solubility of drugs in carriers and the instability of drugs and carriers at elevated temperatures necessary to manufacture capsules.

Introduction

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs,¹ there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage

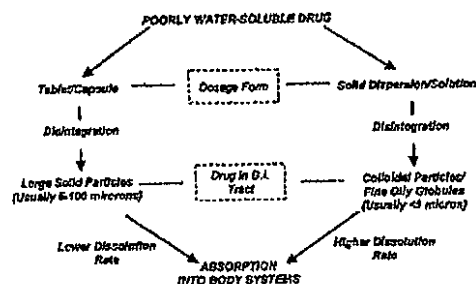


Figure 1—A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

form may also be problematic because of handling difficulties and poor wettability.

In 1961, Sekiguchi and Obi² developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion,³ involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi² suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg et al.^{4,5} demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

The advantage of solid dispersion, compared with conventional capsule and tablet formulations, is shown schematically in Figure 1.⁶ From conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case, an average particle size of 5 μm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation, and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size.

Because of such early promises in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field. Numerous papers on various aspects

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of solid dispersion were published since 1961; Chiou and Riegelman³ and Ford⁷ reviewed the early research in this area. Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, a griseofulvin-in-poly(ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a nabilone-in-povidone solid dispersion (Cesamet, Lilly) were marketed during three decades following the initial work of Sekiguchi and Ohi in 1961. The objectives of the present article are to critically review some of the limitations of solid dispersion that prevented its wider commercial application and to discuss how the situation is now changing because of the availability of new types of vehicles and the development of new manufacturing technologies.

Limitations of Solid Dispersion Systems

Problems limiting the commercial application of solid dispersion involve (a) its method of preparation, (b) reproducibility of its physicochemical properties, (c) its formulation into dosage forms, (d) the scale up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle. Some of the issues are discussed next.

Method of Preparation—In their pioneering study, Sekiguchi and Ohi² prepared solid dispersions of sulfathiazole in such carriers as ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, and urea by melting various drug-carrier mixtures. To minimize melting temperatures, eutectic mixtures of the drug with carriers were used. Yet, in all cases, except acetamide, the melting temperatures were >110 °C, which could chemically decompose drugs and carriers.³ High temperatures (>100 °C) were also utilized by Goldberg et al. in preparing acetaminophen-urea,⁴ griseofulvin-succinic acid,⁴ and chloramphenicol-urea⁵ solid dispersions. After melting, the next difficult step in the preparation of solid dispersions was the hardening of melts so that they could be pulverized for subsequent formulation into powder-filled capsules or compressed tablets. Sekiguchi and Ohi² cooled the sulfathiazole-urea melt rapidly in an ice bath with vigorous stirring until it solidified. Chiou and Riegelman³ facilitated hardening of the griseofulvin-PEG 6000 solid dispersion by blowing cold air after spreading it on a stainless steel plate and then storing the material in a desiccator for several days. In preparing primidone-citric acid solid dispersions, Summers and Enever¹⁰ spread the melt on Petri dishes, cooled it by storing the Petri dishes in a desiccator, and finally placed the desiccator at 60 °C for several days. Allen et al.¹¹ prepared solid dispersions of corticosteroids in galactose, dextrose, and sucrose at 169, 185, and 200 °C, respectively, and then placed them on aluminum boats over dry ice. Timko and Lord¹² also used blocks of dry ice to cool and solidify phenobarbital-citric acid mixtures that had previously been melted on a frying pan at 170 °C. The fusion method of preparing solid dispersion remained essentially similar over the period of time. More recently, Lin and Cham¹³ prepared nifedipine-PEG 6000 solid dispersions by blending physical mixtures of the drug and the carrier in a V-shaped blender and then heating the mixtures on a hot plate at 80–85 °C until they were completely melted. The melts were rapidly cooled by immersion in a freezing mixture of ice and sodium chloride, and the solids were stored for 24 h in a desiccator over silica gel before pulverization and sieving. Mura et al.¹⁴ solidified naproxen-PEG melts in an ice bath and the solids were then stored under reduced pressure in a desiccator for 48 h before they were ground into powders with a mortar and pestle. In another study, Owusu-Ababio et al.¹⁵ prepared a mefenamic acid-PEG solid dispersion by heating the drug-carrier mixture on a hot plate to a temperature above

the melting point of mefenamic acid (253 °C) and then cooling the melt to room temperature under a controlled environment.

Another commonly used method of preparing a solid dispersion is the dissolution of drug and carrier in a common organic solvent, followed by the removal of solvent by evaporation.^{8,16,17} Because the drug used for solid dispersion is usually hydrophobic and the carrier is hydrophilic, it is often difficult to identify a common solvent to dissolve both components. Large volumes of solvents as well as heating may be necessary to enable complete dissolution of both components. Chiou and Riegelman³ used 500 mL of ethanol to dissolve 0.5 g of griseofulvin and 4.5 g of PEG 6000. Although in most other reported studies the volumes of solvents necessary to prepare solid dispersions were not specified, it is possible that they were similarly large. To minimize the volume of organic solvent necessary, Usui et al.¹⁸ dissolved a basic drug in a hydroalcoholic mixture of 1 N HCl and methanol, with drug-to-cosolvent ratios ranging from 1:48 to 1:20, because as a protonated species, the drug was more soluble in the acidic cosolvent system than in methanol alone. Some other investigators dissolved only the drug in the organic solvent, and the solutions were then added to the melted carriers. Vera et al.¹⁹ dissolved 1 g of oxodipine per 150 mL of ethanol before mixing the solution with melted PEG 6000. In the preparation of piroxicam-PEG 4000 solid dispersion, Fernandez et al.²⁰ dissolved the drug in chloroform and then mixed the solution with the melt of PEG 4000 at 70 °C. Many different methods were used for the removal of organic solvents from solid dispersions. Simonelli et al.¹⁶ evaporated ethanolic solvent on a steam bath and the residual solvent was then removed by applying reduced pressure. Chiou and Riegelman³ dried an ethanolic solution of griseofulvin and PEG 6000 in an oil bath at 115 °C until there was no evolution of ethanol bubbles. The viscous mass was then allowed to solidify by cooling in a stream of cold air. Other investigators used such techniques as vacuum-drying,^{20,21} spray-drying,^{22–25} spraying on sugarbeads using a fluidized bed-coating system,²⁶ lyophilization,²⁷ etc., for the removal of organic solvents from solid dispersions. None of the reports, however, addressed how much residual solvents were present in solid dispersions when different solvents, carriers, or drying techniques were used.

Reproducibility of Physicochemical Properties

In their pioneering studies, Sekiguchi and Ohi² observed that manufacturing conditions might greatly influence the physicochemical properties of solid dispersions formed. They cooled drug-carrier melts under vigorous stirring conditions to obtain fine and uniform drug particles in solid dispersions. Various investigators observed that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate, method of pulverization, and particle size may greatly influence the properties of solid dispersions prepared by the melt method. McGinity et al.²⁸ prepared solid dispersions of tolbutamide in urea and PEG 6000 by flash cooling in a bath of dry ice and acetone or by gradual cooling over a period of several hours by immersion in an oil bath. The powder X-ray diffraction patterns of the tolbutamide-urea solid dispersion differed markedly depending on the cooling rate. The slow-cooled solid dispersion of tolbutamide in urea demonstrated a complete lack of crystallinity for both the drug and urea, whereas the flash-cooled dispersions showed only the absence of drug crystallinity. In the powder X-ray diffraction patterns of tolbutamide-PEG 6000 solid dispersions, peaks for both tolbutamide and PEG 6000 were observed; however, their degree of crystallinity in flash-cooled samples was less than that in the slow-cooled

samples. In another study, a metastable amorphous form of nifedipine was formed in its solid dispersions in PEG 4000 and PEG 6000 when the drug-carrier melts were cooled rapidly, whereas slow cooling of melts or powdering of solidified mass resulted in the crystallization of drug.²⁹ Ginés et al.³⁰ studied the effect of fusion temperature on oxazepam-PEG 4000 solid dispersions. Microscopic examination revealed the presence of crystalline oxazepam and the spherulitic form of PEG 4000 in solid dispersions prepared by fusion at 100 °C. In contrast, a fusion temperature of 150 °C produced a solid dispersion with no crystalline form of the drug and the presence of PEG 4000 in a heditic form. Complete dissolution of drug in the carrier at 150 °C in contrast to 100 °C was reported to be responsible for such a difference in physicochemical properties of the solid dispersions produced. Dordunoo et al.³¹ also observed a change of triamterene and temazepam from crystalline to amorphous form in poly(ethylene glycol) solid dispersions when the fusion temperature was increased from 100 to 150 °C. Such changes in physical states of drugs in solid dispersions result into differences in drug dissolution rates in aqueous media.³⁰ Drug-to-carrier ratio and particle size of solid dispersions were also reported to influence the dissolution rate of drug.³²

The properties of solid dispersions prepared by the solvent method may also vary depending on manufacturing conditions. The solvent method usually leads to amorphous forms of drugs. However, some crystallinity of drug may be observed depending on the drug-to-carrier ratio used.³³ Although no detailed studies were reported in the literature, it is expected that the nature of solvent used, drug-to-solvent and carrier-to-solvent ratios, drying method, and drying rate may significantly influence the physicochemical properties of solid dispersions formed.

Dosage Form Development—Solid dispersion must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. As already mentioned, solid dispersions produced by the melt method are usually hardened at very low temperatures and then pulverized with mortars and pestles. Similarly, solid dispersions produced by the solvent method are also pulverized after solvent removal and hardening. Some of the challenges in the dosage form development of such materials are difficulty of pulverization and sifting of the dispersions, which are usually soft and tacky, poor flow and mixing properties of powders thus prepared, poor compressibility, drug-carrier incompatibility, and poor stability of dosage forms. However, there are very few reports in the literature addressing these important issues.⁷ Even the limited number of reports describing any dosage form developmental aspects of solid dispersions only confirm that the task of formulating solid dispersions into capsules or tablets may be a very complex and difficult one. In developing a tablet formulation for the indomethacin-PEG 6000 solid dispersion, Ford and Rubinstein³⁴ reported that the solid dispersion was not amenable to wet granulation because water could disrupt its physical structure. In addition, the dispersion was soft and tacky. To overcome these problems, the authors adopted an *in situ* dry granulation method where the excipients (calcium hydrogen phosphate and sodium starch glycolate) were preheated and rotated in a water-jacketed blender at 70 °C, and the indomethacin-PEG 6000 mixture that melted at 100 °C was then added to the moving powder. After mixing, the granules were passed through a 20-mesh sieve and allowed to harden at 25 °C for 12 h. Then, the granules were mixed with a relatively high concentration of magnesium stearate (1%) and compressed into tablets. To process 100 mg of solid dispersion, 506 mg of other excipients were used, thus making the final weight

of a 25-mg indomethacin tablet 606 mg. Yet, the tablet did not disintegrate in water despite the use of a large amount of excipients. It dissolved slowly by erosion, and the dissolution rate decreased on aging of the tablet. In another study, the same investigators used an essentially similar *in situ* dry granulation method for the preparation of tablet dosage forms for a chlorpropamide-urea solid dispersion, where the drug, the carrier, and the excipients were mixed in a rotating flask on a water bath maintained at 100 °C.³⁵ The properties of these formulations also changed with time, and the authors concluded that aging could "limit their usefulness as prospective dosage forms". During the development of a tablet formulation for a furosemide-poly(vinylpyrrolidone) (PVP) solid dispersion, Akbuga et al.³⁶ observed that method of preparation, choice of disintegrant and particle size of solid dispersions were critical factors in determining the properties of tablets produced. Despite the use of relatively large amounts of disintegrants, the tablets did not disintegrate. Rather, they dissolved by erosion only, and the erosion rate varied depending on the disintegrant used. In addition, the dissolution rate of tablets prepared by double compression (stugging and recompression of dry granules) was much slower than that of the tablets prepared by single compression. The dissolution rate of tablet was also dependent on the particle size of solid dispersion used; the rate decreased by a factor of 5 when 100-mesh particles were used in place of 80-mesh particles. Also, the compressibility of solid dispersion decreased with a decrease in particle size. In another study, Sjökvist and Nystrom³⁷ overcame the compression difficulties due to sticking of griseofulvin-xylitol solid dispersions to dies and punches by lubricating die wall and punch faces with 1% (w/w) magnesium stearate suspension before the compression of each tablet. The authors observed that the dissolution rate of tablet was highly sensitive to compression pressure. The sticking of solid dispersion to dies and punches might become so problematic that Kaur et al.³⁸ resorted to placing small pieces of grease-proof paper between metal surfaces and granules before the compression of tablets.

The lack of disintegration and the slow dissolution of tablets prepared from solid dispersions could be related to the soft and waxy nature of carriers used (e.g., PEG) in many of the reported studies. Such carriers essentially act as strong binders within tablets. During compression, the carriers could plasticize, soften, or melt, filling the pores within tablets and thus making them nondisintegrating. It is also possible that the softened and melted carriers coat the disintegrants and other ingredients used in tablets, and such a coating, along with the reduction of porosity of tablets, make the disintegrants ineffective. Use of a very high ratio of solid dispersion to added excipient might alleviate the problem. In one study,¹⁵ 270 mg of microcrystalline cellulose (Avicel) was used to formulate 30 mg of mefenamic acid-PEG solid dispersion into a tablet with good dissolution. The use of such a high ratio of added excipient would, however, greatly increase the size of tablet and might, therefore, be impractical in most formulations.

Scale Up of Manufacturing Processes—Because very few solid dispersion products prepared by melt or solvent methods have been marketed, there are practically no reports on the scale up of such products. It is apparent from the discussion just presented that the scale up of the methods of preparation of solid dispersions and their dosage forms could be very challenging. In most of the studies reported in the literature, solid dispersions by the melt method were prepared in a small scale by heating drug-carrier mixtures in beakers, frying pans, etc. that were placed on hot plates and then cooling the melts in an ice bath, a dry ice-acetone mixture, etc.^{2-5,7-14} Because there could be condensation of moisture over solid disper-

alons during cooling to low temperatures, strict protection from moisture was necessary in all cases. The scale up challenges may be illustrated with the example of the preparation of a phenytoin-PEG 4000 solid dispersion by Yakou et al.³⁹ The drug-carrier mixture was heated at 250 °C under constant stirring until a clear homogeneous melt was obtained, and the melt was air-cooled by spreading on stainless steel trays. The trays were stored in a desiccator for 3 days to enhance solidification of the solid dispersion. The resulting material was then crushed in a cutter mill, and the powders were sieved to collect a sieve fraction of 105–177- μ m particle size for use in the dosage form. The scale up of such a method would be difficult and it might even be impractical in many cases because of possible degradation of both drug and carrier at high temperatures used. The scale up might also necessitate a large capital investment because a chemical plant-like facility, rather than a common pharmaceutical dosage form manufacturing plant, would be required to process and manufacture the products. For scale up of the cooling process, Lefebvre et al.⁴⁰ recommended such continuous operation as cooling on the surfaces of moving belts or rotating cylinders, and spray congealing. The practical application of the methods, however, was not demonstrated. Kennedy and Niebergall⁴¹ described a hot-melt fluid bed method whereby nonpareils could be coated with PEGs having molecular weights between 1450 and 4600. A similar method can possibly be used to deposit solid dispersions on nonpareils and might in the future find application in the manufacture and scale up of solid dispersion formulations.

The physicochemical properties and stability of solid dispersions may also be affected by scale up because heating and cooling rates of solid dispersions under large-scale manufacturing conditions may differ greatly from that in small beakers.^{28,29} Drug-carrier compatibility at a high temperature also requires careful consideration. Dubois and Ford⁴² reported the chain scission of PEG 600 during fusion with disulfiram, furosemide, chlorthalidate, and chlorpropamide.

The scale up of the solvent method of preparing solid dispersions may also be very challenging. A chemical plant environment would be necessary to evaporate hundreds and even thousands of liters of organic solvents necessary to prepare solid dispersions for kilogram quantities of drugs.^{17,20} The cost of recovery of these solvents may be very high. Removal of residual amounts of potentially toxic organic solvents such as chloroform and methanol from large masses of material may be difficult because the solid dispersions are usually amorphous and may exist in viscous and waxy forms. Solvates may also be formed with drugs and carriers. Because most dosage form manufacturing facilities are not equipped to handle large volumes of organic solvents, one way to resolve the issue might be the designation of solid dispersion as an active pharmaceutical ingredient or bulk drug substance. In that case, the responsibility of the manufacture of solid dispersion can be shifted to the chemical plant. It would be necessary to conduct all developmental activities using the solid dispersion, so this approach might not be suitable for situations where active pharmaceutical ingredients have multiple uses (e.g., oral and parenteral).

The final step in the manufacturing process, which is the conversion of solid dispersions into stable and marketable dosage forms, may be the most difficult one to scale up, optimize, and validate. Most of the commonly used solid dispersion vehicles are soft and sticky and, as a result, the pulverized forms of solid dispersions produced by such vehicles may not be amenable to processing by high-speed capsule or tablet filling machines.

Stability—The physical instability of solid dispersions due to crystallization of drugs was the subject of most published reports in the literature.^{3,7} In a solid dispersion prepared by the melt method, a certain fraction of the drug may remain molecularly dispersed, depending on its solubility in the carrier used, thus forming a solid solution. How the excess drug exists may greatly depend on the method of manufacture of the system; it may, as a whole or in part, form a supersaturated solution, separate out as an amorphous phase, or crystallize out. The supersaturated and amorphous forms may, in turn, crystallize out on aging. Similarly, certain carriers may also exist in thermodynamically unstable states in solid dispersions and undergo changes with time. Chlou⁴³ reported that griseofulvin precipitated out in an amorphous form in a griseofulvin-PEG 6000 solid dispersion during the time of its preparation. The amorphous material crystallized out on aging, except when the drug concentration in the dispersion was 5% or less. Ford and Rubinstein⁴⁴ attributed similar crystallization as the cause for a decrease in dissolution rate of drug from indomethacin-PEG 6000 solid dispersions with time. The decrease in the dissolution rate of indomethacin was also dependent on drug concentration in the solid dispersion. The decrease was greater for a higher drug concentration because a larger fraction of drug crystallized out. In another study, Suzuki and Sunada⁴⁵ observed that on exposure of a nifedipine-nicotinamide-hydroxypropylmethylcellulose (HPMC) solid dispersion to 60% RH at 30 °C or 75% RH at 40 °C for 1 month, nifedipine converted from the amorphous to the crystalline state, thus lowering the dissolution rate of nifedipine drastically. No conversion of nifedipine to the crystalline state was observed when the solid dispersion was stored at an elevated temperature in the absence of humidity. Although the presence of HPMC facilitated the conversion of nifedipine to an amorphous state during the cooling of drug-nicotinamide melt to room temperature at the time of manufacturing, it did not prevent the subsequent crystallization of drug under humid conditions. Pronounced decreases in dissolution rates due to drug crystallization were also reported for tablets prepared from solid dispersions.^{34,35} No such decrease in dissolution rate on aging was observed by Khalil et al.⁴⁶ in corticosteroid-PEG solid dispersions prepared with a drug-to-carrier ratio of 1:99, possibly because most of the drug was molecularly dispersed in the carrier. The corticosteroid, however, exhibited chemical degradation due to oxidation by the peroxides present in PEG. The cooling rate of solid dispersions may also significantly influence their aging behavior. It has been reported that the crystallinity of drug in solid dispersions is less influenced by aging when a slow cooling rate is used because thermodynamically more stable systems are produced during the time of preparation.^{47,48}

The conversion of drug to crystalline state is also the primary stability issue with solid dispersions prepared by the solvent method. PVP, which is commonly used as a carrier in such solid dispersions, is amorphous and does not convert to a crystalline state. However, certain other carriers may convert from their amorphous states to crystalline states in solid dispersions. Zograf and co-workers^{49,50} extensively studied the physicochemical properties of the amorphous states of drugs and excipients and observed that the crystallization of amorphous materials is facilitated by moisture. This effect is why strict protection from moisture is necessary during the preparation and storage of most solid dispersions. Doherty and York⁵¹ studied the stability of furosemide-PVP solid dispersion in the temperature range of 5 to 45 °C and 40% RH for up to 1 year. They did not observe any crystallization of furosemide and suggested that PVP may indeed act as a

stabilizer in the solid dispersion by retarding crystallization of drug at a relatively low humidity. Rapid crystallization of furosemide in the solid dispersion was, however, evident when the humidity was raised to 75% RH. Similar observations were also made by Guillaume et al.⁵² for an oxodipine-PVP solid dispersion where no crystallization was observed under 55% RH at various temperatures, but the drug crystallized out at 80% RH. The stabilization of drugs in amorphous forms in solid dispersions is an active area of research in the pharmaceutical field. For an indomethacin-PVP solid dispersion system, Taylor and Zograf⁵³ suggested that hydrogen bonding between the drug and PVP might offer an explanation for the absence of drug crystallization. Lu and Zograf⁵⁴ recently demonstrated that indomethacin forms a completely miscible amorphous mixture with citric acid and PVP when the weight fraction of PVP in the ternary mixture exceeds 0.3 weight fraction. Thus, both the choice of carrier and the drug-to-carrier ratio are important considerations in the stabilization of solid dispersions.

Breakthroughs in Solid Dispersion Technology

Because of the various limitations just mentioned, it is not surprising that the solid dispersion system, despite its many potential advantages, has not been widely used in pharmaceutical dosage forms. Under the present health care economic climate, the goal of any drug development program in the pharmaceutical industry is to rapidly progress a new chemical entity from the discovery stage to clinical testing to determine whether it is safe and clinically effective. The limited supply of the bulk drug substance at the early drug development phase and the accelerated time line would not allow a formulator to address most of the challenges (vide supra) of a solid dispersion formulation. Most importantly, if a compound proves promising in early clinical testing, the scale up of complex manufacturing processes for the development of marketable dosage forms cannot be ensured.

Two recent breakthroughs in the formulation of solid dispersion systems involve (1) the development of technologies to fill solid dispersions directly into hard gelatin capsules and (2) the availability of surface-active and self-emulsifying carriers. As a result, there is renewed interest in such systems for use in commercial development of drug products.^{54,55}

Direct Capsule-Filling—Although the filling of semi-solid materials into hard gelatin capsules as melts, which solidify at room temperature, was first described by Francols and Jones in 1978,⁵⁶ it was not until much later that the potential application of the technique for solid dispersions was fully realized. Chatham⁵⁷ reported the possibility of preparing PEG-based solid dispersions by filling drug-PEG melts in hard gelatin capsules. By using PEG with molecular weights ranging from 1000 to 8000, Serajuddin et al.,⁵⁸ however, demonstrated that a PEG by itself might not be a suitable carrier for solid dispersion of poorly water-soluble drugs intended for direct filling into hard gelatin capsules. They dissolved a poorly water-soluble drug, REV5901, in molten PEG 1000, PEG 1450, and PEG 8000 and filled the hot solutions into hard gelatin capsules such that each size 0 capsule contained 100 mg of drug and 550 mg of PEG. At room temperature, solid plugs were formed inside the capsules, where the drug remained molecularly dispersed in the carriers. Although a sink condition existed for the dissolution of 100 mg of the weakly basic REV5901 ($pK_a \sim 3.6$) in 900 mL of simulated gastric fluid (drug solubility = 0.7 mg/mL at 37 °C), the dissolution of drug from all PEG-based solid dispersions was incomplete.

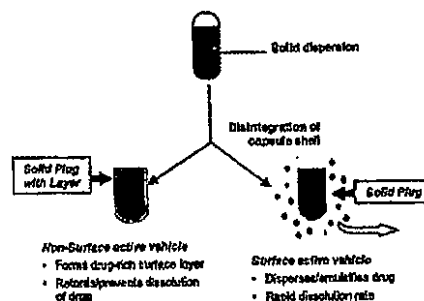


Figure 2—A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus nonsurface-active vehicles.

Because the water-soluble carrier dissolved more rapidly than the drug, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from solid dispersions. The dissolution was practically zero at $pH > 2$, where the solubility of drug was low and a drug layer coated the surface of the solid plug as soon as the capsule shell disintegrated. Corrigan⁵⁹ also reported the possibility of such a retardation of drug dissolution from solid dispersions.

Surface-Active Carriers—The direct filling of melts into hard gelatin capsules would not be a viable method for the preparation of solid dispersions unless the formation of drug-rich layers on the surfaces of dissolving plugs could be prevented. Serajuddin et al.^{58,60} achieved a complete dissolution of drug from solid dispersions by using surface-active or self-emulsifying carriers. The vehicles acted as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers. Although the liberated drug remained undissolved in the dissolution medium when its concentration exceeded its saturation solubility, it was dispersed or emulsified in a finely divided state because of surface activity of the dissolved vehicle.^{59,60} The high surface area of a drug produced in this way would facilitate its dissolution in the gastrointestinal fluid, especially in the presence of bile salts, lecithin, and lipid digestion mixtures.⁶¹

The advantage of a surface-active carrier over a nonsurface-active one in the dissolution of drug from a capsule formulation is shown schematically in Figure 2.⁶ The physical state of drug in a solid dispersion must, however, be carefully considered in evaluating the advantage of a surface-active vehicle. As mentioned earlier, the drug can be molecularly dispersed in the carrier to form a solid solution or it can be dispersed as particles. It can also be both partially dissolved and partially dispersed in the carrier. The potential for the formation of a continuous drug-rich surface layer is possibly greater if the drug is molecularly dispersed, whereas the drug dispersed as particulates may be more prone to dissociation from the water-soluble matrix. It is, however, rare that the drug is dispersed just as particulates and is not at least partially dissolved in the vehicle. Therefore, a surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs.

The interest in surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs increased greatly in recent years.^{58,60,62–67} For ease of manufacturing, the carriers must be amenable to liquid filling into hard gelatin capsules as melts. The melting temperatures of carriers should be such that the solutions do not exceed ~ 70 °C, which is the maximum acceptable temperature for hard gelatin capsule shells.⁶⁸ Some of the manufacturing difficulties mentioned earlier may be en-

countered if solid dispersion products using surface-active carriers are prepared by methods other than direct filling into hard gelatin capsules; for examples, the solvent evaporation method,⁵⁹ compaction into tablets from granules,⁵⁷ etc.

One surface-active carrier that has commonly been used in solid dispersion for the bioavailability enhancement of drugs is Gelucire 44/14 (Gattefossé Corp., France).^{50,62-65,67} It is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopeia as lauryl macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value. Another surface-active carrier that generated certain interest in recent years is Vitamin E TPGS NF (Eastman, Kingsport, TN),⁷⁰ which is prepared by the esterification of the acid group of *D*- α -tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point is, however, relatively low (38 °C) and it may require mixing with other carriers to increase melting temperatures of formulations.

In search of alternative surface-active carriers, Serajuddin and co-workers^{60,71} demonstrated that a commonly used surfactant, polysorbate 80, could be used in solid dispersions by mixing it with solid PEG. Although polysorbate 80 is liquid at room temperature, it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure. As high as 50% (w/w) polysorbate 80 could be incorporated in a PEG with a lowering of <6 °C in its melting point. Even when 75% (w/w) polysorbate 80 was incorporated, PEG remained semisolid, and the lowering of the melting temperature of the PEG used was <12 °C.⁷¹ The crystalline structure of solid PEG was minimally affected by polysorbate 80 because the two compounds have low miscibility in each other. Other investigators also reported enhanced dissolution⁷² and bioavailability⁶³ of drugs from PEG-polysorbate carriers. Law et al.⁷³ reported a >2-fold increase in the dissolution rate of nifedipine from a PEG-based solid dispersion after incorporation of 5% (w/w) phosphatidylcholine. Increased dissolution rate of drug from solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and polysorbate 80, were also reported by Sjökvist et al.⁷⁴ The authors, however, pulverized the waxy material instead of filling them into hard gelatin capsules as melts.

Ease of Manufacturing—Cadé and Madt⁷⁵ and Shah et al.⁷⁶ reviewed various formulation and processing considerations for liquid-filled hard gelatin capsules. Initial formulation development studies can be conducted by filling hot solutions or dispersions into hard gelatin capsule shells manually by using pipets or by using laboratory scale semiautomatic equipment.⁷⁷ Equipment is also available to scale up the manufacturing process and for large scale manufacturing.⁷⁸ As mentioned earlier, the temperature of solutions during the filling of hard gelatin capsules should not exceed 70 °C.⁶⁸ Solutions can also be filled into soft gelatin capsules for which the solution temperature should remain <40 °C.⁷⁹ Several hard gelatin^{80,81} and soft gelatin⁸² capsule products prepared according to these techniques have been marketed in recent years.

Bioavailability Enhancement—The reports on the bioavailability enhancement by solid dispersion in surface-active carriers are promising. The human bioavailability of the poorly soluble REV5901 from a solid dispersion in Gelucire 44/14 under a fasting regimen was much higher than that of a tablet formulation even though the micronized form of drug and a wetting agent were used in the tablet.⁸³ The bioavailability of ubidecarenone in dogs from solid dispersion in Gelucire 44/14 and the Gelucire 44/14—

lecithin mixture were, respectively, two and three times higher than that of commercially available tablet.⁸³ The bioavailability of another poorly water-soluble drug, RP69698, in dogs was 4.5 times higher (27.6% versus 6%) from its solid dispersion in a PEG 3350—Labrasol—polysorbate 80 system than from an aqueous suspension in 0.5% methylcellulose.⁶⁵ Aungst et al.⁶⁷ reported that the bioavailability of an HIV protease inhibitor, DMP323, in dogs from a PEG-based formulation decreased from 49.6 to 5.2% when the dose was increased from 100 to 350 mg. No such drastic decrease in bioavailability was observed in a Gelucire 44/14-based formulation of DMP323; the bioavailability values were 68.9 and 49.5% after doses of 85 and 350 mg, respectively. The bioavailability of ritonavir (Norvir, Abbott), another poorly soluble HIV protease inhibitor (solubility <1 µg/mL at pH >2), was enhanced by formulation as a solid dispersion in a mixture of such surface-active carriers as Gelucire 50/13, polysorbate 80 and polyoxyl 35 castor oil.⁸⁴

Special Considerations for Surfactant-Based Solid Dispersions—Solid dispersion in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drugs. One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers.^{64,65} The desired doses of a drug cannot be solubilized and filled into hard gelatin capsules if adequate solubility in a carrier cannot be obtained. Dordunoo et al.⁶⁴ reported that the particle size of a drug in a solid dispersion remained unchanged if it is just mixed with the carrier instead of dissolving in it. On the other hand, if the drug is dissolved by heating in excess of its solubility in the carrier under normal storage condition, it may subsequently crystallize out from the solid dispersion. Either situation would defeat the purpose of bioavailability enhancement of poorly water-soluble drugs by solid dispersion, as described in Figure 1.

The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market.⁸⁵ The crystallization of drug adversely influenced the dissolution of the ritonavir capsule, and the product was switched to a thermodynamically stable solution formulation. Aungst et al.⁶⁷ also stressed the importance of drug solubility in carriers in the development of capsule formulations. They prepared high-dose formulations of a water-insoluble HIV protease inhibitor by dissolving it in carriers at an elevated temperature only, and the formulations were used for bioavailability testing in dogs within 24 h of preparation when no crystallization occurred. The authors cautioned that precipitation of drug could occur upon storage at room temperature over a longer period of time, and that lowering of drug concentration in the carrier would be necessary to ensure long-term physical stability of the formulation.

To ensure that a drug would not crystallize out of solid dispersion at the desired storage temperature, it is important to screen the drug solubility in different carriers at such a temperature. However, no practical method for determining or estimating drug solubility in a carrier at a relatively low temperature, where the carrier exists in a solid state, has been reported in the literature. The relative solubility of a drug in different carriers may be determined by equilibrating the drug at an elevated temperature where all the carriers exist in a liquid state.⁶⁷ If the solubility of a drug in a carrier at an elevated temperature is much higher than the concentration required for solid dispersion, an accurate estimation of solubility at room temperature might not be necessary and a reasonable assumption might be made that the drug would not precipitate out. When a better estimation of solubility is needed, one practical

approach is the determination of solubility-temperature relationship of drug in a chemically related carrier that exists as liquid at a wider range of temperature. For example, for the purpose of estimating the solubility of a drug in a solid PEG at room temperature, the solubility may be determined at an elevated temperature where the PEG exists in a liquid state. Then the solubility of drug at a lower temperature may be estimated from the solubility-temperature relationship in a related vehicle, PEG 400, which remains liquid at a wider range of temperature. This method assumes, however, that similar temperature-solubility relationships for the drug would exist in both PEGs and that the relationship would not change when one of them solidifies. The solubility may also be estimated by microscopic examination of solid solutions with increasing drug concentration for any possible crystallization of drug, assuming that the drug does not exist as a separate amorphous phase and the crystallization occurs in a relatively short period of time. A similar microscopic technique was used for determining the solubility of diazepam in liquid crystalline phases of lecithin.⁶⁷

Another possible limitation of the use of surface-active carrier reported by Aungst et al.⁶⁷ is that the bioavailability of a drug may vary depending on the amount of carrier administered along with it. This variation is because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid. Serajuddin et al.^{58,60} reported a method whereby the rate and efficiency of dispersion of drug in aqueous media from different formulations can be studied.

In addition to the solubility, careful attention must be given to the drug-to-carrier ratio in the successful development of a formulation. When the solubility of a particular drug is relatively low, a high drug-to-carrier ratio is necessary to deliver it in a solubilized state, and, therefore, the dose has to be low if it is desired that the total dose is delivered as a single unit. As mentioned earlier, any attempt to supersaturate the drug in solid dispersion to reduce drug-to-carrier ratio may lead to stability problems and, ultimately, to product failure.

Attention should also be given to optimization and validation of the manufacturing process. It is not only that the physicochemical properties of the drug is affected by the cooling rate, the properties of carriers in a solid dispersion might also be influenced by the solidification rate of the product.^{68,69} The implication of this observation on bioavailability and stability of drug product is not known.

Future Prospects

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into hard gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts

of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may be the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and *p*-glycoprotein-mediated drug efflux, will require careful consideration.⁶⁰

In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Although a review of literature on this aspect of solid dispersion is outside the scope of the present article, it may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule-filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use,⁶¹ it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market.⁶⁶ so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability. Possible drug-carrier interactions must also be investigated.

Although, as mentioned earlier, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports on the scale up of the technology. Further studies on scale up and validation of the process will be essential. Many problems and challenges still remain with solid dispersion systems. Nevertheless, as a result of recent breakthroughs, it will continue to be one of the exciting frontiers of drug development.

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Evaluation of the Bioavailability of a Solid Dispersion of Phenytoin in Polyethylene Glycol 6000 and a Commercial Phenytoin Sodium Capsule in the Dog

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Abstract □ In this study a solid dispersion of phenytoin in polyethylene glycol 6000 was prepared by the melt method. The content uniformity of the dispersion indicated a range of 98.7–102.0%. X-ray crystallographic data showed no changes in the crystalline structure of the phenytoin in the dispersion when compared with that in the bulk reagent. Scanning electron micrographs of the dispersion show a reduction in the size of the crystals when compared with the bulk reagent. The commercial product and the dispersion were compared using the USP criteria for the prompt phenytoin sodium dissolution test. The salt dissolved at a rate four times greater than the dispersion. Bioequivalency comparisons between the dispersion containing phenytoin and the commercial prompt phenytoin sodium were studied in six mixed-breed dogs. All samples were analyzed using a commercial enzyme immunoassay system. Statistical analysis of the plasma levels obtained from the animal studies indicate no significant differences ($p > 0.05$) between area under the curve, maximum plasma concentration, and time to peak for the commercial salt and the acid formulation.

Keywords □ Phenytoin—bioavailability of the acid and sodium salt in dogs, comparison with *in vitro* dissolution data □ Dissolution—phenytoin and phenytoin sodium *in vitro*, comparison to the *in vivo* bioavailability in dogs

The use of finely subdivided or micronized particles as a means of increasing the rate of dissolution has been considered (1–4). Theoretically, if the dissolution rate is enhanced, the oral absorption rate should be increased if the absorption process is dissolution rate limited. Sekiguchi *et al.* proposed using an inert water-soluble material as a vehicle for a poorly water-soluble drug to enhance the rate and extent of the absorption of the drug (5, 6). Several carriers have been employed to prepare solid dispersions. The most successful include polyethylene glycols (7–11), urea (12), dextrose (12), citric acid (12), succinic acid (13), and polyvinylpyrrolidone (14, 15). Polyethylene glycols have been used to increase the dissolution rate of griseofulvin (7), coumarin (8), dicumarol (9), indomethacin (10), and glyburide (11).

Phenytoin is practically insoluble in water ($\approx 14 \mu\text{g/mL}$)

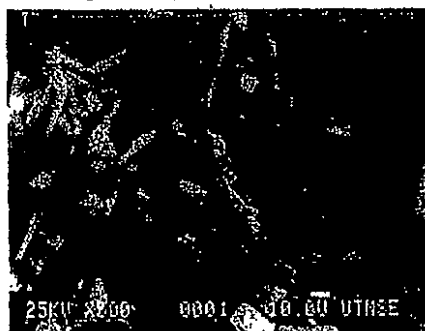


Figure 1—Photomicrograph of the reagent-grade phenytoin (5,5-diphenylhydantoin). The 10- μm calibration bar is located in the lower right corner.

at room temperature (16), whereas the solubility of phenytoin sodium is $\approx 66 \text{ g/dL}$ in water (17). This difference in solubility results in higher bioavailability for the salt (18–20). If the poor solubility of phenytoin in GI fluids is partially responsible for the great variability observed in phenytoin dosing, then enhancing the dissolution step may result in a more uniform absorption and improved bioavailability.

The purpose of this study is to evaluate the bioavailability in dogs of a phenytoin solid dispersion in polyethylene glycol 6000 using a commercial prompt phenytoin sodium capsule as the reference formulation. Data are presented which indicate that the phenytoin dispersion is bioequivalent to the commercial prompt phenytoin sodium, which is contrary to what one would expect based on the *in vitro* data obtained from the USP dissolution test for phenytoin sodium. The designation "prompt" refers to the fast dissolution category of phenytoin sodium set forth in the USP XX.

EXPERIMENTAL

Preparation of Formulation—A 40% (w/w) solid dispersion of phenytoin¹ in polyethylene glycol 6000² was prepared using a melt method. The polymer was melted in a beaker on a thermostatically controlled hot plate at ≈ 65 – 70°C . The reagent phenytoin was added with constant stirring until a clear liquid was observed. This liquid was poured into a glass mortar which was encased in ice. Solidification of the melt occurred on contact. The mass was dried in an oven at $\approx 40^\circ\text{C}$ for at least 1 h to remove excess moisture. The melt was triturated and then dried for at least 6 h. The powder was sieved through a 60-mesh sieve, and the batch was divided into 750-mg units.

Content Uniformity—Five of the 750-mg units of the phenytoin-polyethylene glycol 6000 dispersion were each dissolved in 1000 mL of 0.1 M NaOH, pH 12.5, in volumetric flasks. Duplicate samples were assayed using a commercial enzyme immunoassay³. The five determinations resulted in 98.7–102.0% of the theoretical amount.



Figure 2—Photomicrograph of the 40% phenytoin solid dispersion. The 10- μm calibration bar is located in the lower right corner.

¹ 5,5-Diphenylhydantoin, 99+%, Gold Label; Aldrich Chemical Co., Milwaukee, Wis.
² Lot B-586; Alcon Laboratories, Fort Worth, Tex.
³ EMIT System; Syva Co., Palo Alto, Calif.

Attachment D

Table I—Pharmacokinetic Parameters Obtained in Plasma after Oral Administration of Phenytoin

Parameter	Treatment A ^a		Treatment B ^b	
	Observed Mean (SD)	Calculated Mean ^c	Observed Mean (SD)	Calculated Mean ^c
C_{max} ($\mu\text{g/mL/kg}$)				
All subjects	0.20 (0.076)	0.20	0.22 (0.10)	0.24
Excluding dog 3	0.18 (0.063)	0.18	0.19 (0.049)	0.19
T_{peak} (h)				
All subjects	5.1 (0.41)	3.8	4.5 (1.2)	3.6
Excluding dog 3	5.2 (0.45)	4.0	4.4 (1.3)	3.6
AUC_{0-12} ($\mu\text{g/mL/h}$)				
All subjects	1.49 (0.602)	1.48	1.60 (0.808)	1.52
Excluding dog 3	1.37 (0.585)	1.33	1.22 (0.470)	1.22

^a 300 mg of commercial prompt phenytoin sodium. ^b 750-mg of the 40% phenytoin solid dispersion. ^c Calculated values were obtained using Eq. 2.

icles (Fig. 2) shows no large, discrete crystals in the formulation. The majority of the dispersion particles were $\leq 30 \mu\text{m}$. A very small percentage exceeded $50 \mu\text{m}$. An accurate estimate of the size of the phenytoin crystals in the dispersion could not be made, although some crystalline shapes could be discerned in the particles. Since none of the large rectangular crystals ($>40 \mu\text{m}$) observed in the reagent were noted in the dispersion or the residue, the formulation method used in this study must have reduced the particle size of the crystals. This probably occurred during the rapid solidification of the melt and during the trituration steps.

There is no compendial dissolution medium recommended for the comparison of the phenytoin and its sodium salt. Dissolution criteria do exist for the prompt and extended phenytoin sodium. These criteria were utilized to compare the dissolution rates of the phenytoin solid dispersion and the commercial prompt phenytoin sodium. Use of this dissolution test would indicate whether the commercial prompt phenytoin sodium samples would meet compendial standards. It would also serve to indicate whether one could use these dissolution criteria to compare two chemically different commercially available phenytoin products: the salt and the acid. The USP dissolution test for phenytoin sodium stipulates the use of 900 mL of water at $37 \pm 0.5^\circ\text{C}$ in Apparatus 1⁶ (basket assembly) rotating at 50 rpm.

Prior to the dissolution test, all samples were placed in size 1 gelatin capsule. This was done to compare the rates of dissolution from a uniform capsule size. The percent dissolved of the commercial prompt phenytoin sodium at 30 min was 75.9%, which is much greater than the value obtained at 30 min for the solid dispersion (14.1%), or the reagent phenytoin (7.3%). At 60 min, 22.2 and 11.4% of the solid dispersion and the reagent phenytoin, respectively, were dissolved. After 180 min the percent dissolved in both preparations was almost equal: 29.4% for the reagent and 29.2% for the dispersion. The commercial prompt phenytoin sodium was 91.5% dissolved at 60 min.

The faster dissolution rate of the dispersion, when compared with the reagent phenytoin, may be due to the particle size reduction as previously noted in the electron micrographs. The X-ray diffraction data indicate that any change in the solubility of the two phenytoin samples cannot be due to a more-soluble polymorph existing in the dispersion. Comparison of the rate of dissolution of each preparation is presented in Fig. 3. Each point represents six capsules sampled and assayed in duplicate.

The USP states that at least 85% of a commercial prompt phenytoin sodium capsule should be dissolved in 30 min. Two of the size 1 capsules containing the transferred commercial prompt phenytoin sodium did not meet this specification. Thus, an additional study was undertaken. Six intact 100-mg capsules from the same lot were tested using the USP basket dissolution method as specified for phenytoin sodium capsules. At 30 min duplicate samples were taken and filtered through a $0.45\text{-}\mu\text{m}$ filter. Samples were kept in a water bath at $\sim 37^\circ\text{C}$ and assayed within 1 h after sampling. Each sample was assayed in duplicate. The six intact capsules showed an average dissolution of 81.5%, with $SD = 14.5$ and $CV = 17.8\%$. The large variation noted in the six capsules may be due to two samples that had capsule-shaped masses which remained in the rotating basket apparatus after 30 min. The presence of these masses after a dissolution test has been noted in a previous study done with commercial phenytoin sodium products (25). A Student's t test was done to compare the data obtained from the transferred capsules versus the intact capsules. No significant difference was found ($\alpha = 0.05$).

In Vivo Studies—Each animal received 750 mg of the 40% solid dispersion, 300 mg of the commercial prompt phenytoin sodium, or 300 mg of the commercial intravenous phenytoin sodium. The oral doses were administered in three hard gelatin capsules. The 300-mg dose of each oral formulation was used to represent actual dosage strengths commercially available and dosing practices. The individual plasma levels obtained from these treatments are

represented in Figs. 4 and 5. The plasma levels of the phenytoin sodium were normalized according to the phenytoin. It should be noted that dog 3 exhibits the highest blood levels in both Figs. 4 and 5. The difference in the curves demonstrates the effect of dog 3 on the data. Therefore, the t tests on C_{max} , T_{peak} , and AUC_{0-12} were done with and without the data obtained from dog 3. These data are presented in Table I. All areas were calculated using the trapezoidal rule. The probability values in the t tests, C_{max} , and AUC were the same regardless of whether or not dog 3 was included. In all cases, $p > 0.2$.

Speculation on the cause of the large difference in the C_{max} found in dog 3 should include the observation that phenytoin exhibits nonlinear kinetics in dogs (26). Dog 3 was also the smallest dog and, therefore, received the largest mg/kg dose since all subjects received the same amount. It is possible that the small increase in the amount of phenytoin in the dispersion, when

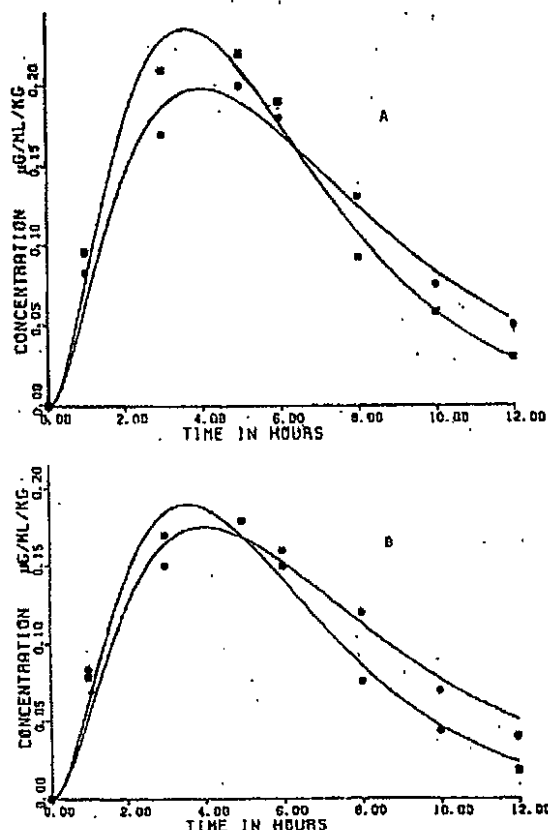


Figure 6—Plots obtained from fitting averaged data to Eq. 2. Plot A represents the fit of all six animals, plot B represents the fit without the data from dog 3. Key: (■) 40% phenytoin dispersion; (●) commercial prompt phenytoin sodium.

⁶ East-Lab Dissolution Test Station; Hanson Research Corp., Northridge, Calif.

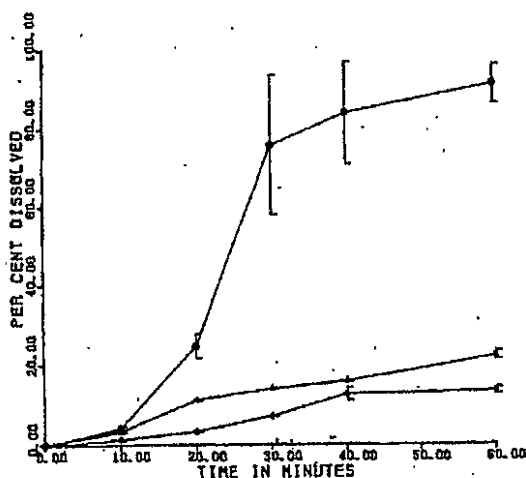


Figure 3—Dissolution of the test preparations. Each point represents six capsules sampled and assayed in duplicate. All doses are equivalent to 92 mg of phenytoin. Key: (●) 100 mg of prompt phenytoin sodium; (▲) 230 mg of 40% solid dispersion of phenytoin in polyethylene glycol 6000; (◆) 92 mg of the reagent phenytoin. Bars represent 1 SD.

Assay Procedure—A commercial enzyme immunoassay technique was utilized to assay all samples. This technique has been shown to be comparable in specificity and reproducibility (21, 22) to RIA (21, 23) and GC (21-24), and superior to spectrophotometry (21, 23). The range recommended was expanded by adding or deleting one dilution. Calibrated solutions provided by the manufacturers were used to check the effect of dilutions of samples on accuracy. A coefficient of variation of <10% was observed in each procedure.

Electron Microscopy—The sizes of the various particles were estimated by observation under a scanning electron microscope. Figure 1 shows a sample from the reagent phenytoin. A great variability in dimensions is observed. Figure 2 is a micrograph of the dispersion particles. The large particles are $\sim 10 \times 40 \mu\text{m}$ with several smaller fragments.

Dissolution Studies—Six 100-mg capsules of the commercial prompt phenytoin sodium were compared with six 92-mg samples of the reagent phenytoin and six 230-mg samples of the 40% (w/w) solid dispersion. All

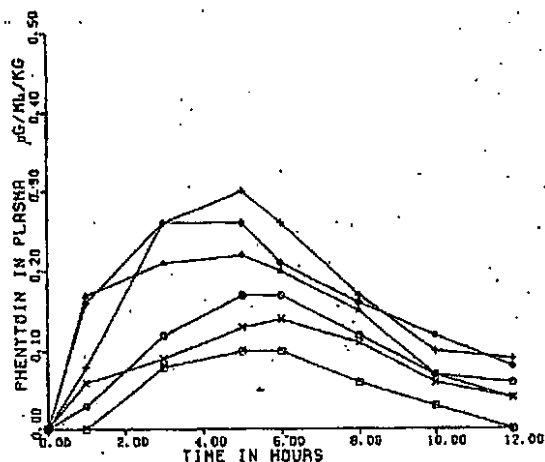


Figure 4—Observed plasma concentrations of phenytoin obtained from six dogs (13-24 kg). Each animal received 300 mg of the prompt phenytoin sodium.

* Millipore Corp., Bedford, Mass.

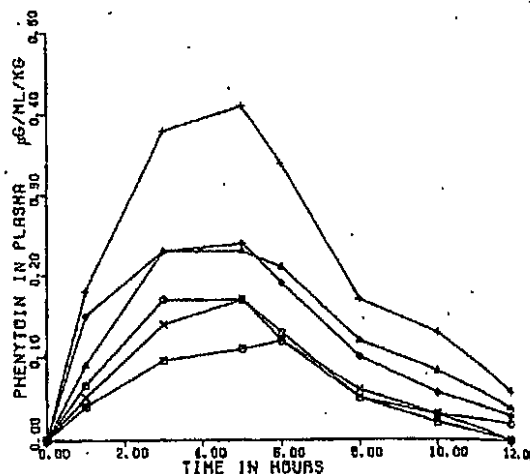


Figure 5—Observed plasma concentrations of phenytoin obtained from six dogs (13-24 kg). Each animal received 750 mg of the 40% phenytoin solid dispersion.

samples, equivalent to 92 mg of the phenytoin, were placed in size 1 gelatin capsules. The dissolution criteria were those stipulated for the oral phenytoin sodium in the USP XX. Duplicate samples were drawn and filtered through $0.45\text{-}\mu\text{m}$ filters⁴, and were assayed at least twice. An additional study of six intact commercial prompt phenytoin sodium capsules using the same criteria was also performed.

X-ray Diffraction—Spectra were obtained from the reagent phenytoin, polyethylene glycol 6000, and the dispersion. A scanning rate of $3^\circ/\text{min}$ was made from 6° to 70° . The minimum peak height was 2% of the reference peak. Spectra indicate that the phenytoin in the dispersion is the same crystalline form as that in the reagent. Also, no change was noted in the polyethylene glycol 6000 spectra.

Bioequivalence Studies—Six mixed-breed dogs (three of each sex), $\sim 13\text{-}24$ kg in weight, were used in this study. The animals were housed at the Animal Resources Center, The University of Texas. The dogs were fasted overnight prior to drug administration; water was allowed *ad libitum*. Each animal received 30 mL of water prior to and immediately after oral administration. The dogs were observed for 30 min and then returned to their cages for blood sampling.

The experimental design in the study is a balance of preparations over weeks and each animal received each preparation. The design was repeated twice for a total of two Latin squares. Two dogs received either 300 mg of the commercial prompt phenytoin sodium, 300 mg of phenytoin in the 40% dispersion, or 300 mg of a commercial intravenous phenytoin sodium on each study day. Studies were separated by 1-week wash-out periods to allow for drug elimination as well as to allow for stabilization of the animals' blood volume.

Blood samples were drawn by serial venipuncture. Sampling times after oral administration were at 0, 1, 3, 5, 6, 8, 10, 12, 24, 72, and 96 h. Samples were drawn at 0, 10, 20, 30, 45, and 60 min, and 2, 4, 12, 24, 48, 72, and 96 h after intravenous infusion at 50 mg/min. All blood samples were collected in heparinized evacuated tubes⁵ which were gently inverted to allow for complete mixing. The samples were centrifuged at 2500 rpm for 15 min. The plasma was transferred into polyethylene tubes and frozen until assayed.

Statistical Analysis—A three-way ANOVA was performed on the *in vivo* data. The *F* ratio, as expected, was significant ($\alpha = 0.05$) for the intravenous data for AUC_{0-12} when compared with either of the oral preparations. The *F* ratio was not significant ($\alpha = 0.05$) when the two oral formulations were compared. Paired *t* tests compared the 40% phenytoin solid dispersion and the commercial prompt phenytoin sodium; this resulted in $p > 0.2$ for C_{max} , t_{peak} , and AUC_{0-12} .

RESULTS AND DISCUSSION

In Vitro Studies—Figure 1 is the electron micrograph of the reagent phenytoin. It shows a great variation in crystal size; many of the crystals exceed $40 \mu\text{m}$ in length and $10 \mu\text{m}$ in width. The micrograph of the dispersion par-

⁵ Vacutainer, B. D. Dickinson & Co.

Table II—Estimates of the Parameters Obtained from the Averaged Phenytoin Plasma Concentrations Utilizing Eq. 2

Parameter	Treatment ^a			
	A	B	C	D
k_1 (h ⁻¹)	0.557	0.434	0.419	0.447
k_2 (h ⁻¹)	0.721	0.820	1.20	1.19
k_e (h ⁻¹)	0.414	0.482	0.268	0.241
C_0 (μg/mL/kg)	0.673	0.632	0.460	0.379

^a Key: (A) 750 mg of 40% phenytoin solid dispersion, $n = 6$; (B) 750 mg of 40% phenytoin solid dispersion, $n = 5$ (without dog 3); (C) 300 mg of commercial prompt phenytoin sodium, $n = 6$; (D) 300 mg of commercial prompt phenytoin sodium, $n = 5$ (without dog 3).

compared with the same milligram dose of the salt, may have been enough to cause this animal to enter the nonlinear kinetics range.

The averaged data were fitted to a model with two first-order input steps:



where k_1 and k_2 are the apparent first-order rate constants for the overall absorption process and k_e is the apparent elimination rate constant. The equation used to calculate the theoretical line is:

$$C_t = k_1 k_2 C_0 \left[\frac{e^{-k_1 t}}{(k_2 - k_1)(k_e + k_1)} + \frac{e^{-k_2 t}}{(k_1 - k_2)(k_e - k_2)} + \frac{e^{-k_e t}}{(k_1 - k_e)(k_2 - k_e)} \right] \quad (\text{Eq. 2})$$

where C_0 is the fraction of the dose absorbed divided by the volume of distribution.

The estimates for k_1 , k_2 , k_e , and C_0 were obtained using a nonlinear digital computer program (27) and are presented in Table II. The plots of the average data and the lines generated from Eq. 2 are represented in Fig. 6. Other equations representing biexponential or triexponential oral absorption models, including those that utilized a lag time, were attempted; however, this fit resulted in a smaller sum of squared deviations and larger r and r^2 values. Weights of 1 were used. The parameters obtained were used to calculate the $AUC_{0-\infty}$, C_{max} , and t_{peak} . Good agreement is observed between the estimates obtained from the computer fits and the observed data, as seen in Table I. The relative bioavailability of the observed data is 1.01 for all subjects and 0.90 when excluding dog 3.

The data indicate that the dispersion is bioequivalent to the commercial prompt phenytoin sodium whether or not the data from dog 3 are included in the statistical analysis. Since the solubility of the salt and the acid are very different, the formulation method must be partially responsible for the increased acid solubility. The particle size reduction, as verified by the micrographs, of the phenytoin has been shown to increase plasma levels in dogs (18). The polyethylene glycol 6000 may have also affected the solubility of the dispersion. Previous studies have stated possible vehicle effects: a solubilizing effect by the vehicle (13), increased wettability (5), and a decrease in aggregation and agglomeration in hydrophobic drugs (28).

In this study, the combined effects of phenytoin crystal size reduction and any vehicle effects demonstrated bioequivalency with the much more water-soluble salt. This contradicts the *in vitro* dissolution study, which demonstrated a fivefold difference in the percent dissolved at 30 min, and a fourfold difference at 60 min. If the absorption of phenytoin is dissolution rate limited, then a significant difference should exist in the blood levels obtained from these two products. But according to the C_{max} , t_{peak} , and AUC data obtained from the animal studies, no statistical difference exists. This implies that the dispersion method must have increased the bioavailability of phenytoin.

It is possible that the particle size reduction and any vehicle effects on the *in vivo* microenvironment may be responsible for the increased dissolution rate of phenytoin. It is also possible that in an aqueous acidic environment, the relatively high concentration of free phenytoin provided by the dissolution of the salt may result in some precipitation of the free acid, as has been previously postulated (29). If this occurred, then the rate of absorption of the precipitated crystals may be comparable to the rate of absorption of the reduced crystals found in the 40% solid dispersion, and thus, demonstrate

bioequivalency. If, indeed, this is a valid consideration, then any conclusions based on the greater dissolution rate of the salt implying better bioavailability must be reexamined.

The results of this study indicate that the phenytoin solid dispersion dissolution profile does not meet the criteria used by the USP XX to define a "prompt" phenytoin sodium, yet the dispersion was found to be bioequivalent to the prompt phenytoin sodium. Unless the vehicle played a very significant part in the phenytoin-microenvironment interaction *in vivo*, the use of a more representative dissolution medium to simulate the gastric fluid should be considered to improve the *in vitro-in vivo* correlation of the different phenytoin products. This study demonstrates once again the difficulties that may be encountered when selecting appropriate dissolution criteria to predict bioavailability.

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PT 6089

DISSOLUTION ENHANCEMENT OF THREE GLUCOCORTICOSTEROIDS USING CYCLODEXTRINS AND LIQUIDSOLID COMPACT TECHNOLOGY.

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Proflonon, prednisolone and hydrocortisone, three water-insoluble glucocorticosteroids, were used as the model drugs to study the effects of cyclodextrins on the release properties of liquidsolid systems. Liquidsolid compact technology enables one to convert liquid lipophilic medications, or solutions of nonpolar drugs in cosolvents, into acceptably flowing and compressible admixtures by simple blending with calculated amounts of selective powders. The enhanced release profiles exhibited by such systems are due to the increased wicking properties and surface of drug available for dissolution. On the other hand, beta-cyclodextrins (β -CDs) are widely claimed as an effective formulation additive which enhances, in various contexts, the dissolution of water-insoluble and poorly bioavailable drugs. In the present studies, the dissolution profiles of these three glucocorticosteroids prepared in liquidsolid tablets containing various β -CD levels were evaluated. Two types of β -CDs, namely, Kleanco[®] (plain β -CD) and Kleptose[®] DC (direct compression β -CD), were used. Moreover, reference tablet formulations, such as direct compression variations of the drugs with or without β -CDs, and plain liquidsolid compacts of the drugs, were prepared and their release properties were compared to those of liquidsolid formulations containing β -CDs. The obtained dissolution data indicated that the inclusion of almost negligible amounts of β -CDs in liquidsolid compacts, contributes in significantly improving (up to 50% higher) the inherent drug release rates. Since plain liquidsolid compacts have already displayed superior *in-vitro* release patterns as compared to commercial products, the present findings imply that liquidsolid compacts combined with β -CDs might be an even more promising formulation alternative for the production of rapid-release and hence, readily bioavailable solid dosage forms of water-insoluble drugs.

PT 6090

NON-CRYSTALLINITY, SUPERSATURATION AND RELATIVE BIOAVAILABILITY: EXPERIENCES WITH A NON-PEPTIDIC HIV-PROTEASE INHIBITOR. RJWald¹, GLZipp, LShiao, LLConnell, ACMartino, JASyama, MJBurwart, EDRush, KFWilkinson, WYZhong, MGWilliams. The Upjohn Company, Kalamazoo, MI, USA.

U-103017 is a weakly acidic non-peptidic HIV Protease Inhibitor with a low solubility (4-12 μ g/ml over pH 2-6), a log P_{ow} = 4.6, and a MW=182¹. Oral absorption of disodium salt (solubility > 500 mg/ml) and solution formulations is very good in both dogs and humans; however, absorption of crystalline free acid (FA) is extremely poor. Particle size reduction only marginally improves FA absorption. This report will show, however, that if FA is presented in a non-crystalline (NC) state, oral relative bioavailability (Beagle dogs) is comparable to salt formulations. NO FA formulations evaluated include a suspension of amorphous FA and both enteric and non-enteric solid solution powders prepared by spray drying. *In-vitro* dissolution at pH 5 and 6 shows that NC FA and salt formulations both produce highly supersaturated solutions that are maintained for >8 hours. The NC FA formulations dissolve directly to form clear supersaturated solutions. The salt first precipitates as amorphous FA particles; these then dissolve to form clear supersaturated solutions. Seeding of supersaturated solutions with crystalline FA results in a decline (hrs) in U103017 concentration to the limiting solubility. Solid dispersion formulations that contain a mixture of NC and crystalline FA result in intermediate bioavailability. They also exhibit dissolution profiles with partial supersaturation then spontaneous decline, presumably due to the crystal seeds present in the formulations. We conclude that U-103017's propensity to form stable supersaturated solutions *in-situ* is responsible for the excellent absorption observed from both salt and NC FA formulations.

PT 6091

USE OF A MCCORNE MICRONIZING MILL FOR SMALL SCALE MILLING/MICRONIZATION OF RADIOACTIVE, TOXIC OR POTENT DRUGS. RJWald¹, RSHaf, JAEaster, LJLarson, GEAmdon, GLZipp, and RHMcAury. The Upjohn Company, Kalamazoo, MI, 49001.

The McCrone Micronizing Mill (McCrone Research Associates Ltd., London, England), a batch vibratory mill that uses a 5x3 ordered array of agate cylinders in a sealed grinding jar, has been shown to be very useful for milling/micronizing small amounts of drugs that are radiolabeled, highly potent or toxic, or in short supply. Additionally, the mill (MMM) has been found to be useful for directly preparing suspensions of drugs for use in preclinical animal toxicity and metabolism studies. The batch size range has varied between 0.1 to 5.0 g, however 1-3 g is preferred. Although the MMM is capable of dry milling operations, wet milling in an appropriate nonsolvent has been found to be the safest and most efficient. Depending on the application, freeze drying, filtration/oven drying, and roto-evaporation have all been used to remove grinding fluid. Median particle sizes of under 5 μ m are routinely obtained; even submicron particle sizes are feasible for some materials. Data will be shown to illustrate the influence of drug type, grinding time, grinding fluid, particle size of the feed material, and drug:fluid ratio on resultant median particle size and distributions. Grinding time vs median particle size generally follows a log-linear relationship and the lot-to-lot precision is excellent. We conclude that the MMM is an ideal tool for these applications because it provides: a sealed milling chamber for operator safety, virtually 100% processing yield, efficient milling process with minimal heat stress, wet or dry processing options, portability, ease of operation and cleaning, and parameter controls to obtain a wide range of particle sizes.

PT 6092

VALIDATION STUDY OF "WET-GRANULE SIEVING" METHOD FOR ENDPOINT DETECTION. PART I. Ken Yamamoto, Randy J. Wald, Hisatoshi Enoki, Shouichi Narita, Teruhisa Yoshizawa, Toshiki Nishibata and Gregory E. Amdon. The Upjohn Company, Tsukuba, Japan and Kalamazoo, MI.

For a wet granulation process, the consumption of electricity and/or amperage of the main impeller is usually employed as an indicator for end-point determination. However these values are frequently dependent on equipment volume and design. To overcome this difficulty, a new *in-process* method has been developed which utilizes sonic sifting of the wet granulation. Since wet granulation progression is determined based on wet granule particle size, it is expected that this system will be independent of granulation equipment and design. The principle objective of the present study was to validate the "wet-granule sieving method" as a tool for monitoring the progression of the granulation process. Reproducibility of the method was evaluated by conducting three consecutive measures at different points during the granulation process. Small standard deviations at all time points for all particle sizes of wet-granules were obtained. The robustness of the wet granule sieving operating conditions was also examined: neither sieving intensity nor sieving time significantly influenced particle size results over the ranges investigated. However, the measured particle size distribution changed when "wet-granule" sample was left longer than 15 minutes. We conclude from these studies that the "wet granule sieving" method provides useful and reproducible data and that "wet fines" (fraction through 80 mesh; held on 82 μ m screen) serves as a rapid and flexible method for monitoring the progression of the granulation as well as for granulation endpoint detection.