

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Patente de Invención ☒ Patente de Modelo de Utilidad

Vía Nacional

Vía PCT (Fase Nacional) ☒ Capítulo I ☒ Capítulo II

Nº. Solicitud Internacional PCT/EP2007/005764
Fecha de Presentación Internacional 29/Junio/2007

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 94 a 158	06/Enero/2009
Reivindicaciones:	Folios 159 a 170	06/Enero/2009
	Folios 364 a 366	20/Septiembre/2010
	Folios 457 a 458	12/Enero/2012
Oposiciones:	Folios 197 a 238	Gynopharm 16/Julio/2010
	Folios 239 a 259	Lafranco 19/Julio/2010
	Folios 260 a 359	Tecnoquímicas 19/Julio/2010
	Folios 368 a 384	Tecnoquímicas 11/Octubre/2010
Respuesta del solicitante:	Folios 395 a 476	12/Enero/2012
Prioridad:	EP 06014002.7	06/Julio/2006

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

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3. Objeto de la invención

Título de la solicitud: "COMPOSICION FARMACEUTICA QUE CONTIENE UN ACIDO TETRAHIDROFOLICO"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una formulación anticonceptiva que permita corregir concentraciones séricas bajas de folato y garantizar la liberación de los principios activos.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica sólida que comprende un progestágeno, un estrógeno, un ácido tetrahidrofólico o una de sus sales, y por lo menos un excipiente o vehículo adecuado para uso farmacéutico.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 9/20 // 31/585 // 31/567 // 31/525; A 61 P 15/18

4. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque no define las características técnicas esenciales de la invención por cuanto las composiciones farmacéuticas que contienen un ácido tetrahidrofólico ya son conocidas en el estado de la técnica, por lo cual se sugiere al Solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es concisa cuando menciona los términos "un progestágeno" y "un estrógeno" los cuales no definen un componente como tal. Se observa según los ejemplos que el progestágeno utilizado corresponde a drospirona y el estrógeno utilizado corresponde a etinilestradiol. Se sugiere restringir la solicitud a los compuestos que han sido sintetizados ó probados, es decir, que se encuentran debidamente sustentados.

Las reivindicaciones 2 y 4 no se encuentran sustentadas en la descripción cuando mencionan varios principios activos de tipo progestágeno y estrógeno. Al revisar en la descripción se observa en los ejemplos que el progestágeno utilizado corresponde a drospirona y el estrógeno utilizado corresponde a etinilestradiol. Se sugiere restringir la solicitud a los compuestos que han sido sintetizados ó probados, es decir, que se encuentran debidamente sustentados.

5. Análisis de las Oposiciones

Argumentaciones de Gynopharm

Dice el oponente que esta solicitud pretende obtener patente para el uso de

composiciones farmacéuticas ya comprendidas en el estado de la técnica argumentando que el documento WO03070255 revela píldoras anticonceptivas que comprenden levonorgestrel, etinilestradiol, ácido fólico y excipientes y que por lo tanto la solicitud carece de novedad.

Argumentaciones de Lafranco

Afirma el oponente que esta solicitud pretende obtener patente para el uso de combinaciones farmacéuticas ya comprendidas en el estado de la técnica por lo cual anexa copias tomadas de "The Index Merck" referentes a Norgestrel, Dienogest, Ciproterona, Estradiol y Drospirenona y referencia los documentos BE623844, US3959322, DE 2718872, US4167517, DE1189991, US3234093, US2096744, DE2652761 y US 4129564 argumentando que las combinaciones reivindicadas por el solicitante comprenden moléculas plenamente identificadas y utilizadas.

Argumentaciones de Tecnouímicas

Afirma el oponente que esta solicitud pretende obtener patente para usos y métodos terapéuticos los cuales no son patentables. Refiere igualmente que el objeto de la solicitud ya es conocido en el estado de la técnica combinaciones farmacéuticas ya comprendidas en el estado de la técnica por cuanto ya se conocen los procesos de micronización de componentes dentro de una formulación farmacéutica así como los procesos de complejación con moléculas de un ligando como lo son las ciclodextrinas, al igual que los procesos de granulación utilizando lechos fluidizados y la adición de derivados de tetrahidrofolatos a métodos anticonceptivos orales. Motivo por el cual anexa los documentos WO99/53910, WO03/070255, el artículo científico "Folate and the risk of colorectal, breast and cervix cancer: the epidemiological evidence" y copias del texto "Tecnología Farmacéutica. Volumen I" referentes a compuestos cristalinos, formación de complejos, granulación y preparación de comprimidos. En una posterior ratificación de la oposición anexa los documentos "Carbohydrate metabolism during treatment with estrogen, progestogen, and low-dose oral contraceptives" y los abstracts de los documentos "Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol" y "Effect of Administration of a Combined Estrogen-Progestin Contraceptive on the Level of Individual Plasma Proteins".

Respuestas del Solicitante

El solicitante presenta un nuevo capítulo reivindicatorio en el cual se limita la Reivindicación 1 a una composición que contiene i) una sal farmacéuticamente aceptable del ácido 5-metil-(6S)-tetrahidrofólico, y ii) gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina. Anexa copias del texto "Remington's Pharmaceutical Sciences" referentes a preparación de fármacos poco solubles en la cual no se referencia la celulosa microcristalina como un diluyente a usar debido a su insolubilidad en agua al igual que el documento EP1214076 en el cual se divulga la importancia de proporcionar drospirenona en una forma de liberación inmediata y el documento "Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets" según el cual se explica que la

celulosa microcristalina se usa ampliamente como excipiente en los procesos de compresión directa pero no enseña nada respecto del empleo de la celulosa microcristalina en relación con la granulación. Motivo por el cual el solicitante considera que la solicitud es novedosa e inventiva con frente al arte previo citado por los opositores.

Respuesta del Examinador Técnico

El solicitante ha presentado un capítulo reivindicatorio modificado el cual se acepta por no corresponder a una ampliación de la materia y sobre el cual se analizarán si los documentos presentados por el oponente desvirtúan la novedad o el nivel inventivo.

El documento WO 03/070255 referenciado por Gynopharm y por Tecnoquímicas afecta la patentabilidad de la solicitud ya que divulga una composición que comprende una sal del ácido 5-metil-(6S)-tetrahidrofólico, un progestágeno, un estrógeno y excipientes.

En cuanto a los documentos presentados por Lafrancol, estos no afectan la patentabilidad de la solicitud debido a que el objeto de la solicitud se refiere a una forma de dosificación unitaria, oral y sólida que comprende una sal del ácido 5-metil-(6S)-tetrahidrofólico; y gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina y no a la existencia de combinaciones con los fármacos Norgestrel, Dienogest, Ciproterona, Estradiol y Drospirenona por lo cual la existencia de estos principios activos no afecta la patentabilidad de la solicitud. Los documentos presentados por el opositor no divulgan específicamente la formulación farmacéutica reclamada por el solicitante.

En cuanto a los documentos presentados por Tecnoquímicas el documento WO 99/53910 no afecta la patentabilidad de la solicitud por cuanto el documento no divulga el ácido 5-metil-(6S)-tetrahidrofólico como el principio activo utilizado. Los documentos referentes a granulación no fueron tenidos en cuenta en el examen de patentabilidad debido a que no divulgan ni sugieren el efecto de la celulosa microcristalina para aumentar la estabilidad y el perfil de liberación de los principios activos. Los documentos referentes al uso de folatos y al uso de combinaciones de progestágenos y estrógenos no fueron tenidos en cuenta en el examen de patentabilidad por cuanto la combinación de progestágenos, estrógenos y derivados de ácido fólico es ya divulgada en el documento D1 (WO 03/070255).

El uso de celulosa microcristalina como excipiente en procesos de granulación es ya conocido en el estado de la técnica según se explicará en el examen de patentabilidad, luego el uso de este excipiente como diluyente para aumentar el perfil de liberación de un fármaco no proporciona novedad o nivel inventivo a la solicitud.

El documento WO 03/070255 será tenido en cuenta en el examen de patentabilidad.

6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: Julio 06 de 2006, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

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Item	Documento	Título	Fecha de Publicación
D1	WO03070255	Pharmaceutical Compositions Comprising one or more Steroids one or more Tetrahydrofolate Components and Vitamin B12	28/Agosto/2003
D2	Swarbrick J. Drugs and The Pharmaceutical Sciences. Handbook of pharmaceutical granulation	Handbook of pharmaceutical granulation	2005

D1

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=03070255A1&KC=A1&FT=D&ND=3&date=20030828&DB=worldwide.espacenet.com&locale=en_EP divulga (páginas 4 a 6, página 13 ejemplos 1 y 2) una composición que comprende una sal del ácido 5-metil-(6S)-tetrahidrofólico, un progestágeno, un estrógeno y excipientes.

D2 divulga (páginas 204-209, 414, 535-542) (Ver folios 501 a 515) divulga el uso de celulosa microcristalina como diluyente en procesos de granulación y el efecto del proceso de granulación en la biodisponibilidad de un fármaco.

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una forma de dosificación unitaria, oral y sólida caracterizada porque comprende:

- i) una sal, aceptable desde el punto de vista farmacéutico, del ácido 5-metil-(6S)-tetrahidrofólico; y
- ii) gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

SOLICITUD	D1	D2
Forma de dosificación unitaria, oral y sólida caracterizada porque comprende: i) una sal, aceptable desde el punto de vista farmacéutico, del ácido 5-metil-(6S)-tetrahidrofólico; y ii) gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina	Ejemplo 1 Kit que comprende: 21 píldoras que contienen Levonorgestrel Etinilestradiol Acido folínico Vitamina B12 Vitamina B6 Excipientes 7 píldoras que contienen Acido folínico Vitamina B12 Vitamina B6 Excipientes	Uso de celulosa microcristalina como diluyente en granulación y efecto de la granulación en la biodisponibilidad de un fármaco

D1 divulga un kit que comprende uno o más esteroides seleccionados del grupo consistente en estrógenos y progestágenos, uno o más componentes tetrahydrofolato y excipientes. Este kit comprende 21 píldoras que contienen levonorgestrel, etinilestradiol, ácido folínico (ácido 5-formil tetrahydrofólico) y excipientes; y 7 píldoras que contienen ácido folínico (ácido 5-formil tetrahydrofólico), vitamina B y excipientes (Ver ejemplo 1 página 13) El documento divulga que el componente tetrahydrofolato puede corresponder a ácido 5-metil-6(S)-tetrahydrofólico (Ver página 4), el fármaco de tipo progestágeno puede corresponder a drospirenona (Ver página 5) y los excipientes comprenden materiales celulósicos como diluyentes (Ver página 6).

La diferencia entre la invención, definida en la reivindicación 1 y la composición de D1 consiste en que D1 no divulga específicamente la mezcla de una sal del ácido 5-metil-(6S)-tetrahydrofólico; con gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina.

D2 divulga el uso de celulosa microcristalina como diluyente en procesos de granulación (páginas 204-209, 414, 539, 540) y el efecto del proceso de granulación en la biodisponibilidad de un fármaco (páginas 535 a 542) (Ver folios 501 a 515).

El efecto que logra el incluir la mezcla entre una sal del ácido 5-metil-(6S)-tetrahydrofólico; con gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina es que aumenta la estabilidad del ácido 5-metil-(6S)-tetrahydrofólico y el perfil de liberación de la drospirenona.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar la composición conocida en D1 para aumentar la estabilidad del ácido 5-metil-(6S)-tetrahydrofólico y el perfil de liberación de la drospirenona.

Sin embargo, la utilización de celulosa microcristalina como diluyente en proceso de granulación, y el efecto del proceso de granulación para aumentar la biodisponibilidad de un fármaco ya está divulgada en el documento D2 (páginas 204-209, 414, 535-542) (Ver folios 501 a 515)

En consecuencia, resulta obvio para la persona del oficio normalmente versada en la materia, separar físicamente el principio activo (ácido 5-metil-(6S)-tetrahydrofólico) para evitar problemas de inestabilidad durante el proceso de granulación así como el hecho de someter a un proceso de granulación con celulosa microcristalina a los fármacos de tipo progestágeno y estrógeno divulgados en D1 para aumentar el perfil de liberación de estos dados la capacidad de la celulosa microcristalina como diluyente y desintegrante ampliamente conocida en el estado de la técnica¹ y el conocido efecto del proceso de granulación para aumentar el perfil de disolución y de liberación de un fármaco para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

En conclusión la reivindicación 1 cumple el requisito de novedad (Art. 16), pero no

¹ Lieberman H, Lachman L, Schwartz J. Pharmaceutical Dosage Forms: Tablets Volumen I
páginas 175, 549, 550 (Ver folios 516 a 518).
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cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones 2 a 13 no presentan características inventivas adicionales tampoco se pueden considerar inventivas

En consecuencia las reivindicaciones 1 – 13 cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO03070255	1 - 13	Nivel Inventivo
D2	Handbook of pharmaceutical granulation	1 – 13	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
29 JUN. 2012

Elaborado por: Rodolfo Cadena Amaya. *0 ut*
Revisado por: Gloria Jacqueline Alfonso.

required amount of liquid binder based on the formulation composition. However, this is a challenging task, since the liquid binder required for high-shear granulation depends on a number of formulation and process factors, such as physicochemical properties of the starting materials (API and excipients), type of the binder used, impeller speed, wet-massing time, etc.

5. FACTORS AFFECTING THE GRANULATION PROCESS AND GRANULE PROPERTIES

Performance and physical properties of the compressed tablets are driven by properties of the granules. Yajima et al. (19) examined the relationship between particle size distribution and physical properties of the obtained granules (e.g., angle of repose, angle of spatula, loose bulk density, tapped bulk density, compressibility) and the resulting tablets (hardness and weight variation of tablets). The particle size distribution of the granules used for tablet compression was expressed as a function of median particle size, and standard deviation with a logarithmic normal distribution. Physical properties of granules and the compressed tablets were significantly affected by this factor. Tablet hardness increased as the median particle size decreased, when the standard deviation was <1.0 .

In another example, Wikberg et al. (20) produced 11 granulations of a common filler (lactose) and three granulations of a high-dose drug (dipentum) by wet granulation with polyvinylpyrrolidone (PVP) as binder, in a high-shear mixer granulator. The agglomeration process was varied to produce granules with varying granule porosity. The granule fragmentation during compression was evaluated by measurements of air permeability of the tablets. The results showed that the degree of granule fragmentation during compression was related to the granule porosity before compaction. A granulation with a higher porosity had a higher fragmentation propensity during compression. The tablet strength correlated well with the degree of fragmentation, i.e., a granulation with a higher degree of fragmentation yielded tablets of a higher hardness. Variations in compactibility can be explained by variations in granule porosity for the same formulation that was wet granulated under different process conditions. Therefore, the formulation variables and granulation process should be controlled to produce granules with the desired properties. Since granule formation in high-shear wet granulation is dependent on the degree of liquid saturation, the factors that influence the degree of liquid saturation should be optimized to obtain an optimal granulation formulation. The factors that affect the degree of liquid saturation (which depends on the amount of liquid added as well as on the densification of the granules) are formulation, process, and apparatus variables. Hence, the granulation process and the properties of the granules are affected by the aforementioned variables.

5.1. Formulation Variables

Besides the API, excipients such as a filler or fillers, a disintegrant (not applicable to controlled release), and a binder are also included in the powder mixture of a tablet formulation. The fillers used in tablet formulations can be classified into two categories, based on their water solubility: soluble fillers such as lactose, sucrose, mannitol, etc., and insoluble fillers such as MCC, starch, calcium carbonate, calcium phosphate, etc. The binders used in the wet granulation process are water-soluble

polymers such as gelatin, PVP, HPMC and sugars such as glucose, sucrose, and sorbitol. Some of the commonly used disintegrants are sodium starch glycolate, cross-linked PVP, and cross-linked sodium carboxymethylcellulose. These excipients are available in various grades from vendors. Hence, the physical properties such as particle size distribution, particle shape, surface morphology, surface area, and solubility of API and excipients in the binder solution could vary considerably. The rate and the final degree of densification are controlled by the physical properties such as particle size distribution, particle shape, surface morphology, surface area, solubility in the binder solution, etc., of the starting materials. Therefore, the physical characteristics of drug and drug loading, the types and amount of excipients, and the type and amount of binder used could affect the rate and the final degree of densification of the resulting granules. Moreover, these aspects of the powder mixture can also affect the amount of liquid required for granulation and the degree of liquid saturation in the agglomerates, during the wet-granulation process, which in turn affect the physical properties of the obtained granules.

5.2. Effects of Starting Materials

The physical properties of the granules are influenced by the physical properties of the starting materials. For example, the shape, size, and size distribution of the particles of the starting materials can affect the packing pattern of a powder mixture, and ultimately the final degree of densification and the strength of the resulting granules. The extent of granule densification affects the degree of liquid saturation of the powder mixture, and the amount of liquid binder required for granulation. The total surface area of the starting materials, related to the particle size and porosity of the starting materials, will affect the amount of liquid binder required for granulation. The liquid adsorption of the starting material could also affect the amount of liquid binder required for wet granulation. Therefore, the amount of binder solution required for granulation depends on the formulation composition, and the physical characteristics of the starting materials. In a study by Schaefer et al. (21), when the mean particle size of lactose was decreased, the amount of liquid required for granulation was increased to obtain a similar particle size of granules in high-shear granulation.

The influence of the primary particle size of DCP on granule growth in a Lödige M5GR high-shear mixer granulator was investigated by Schaefer et al. (22). Two batches of DCP, one with a narrower particle distribution and smaller geometric mean diameter, and the other with a wider particle size distribution and a larger geometric mean diameter were used. The batch with the narrower particle size distribution and smaller geometric mean diameter was more easily densified than the one with the wider particle size distribution and a larger geometric mean diameter, because it was overwetted at lower moisture content. The granules with wider particle size distribution were produced from the DCP with a wider particle size distribution and larger geometric mean diameter.

The strength of wet agglomerates can be dominantly affected by the degree of liquid saturation and the primary particle size of the starting materials. Consequently, the growth mechanism and drug content uniformity of the resulting granules can be affected.

The influence of the primary particle size of lactose on the breakage of erythrosine granules was investigated by van den Dries et al. (4). The results showed that a decrease in particle size of the starting material, lactose, led to a decrease in

breakage of granules. When granule breakage was absent, the granules remained intact and the preferential layering of the smallest particles yielded inhomogeneous granules.

The effect of particle size of the lactose on the homogeneity of low-dose steroid hormone distribution in granules produced in high-speed mixers was studied by Vromans et al. (23). When a micronized low-dose steroid hormone was granulated with unmiconized lactose at 250 rpm, inhomogeneity of active was observed. The coarse particle size fractions of the granules were found to be superpotent, up to 150% of the mean drug content, whereas the fine size fraction showed a corresponding subpotency of 50%. However, when the particle size of lactose was reduced, a better drug distribution was seen. This was attributed to an increase in the tensile strength of the nuclei due to the smaller particle size of lactose.

The effect of particle size of lactose on the homogeneity of estradiol granules prepared in a 10 L high-shear mixer was studied by van den Dries et al. (15). Three different particle sizes of lactose were granulated with 0.1% micronized estradiol (5 μm) using an aqueous solution of hydroxypropyl cellulose (HPC) as a binder. Granules prepared with the largest lactose particles (141 μm) yielded a homogeneous granulate. However, after a prolonged processing time, demixing was observed. Contrary to the largest particles, granulation with the smaller lactose particles (23 and 50 μm) led to demixing in the first minute, although to a lesser extent. It was concluded that granulation with the largest particles resulted in breakage of the granules, thereby preventing demixing. However, once the granules were strong enough (smaller particle size and prolonged process time) to survive the shear forces, demixing was observed. The extent of demixing depended on the particle size difference.

The size distribution of granules prepared from three different tablet excipients, lactose, glucose, and mannitol, in a high-shear granulator, were studied by both sieve analysis and laser light diffractometry (24). Both the shapes and the size distribution of the granules produced from the three excipients differed.

The crystallinity of the starting materials affected the granulation process and the properties of the granules. The effect of crystallinity of MCC on wet granulation, in binary mixtures of MCC and corn starch (CS), was investigated by Suzuki et al. (25). The crystallinity of MCC was modified, producing amorphous material by milling in a jet mill (J-MCC) and a vibrational rod mill (R-MCC). Crystallinity of J-MCC was nearly equal to that of intact MCC (I-MCC), but that of R-MCC was remarkably low due to the mechano-chemical effect. The growth rate of granules with R-MCC was greater than that with I-MCC and J-MCC. The formulations containing I-MCC and J-MCC produced granules with a core (MCC and CS) around which CS was layered. R-MCC provided granules in which CS and abraded MCC were homogeneously mixed. In addition, R-MCC remarkably decreased the difference in drug content among the size fractions of granules compared with I-MCC. The decrease in crystallinity of MCC increased the abrasion of the material by the impeller. This resulted in a greater growth rate of granulation.

The physical properties of the API also affect the wet granulation process and the properties of the resulting granules. For example, when the particle shape of the API was changed from spherical to plate like due to a change in the crystallization solvent, the compressibility of the resulting granules dramatically decreased (26).

The effect of the particle size of DPC 963 (API) on the characteristics of granules prepared by high-shear wet granulation was evaluated by Badawy et al. (27). Particle agglomeration was affected by the particle size of the drug substance. Granule geometric mean diameter and fraction with particle size greater than

250 μm was inversely proportional to the particle size of the drug substance. The granules prepared with the smaller particle size had higher porosity, thus suggesting lower tendency for granule densification than those manufactured with the larger particle size. The compressibility of the granules was increased with decreasing particle size of the drug substance. The effect of particle size on granulation growth is the result of increased densification propensity from increased drug particle size.

In another study, a high-shear mixer granulator was used for pelletizing a drug. High-dose pseudoephedrine-HCl pellets were produced with MCC in a high-shear mixer granulator (28). The drug loading and drug particle size influenced the bulk and true densities of the resulting pellets.

5.3. Effects of Type and Amount of Binder Solution Used

A binder is normally required for the wet-granulation process. The binder can be added into the powder mixture as a dry powder followed by the addition of water, or an appropriate solvent to activate binding. Alternatively, the binder can also be added into the powder mixture as a binder solution. Because of the higher densification of the wet agglomerates, the high-shear granulation process normally only needs two-thirds to three-quarters of the liquid required during the low-shear granulation process (18). The bonding characteristics of the binders used for wet granulation could vary due to the differences in their physicochemical properties. Therefore, the type of binder used for granulation can influence the granulation process, the amount of binder required for granulation, and the physical properties of the obtained granules.

For example, the effect of binder solutions on the size of DCP granules was investigated by Ritala et al. (29). Five different binders, PVP (Kollidone 90), polyvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA copolymer), hydrolyzed gelatin and HPMC (Methocel E5 and Methocel E15) were studied. The granules prepared with PVP and hydrolyzed gelatin possessed a larger mean particle size and lower intragranular porosity when the same volume of binder solutions was used. The other three binder solutions behaved similarly. This could be due to the higher densification of DCP granule caused by PVP and hydrolyzed gelatin. Thus, the granules had higher liquid saturation with lower volumes of the binder solutions. It was apparent that increasing the concentration of the binder solution in the powder mixture increased the mean granule size.

In another study, Ritala et al. (30) investigated the differences between five binders during wet granulation using a high-shear granulator. The binders used for the study were PVP K90, PVP K25, PVP-PVA copolymer, Methocel E5, and Methocel E15. The results demonstrated that the binder solutions with high surface tension, such as PVP solutions, produced denser granules with larger mean particle size than those with low surface tension, such as PVP-PVA copolymer, Methocel E5, and Methocel E15. The difference of granule growth by different binders in high-shear wet granulation could be due to the variation of surface tension of the binder solutions.

The amount of binder and granulating liquid used during granulation affect the granulation process and the physical characteristics of the prepared granules. In general, the granules are finer when the amount of granulating liquid used for granulation is decreased. For example, the size of the granules prepared from three tablet excipients, lactose, glucose, and mannitol, increased when the amount of granulation liquid was increased (24). Similar results were observed for granulating

mixtures of mannitol and MCC (31). When the mixtures were granulated in a high-shear mixer using HPC as the binder, the mean particle size of the granules increased with increasing amounts of water and concentration of the binder.

Generally, an increase in binder concentration could result in the production of larger granules. However, this is not always the case with starch paste since it could behave differently from the other binders. For example, a high-shear mixer was utilized for evaluation of pregelatinized and pregelatinized, cross-linked, waxy corn starches as binding agents in the wet-granulation process (3). Increasing the concentration of the binders decreased the average granule size; however, no difference in friability of the granules was observed. The use of pregelatinized or pregelatinized, cross-linked starches as a paste provided larger and less friable granules than when the binder was added in the dry form.

The effect of starch paste concentrations on the particle size distribution of fine granules, produced by high-speed mixer, was investigated by Makino (32). When a low concentration (5%) of starch paste was used, the growth of granules occurred mainly during the massing time, since a relatively large amount of free water was available from the paste. Only the mean particle size of the granules became larger without changing the particle size distribution of the granules during granulation. However, when a high concentration (15%) of starch paste was used, rapid deaggregation of granules occurred due to the applied shear force, following the formation of large granules, immediately after the addition of the starch paste. Deaggregation of these large agglomerates became predominant during the wet-massing stage, and hence, the size distribution of the granules became narrower. Longer massing time was also required when a high concentration (15%) of starch paste was used, since only a small amount of water exuded from the more concentrated starch paste during the agitation.

Besides the effect on the particle size of the granules, the amount of binder solution used in the wet-granulation process can also affect the content uniformity of the granules. The effects of the amount of binder solution on the content uniformity of the oily drug D-alpha-tocopheryl acetate (VE) in granules obtained by high-shear wet granulation was investigated by Kato et al. (33). When the amount of binder solution was below the amount of water required to reach the plastic limit (minimum amount of water required for the powder mixture to form a large agglomerate when kneaded), the content of VE was <50% in the fractionated fine granules, but was >200% in the fractionated large granules. Large variations were seen in the contents of VE even if the granulation time was extended up to 30 min. When the amount of binder solution was at or above the amount of water required to reach the plastic limit, less variation was observed in the content of VE throughout the granules, and the content of VE was fairly uniform.

In another study, the effect of the amount of water as the granulating liquid and HPC as a binder on the pharmaceutical properties of granules of two model drugs, ascorbic acid and ethenzamide, was investigated by Miyamoto et al. (34). The dependence of drug content uniformity of these two model drugs on the granule size was also investigated in this study. For a water-soluble drug, ascorbic acid, an appreciable dependence of drug content on granule size was not observed in model formulations. However, for a poorly water-soluble drug, ethenzamide, more drug was found in small-size granules (<75 µm). The drug content of ethenzamide in small-size granules decreased with increasing amounts of HPC and granulation liquid. These observations suggested that drug content uniformity is influenced

not only by drug solubility in the binder solution, but also by the amounts of granulation liquid and the type of the binder used.

Granule friability is also influenced by the binder concentration and the amount of granulating liquid added to the formulation during granulation. For a new API granulated with lactose and Avicel PH 101 using low-viscosity HPMC (Pharmcoat 603), increasing the binder concentration and the amount of water tended to produce higher wet-mass consistencies. Granule friability decreased with an increase in the binder level. An inverse relationship was observed between granule friability and the amount of water added to the formulation, especially at lower drug concentrations (35).

The binder can influence not only the physical properties of the granules, but also the performance of the finished tablets. For example, within a certain range of binder concentrations and granulating liquid, increasing the amount of binder or granulating liquid actually decreases the compressibility of the granules (26). In another study, the effect of different types of binders such as PVP K30, HPMC (Cellulose HP-M 603), maltodextrin (Lycatab DSH), pregelatinized starch (Lycatab PGS), and low substituted hydroxypropyl cellulose (L-HPC) (type LH 11) on the hardness of placebo and paracetamol tablets using high-shear granulation technique was compared by Becker et al. (36). The placebo granules comprised only lactose and MCC (Avicel PH 102). The binders were added at 2%, 6%, and 10% in the dry form and water was used as the granulating liquid. The median particle size increased with increasing binder concentrations from 2% to 6% except when L-HPC was used as the binder. The median particle size of the granules decreased with increasing binder concentrations from 2% to 6% when L-HPC was used as the binder. The granule strength, and the hardness (crushing strength and friability) of the resulting tablets increased with increasing binder concentrations. In the preparation of model tablets containing paracetamol, PVP K30 (6%) and Cellulose HP-M 603 (6%) turned out to be the binders of choice with respect to crushing strength of the finished tablets. Lycatab PGS, Lycatab DSH, and L-HPC-LH 11 could not be used to produce paracetamol tablets that met the requirements.

The amount of granulating water can also affect the physical properties and compressibility of MCC, which is one of the most commonly used fillers. The mechanism of forming hard granules with MCC, using a high-shear mixer granulator, was investigated by Suzuki et al. (37). The hardness of the MCC granules increased with granulation time and the amount of water added. The specific surface area decreased during the granulation process. Crystallite size of cellulose decreased with granulation time and with increasing amounts of water added. MCC granules were strengthened with longer granulation time and greater amounts of water, thus resulting in a more intricate network due to the strong shear force of the impeller.

The effect of granulating water level on the physical-mechanical properties of MCC and silicified microcrystalline cellulose (SMCC) was investigated by Habib et al. (38). Granules containing either MCC or SMCC were prepared at different water levels using a high-shear mixer. The resulting granules were tray dried. The water level ranged from 0% to 100%. Increasing the water level affected the granule particle size, increased the granular density and flow properties of the granules, and decreased the porosity and compactibility. The compactibilities of both materials were similar and acceptable at each granulating water level up to 40%. However, both the materials showed poor compactibility at higher water levels. The effect of amount of water used for granulation did not have a statistically significant difference on the compressibility of MCC and SMCC. SMCC did not offer practical advantages over MCC, other than better flow in the powder form, which could be

agent and it must be present at an optimal concentration to maximize the solubility of a poorly water-soluble drug. Table 4 lists some of the common solubilizing agents. One commonly used additive is cyclodextrin. Cyclodextrins are bucket-shaped oligosaccharides produced from starch.

As a result of their molecular structures and shapes, cyclodextrins are able to entrap poorly water-soluble drugs in the hydrophobic cavities forming water-soluble inclusion complexes with the poorly water-soluble drugs. Cavallari et al. (30) showed that complexation and granulation of piroxicam with β -cyclodextrin by steam granulation in a single process improved in vitro drug release when compared to a physical mixture of drug and β -cyclodextrin in the same composition. 2-Hydroxypropyl- β -cyclodextrin was employed by Uekama et al. (31) to form water-soluble inclusion complex with nifedipine. The drug and additive were dissolved in ethanol-dichloromethane and subsequently spray dried. Tablets prepared using the inclusion complexes were found to promote nifedipine in vitro release rate. Upon feeding the test tablets to dogs, superior oral bioavailability was obtained. Storage at 60°C and 75% relative humidity did not result in nifedipine crystal growth because the nifedipine molecules were basically entrapped within the 2-hydroxypropyl- β -cyclodextrin, minimizing the opportunity for the nifedipine molecules coming together and recrystallizing. Thus, the stability in dissolution profile could be achieved throughout the entire period of study.

2.2.2. Effervescent Agent

Effervescence is defined as the evolution of bubbles of gas from a liquid as the result of a chemical reaction. The generation of gas, which is usually carbon dioxide, is usually achieved by spontaneous chemical reaction between a soluble acid source and an alkali metal carbonate in the presence of water. The reaction can be triggered in the presence of a small amount of water, thus moisture protection of such oral dosage forms is paramount. This is because effervescence reaction when initiated will proceed spontaneously because one of the by-products is water.

Several researchers had found that the bioavailability of aspirin from effervescence tablet was higher than conventional or enteric-coated tablets (32–34). The reasons for this included the dramatic disintegration rate of the tablets that enabled rapid release of the drug particles for dissolution and the increase in gastric emptying rate.

2.2.3. Hydrophilic Agent

In the formulation of rapid release granules, it is important to consider the formulation in its totality. It is always better to employ more hydrophilic agents which may be water-soluble or water-insoluble as binders or fillers in the formulation so that water penetration into the granules will not be impeded. Hydrophilic agents commonly employed include hydroxylpropylcellulose, hydropropylmethylcellulose, lactose, microcrystalline cellulose, polyvinylpyrrolidone, starch, and many others. These additives aid in wetting the poorly water-soluble drug. Polyvinylpyrrolidone K30 was able to improve the wetting of nifedipine complexed with 2-hydroxypropyl- β -cyclodextrin, thus negating the decrease in nifedipine release brought about by the poor wettability and good compressibility of the complex (35).

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Bioavailability and Granule Properties

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1. INTRODUCTION

The most important property of a dosage form is its ability to deliver the active ingredient to the "site of action" in an amount sufficient to elicit the desired pharmacological response. This property of a dosage form has been variously referred to as its physiological availability, biological availability, or bioavailability.

Bioavailability may be defined more accurately as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly, the absorption of a drug following intravenous administration is extremely rapid and complete. However, due to convenience and stability problems, drugs are often administered orally in a tablet or capsule dosage form. Therefore, it is imperative that their rate and extent of absorption in individual be known accurately. Furthermore, it is equally important that the factors that influence the rate and extent of absorption of drugs be also known and understood by formulators.

The subject of bioavailability began to receive growing attention as studies showed that the therapeutic effectiveness of a drug from the dosage form depends, to a large extent, on the physiological availability of their active ingredient(s), and is a function of the drug concentration in the patient's blood or plasma. The importance of bioavailability in drug therapy, therefore, stems from the fact that the rate and extent of absorption of a drug from a dosage form can, in fact, affect the patient's response to a drug. In light of these facts, the determination of bioavailability has become one of the ways to assess the *in vivo* performance of a dosage form following its formulation development. It must, however, be remembered that bioavailability studies, very often, are conducted in normal, fasted, and a small number of subjects and, therefore, the results of these studies may not always reflect the true efficacy relationship in patients under treatment conditions.

For many years it was assumed that if a dosage form contained the labeled amount of a drug, its performance could be taken for granted. However, it is now evident for some time that many factors acting individually or in concert may produce the therapeutic failure.

2. BIOAVAILABILITY PARAMETERS

In assessing the bioavailability of a drug from a dosage form, three parameters are measured following the administration of a drug through a dosage form and obtaining the drug blood concentration time profile (Fig. 1):

- 1. Peak concentration $(C_p)_{max}$
- 2. Peak time, t_{max}
- 3. The area under the concentration time curve, $(AUC)_0^\infty$

The parameters t_{max} and $(C_p)_{max}$ are the measure of the rate of absorption and the $(AUC)_0^\infty$ is a measure of the extent of absorption.

2.1. Peak Time

This parameter represents the length of time required to attain the maximum concentration of drug in the systemic circulation. The parameter reflects the onset of action and, hence, can be utilized as a measure of the rate of absorption. The faster the rate of absorption, the smaller the value for the peak time and the quicker the onset of action of the drug. The peak time is determined by using the following equation:

$$t_{max} = \frac{\ln(K_a/K)}{(K_a - K)} \tag{2.1}$$

where K_a and K are the first-order absorption and elimination rate constants, respectively.

Eq. 2.1 clearly indicates that larger the value of the absorption rate constant (K_a), the smaller is the value of peak time (t_{max}) and the quicker is likely to be the onset of action.

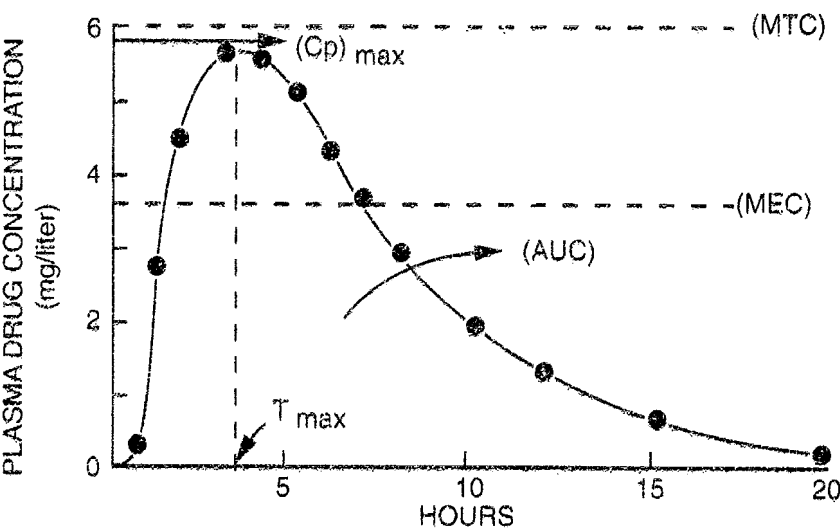


Figure 1 A graphical representation of plasma/serum drug concentration data following the administration of a drug by an extravascular route.

The elimination rate constant (K) is constant for a drug in normal healthy individuals and it changes when organs responsible for the elimination of the drug (i.e., kidney and liver) exhibit abnormalities. The absorption rate constant (K_a), on the other hand, depends on the route of administration, the dosage form, and the formulation of a drug. And, for hydrophobic drugs or when the absorption is dissolution rate limited, the faster dissolution is generally reflected in the higher value for the absorption rate constant. Therefore, by changing the formulation of a drug or route of administration, one can alter the peak time and, therefore, the rate of absorption and time for the onset of action.

2.2. Peak Plasma Concentration (C_p)_{max}

This parameter represents the highest drug concentration in the systemic circulation or the plasma concentration that corresponds to the peak time. Furthermore, this parameter is often associated with the intensity of the pharmacologic response of the drug. Therefore, the peak plasma concentration (Fig. 1) of a drug following the administration of a dosage form should be above the minimum effective concentration and below the minimum toxic concentration. The peak plasma concentration can depend on the absorption rate constant (K_a) and the fraction of the administered dose that eventually reaches the systemic circulation. The higher the absorption rate constant and fraction that reaches the general circulation, the greater is the peak plasma concentration for the administered dose. The route of administration, the dosage form, and the formulation can therefore influence the peak plasma concentration. It is determined by using the following method:

$$(C_p)_{\max} = \frac{K_a F(X_a)_0}{V(K_a - K)} (e^{-Kt_{\max}} - e^{-K_a t_{\max}}) \quad (2.2)$$

where F is the fraction of the dose that eventually reaches the systemic circulation, $(X_a)_0$ is the administered dose, V is the apparent volume of distribution of a drug, and $t_{\max}$ is the peak time.

Since the term $(K_a F(X_a)_0)/(V(K_a - K))$ in Eq. 2.2 constitutes the intercept of the plasma concentrations against the time profile, Eq. 2.3 can be written as

$$(C_p)_{\max} = I(e^{-Kt_{\max}} - e^{-K_a t_{\max}}) \quad (2.3)$$

where I is the intercept ($\mu\text{g/mL}$) of the plasma concentrations against time profile.

2.3. Area under the Plasma Concentration Time Curve

This parameter represents the extent of absorption of a drug following the administration of a dosage form. The greater the fraction of the dose that reaches the general circulation the greater is the extent of the absorption and, hence, $(\text{AUC})_0^\infty$. The term $(\text{AUC})_0^\infty$, expressed as $\mu\text{g/mL/hr}$, for a drug following its administration by various extravascular routes or various dosage forms that are administered extravascularly, is determined by employing the following equation:

$$(\text{AUC})_0^\infty = \frac{K_a F(X_a)_0}{V(K_a - K)} \left[\frac{1}{K} - \frac{1}{K_a} \right] \quad (2.4)$$

All the terms of the Eq. 2.4 have been defined previously. Eq. 2.4 can further be reduced to

$$(AUC)_0^\infty = \text{Intercept} \left[\frac{1}{K} - \frac{1}{K_e} \right] \quad (2.5)$$

the intercept in Eq. 2.5 being the intercept of the plasma concentration time profile. The extent of absorption can also be determined by using the following equation:

$$(AUC)_0^\infty = \frac{F(X_a)_0}{VK} \quad (2.6)$$

where, the term VK is the systemic clearance of the administered drug. This parameter being independent of the route of administration, the formulation, and the extravascularly administered dosage form, it is ostensible that the extent of absorption [i.e., $(AUC)_0^\infty$] is controlled by the product of the fraction of the administered dose reaching the general circulation and the administered dose [i.e., $F(X_a)_0$].

2.4. Factors Affecting the Bioavailability

There are a number of factors responsible for the variation in bioavailability. Broadly speaking, these factors can be classified as patient related or dosage form related. Patient related factors include age, disease state, abnormal genetic characteristics, and gastrointestinal physiology. The detailed discussion on these factors is beyond the scope of the objectives of this chapter.

Dosage form related factors include formulation and manufacturing related variables such as particle size, type, and quantity of excipient used, method of manufacturing, compression pressure, derived properties of the powder, and many other factors.

The fact that the bioavailability of a drug may be significantly affected by its physical state of the drug and the dosage forms via which it is administered has been unequivocally demonstrated. And, because drugs are administered through dosage forms, these dosage forms should have adequate stability, consistent bioavailability, and uniform composition.

Following the administration of a drug through a solid dosage form, a sequence of steps are required before the drug reaches the systemic circulation. As shown in Figure 2, an orally administered solid dosage form undergoes disintegration and deaggregation, followed by the dissolution of the drug. The dissolved drug molecules must penetrate the gastrointestinal membrane and picked up by the blood. Each of the steps involved may limit how fast the drug molecules reach the general circulation and, therefore, site of action. The step that offers the maximum resistance is referred to as the rate-limiting step. Which step will be rate limiting, on the other hand, will depend on the physicochemical properties of the dosage form and the physiology of the gastrointestinal tract. The focus of the discussion here, however, will be on the physicochemical properties of the dosage form.

As illustrated in Figure 2, solid dosage form must disintegrate or deaggregate before much of the drug is available for absorption. Drug dissolution subsequently occurs from the resulting granules. Therefore, the properties of granules are important in understanding how dissolution is influenced by these properties. Following the ingestion of a solid dosage form, whether or not a drug is deaggregated, it will not be absorbed until it has dissolved into the luminal fluids of the gastrointestinal tract. Because of the effects of disintegration and deaggregation on the dissolution, the remaining discussion will focus on the factors influencing the dissolution of the drug.

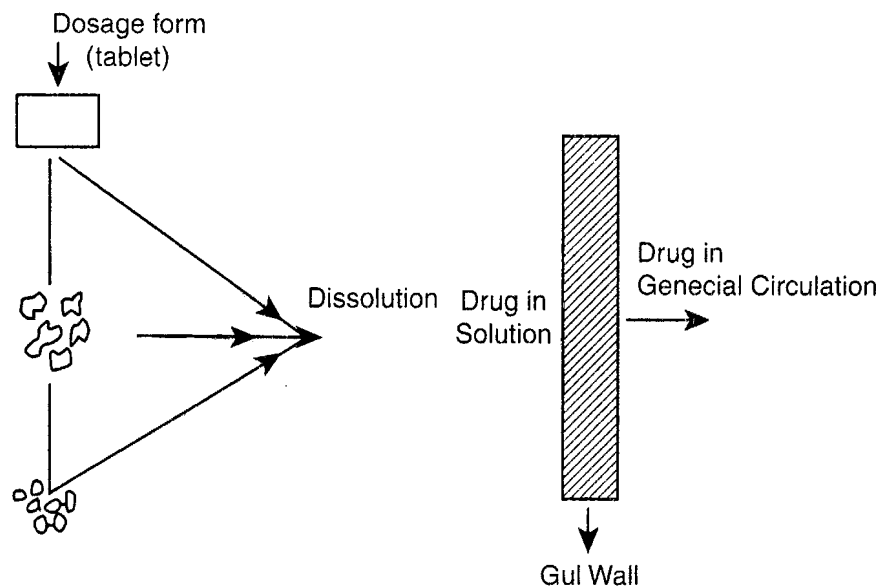


Figure 2 Schematic representation of the process of the drug dissolution and its entry into the general circulation.

2.5. Dissolution and Granule Properties

Amongst available dosage forms, compressed tablets are the most widely used dosage form. Tablets are generally obtained by using either wet granulation or direct compression process. Wet granulation process consists of mixing a drug with other powdered material and wetting the mixture with an aqueous or hydroalcoholic solution of a suitable binder such as gelatin, starch, or polyvinylpyrrolidone. The damp mass is passed through the screens of 8–12 mesh and dried to produce cohesive granules. Each granule, in theory, is a blend of an active ingredient and excipients. The granules flow easily through the hopper into the tablet press and are easily compressed.

Many derived properties of the powder greatly influence the granule properties, which, in turn, influence the dissolution of an active ingredient from the dosage form. These derived properties include powder density, porosity, specific surface, particle number, and powder flow. These derived properties are, in essence, determined by the particle size and size distribution. Consequently, particle size and size distribution play a vital role in influencing the bioavailability of drugs, particularly, when dissolution is the rate-limiting step in the absorption process. The important role these properties play in influencing the bioavailability must, therefore, be recognized and taken into consideration during optimization of a dosage form formulation. For example, a smaller particle size is desirable, if the drug is hydrophobic, to improve the drug dissolution due to increased specific surface; however, too small a particle size may adversely affect the powder flow and content uniformity of a dosage form. Other derived powder properties like true and bulk density and particle size will play an important role in the mixing of powder blends, prior to granulation and compression. Powder flow is another derived property of importance. Flow of the powder and granules can present difficulties in the manufacturing of a tablet

dosage form, which, in turn, can affect the content uniformity of a drug and the bioavailability.

Many processes used in the tablet manufacturing greatly influence the dissolution rates of the active ingredient. The method of manufacture, the size, the moisture content, age and the flow property of the granules, the order of mixing of ingredients during the granulation, as well as the compression force employed in the tableting process, all contribute to the dissolution characteristics of the final product and, therefore, may be the bioavailability of a drug from the finished product.

Several studies have demonstrated that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs (1). The use of diluents and fillers such as starch (2), anhydrous (3) and spray dried lactose (4,5), microcrystalline cellulose (6), and compression force, particle size and lubricants (7) tends to enhance the hydrophilicity of the active ingredients and improve their dissolution characteristics. In this regard, the wet granulation procedure was considered a superior method compared to other methods. However, newer tableting machines and excipients, accompanied by careful formulation and proper mixing sequence, will permit preparation of tablets with good dissolution characteristics and not dictated by the method of preparation per se.

Marlow and Shangraw (8) reported that sodium salicylate tablets prepared by direct compression with spray dried lactose uniformly exhibited more rapid and complete dissolution compared to those prepared by wet granulation. Furthermore, it was reported that the presence of disintegrate in the dry compression was essential for good dissolution. Finholt et al. (9) reported, in a separate comparative study, utilizing phenobarbital tablets that were manufactured by both wet and dry granulation that both procedures yielded comparable dissolution rates provided a disintegrate was incorporated and mixed with drug before dry granulation. However, the incorporation of disintegrate following the dry granulation of a drug resulted in slower dissolution rates.

In the manufacturing of tablets by the conventional wet granulation method, there are many independent factors that affect the property of granules and, therefore, the dissolution rate. Recent advances in granulation technology and the employment of high-shear mixers and fluid bed granulating equipment have helped to identify several critical in-process variables. The systematic control of variables such as the type and time of mixing of the granules, time and temperature of drying, blending time with lubricant, age of the granules, moisture content of the granules at the time of compression, and the tablet crushing strength are of importance to ensure the consistency in the dissolution and, hence, bioavailability.

In early studies on the physics of tablet compression, Higuchi et al. (10) recognized the influence of compressional forces employed in the tableting process on the apparent density, porosity, hardness, disintegration time, and average particle size of the compressed tablets. Hardness is a measure of resistance of a dosage form to the mechanical deforming. It is a function of high compression forces used in the manufacturing, and it may change with the aging of granules. Higuchi et al. (10) reported a linear relationship between hardness and the logarithm of the compressional force, and the specific surface of the compressed tablets was found to undergo marked changes during the compressional process. The high compression may increase the specific surface and, hence, may enhance the dissolution. On the other hand, the high compression may also inhibit the wettability of a tablet due to the formation of a firmer and more effective sealing layer of the lubricant due to high pressure and temperature that accompany a strong compressional force. Levy et al. (2) reported

that salicylic acid tablets, when prepared by double compression, showed an increase in the dissolution with an increase in the pre-compression pressure due to fracturing of drug particles at higher pressure. The higher compression may also produce slower dissolution, at least in the initial period, due to an increased difficulty of fluid penetration into the compressed tablets. Luzzi et al. (11) and Jalsenjak (12) observed the dissolution rate of sodium phenobarbital to be inversely proportional to the hardness from tablet and microcapsule, respectively.

Another important granule property that influences the dissolution of drug is the moisture content of the granule at the time of compression. Chowhan et al. (13–17) studied the effect of moisture content and crushing strength on ticlopidine hydrochloride tablet friability and dissolution. It was observed (16) that at the moisture content of 1–2%, the drug dissolution was inversely related to the tablet crushing strength. However, at the moisture content level of 3–4%, there was no clear relationship between the dissolution and the crushing strength.

In later studies by Chowhan et al. (14,17), it was reported that the granules prepared by high-speed shear mixer were less porous than those prepared by planetary mixer, and the porosity of the tablet may improve the dissolution of drug by facilitating solvent penetration provided the entrapment of air in the pores is minimized or avoided.

In yet another important study, Levy et al. (2) studied the effect of the granule size on the dissolution rate of salicylic acid tablets and found that the dissolution rate increased with a decrease in the granule size; the increase in dissolution rate, however, was not proportional to the increase in the apparent surface area of the granules. Furthermore, it was also reported that the dissolution rate decreased significantly with the increase in the age of the granules.

The chemical components of the formulation have also been shown to prolong disintegration time, which subsequently affect the drug dissolution and bioavailability. Inert fillers have been found to potentiate the chemical degradation of active ingredient causing alteration in the disintegration and dissolution time of compressed tablets to change with storage. Alam and Parrott (18) have shown that hydrochlorothiazide tablets, granulated with acacia and stored at temperatures ranging from room temperature to 80°C increased in hardness with time. This was reflected in increased disintegration and dissolution time. On the other hand, tablets granulated with starch and polyvinylpyrrolidone did not show any change in disintegration and dissolution time.

3. CONCLUSION

Drug availability following the oral dosing may be thought of as the result of the following steps:

1. Getting the drug into solution.
2. Moving the drug molecules through the membrane of the gastrointestinal tract.
3. Moving the drug away from the site of administration into the general circulation.

It is clear from the discussion that the bioavailability of drugs, particularly poorly soluble drugs, mainly depends on the ability of the drug to dissolve at the site of administration. The dissolution, in turn, especially from solid dosage forms such

as tablet and capsule, depends on the powder properties, granule properties, and the processing variables used in the manufacture of the dosage forms. The granule properties and other variables, which determine and influence the granule properties, will serve as major topics of discussion in subsequent chapters. Knowledge of these factors and their role in influencing the bioavailability of a drug will allow the formulators to develop an optimum drug dosage form by selecting the process and preparation variables involved in a rational manner.

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to conventional manufacturing techniques, especially to wet granulation. There are many classical theories that attempt to explain the mode of action of disintegrants, especially starches. One theory is that the disintegrant forms pathways throughout the tablet matrix that enable water to be drawn into the structure by capillary action, thus leading to disruption of the tablet. An equally popular concept relates to the swelling of starch grains on exposure to water, a phenomenon that physically ruptures the particle-particle bonding in the tablet matrix. Neither of these mechanisms explains the dramatic explosion that often takes place when tablets containing starch are exposed to water. Unique work carried out by Hess [72] would seem to suggest that on compression there is a significant distortion of the starch grains. On exposure to water, these grains attempt to recover their original shape, and in so doing release a certain amount of stress which, in effect, is responsible for the destruction of interparticulate hydrogen bonds and causes the tablet to be literally blown apart. Starch thus functions as the classical disintegrant. Starch 1500, by virtue of its manufacturing process, retains the disintegrant qualities of the parent corn-starch. These qualities make it a versatile disintegrating agent as both an internal and external disintegrant in tablet formulations (Example 19).

Avicel (microcrystalline cellulose) is a highly effective disintegrant. It has a fast wicking rate for water, hence, it and starch make an excellent combination for effective and rapid disintegration in tablet formulations. One drawback to its use is its tendency to develop static charges with increased moisture content, sometimes causing striation or separation in the granulation. This can be partially overcome by drying the cellulose to remove the moisture. When wet-granulated, dried, and compressed, it does not disintegrate as readily as when unwetted. It can be used with almost all drugs except those that are moisture-sensitive (such as aspirin, penicillin, and vitamins) unless it is dried to a moisture content of less than 1% and then handled in a dehumidified area.

Solka floc (purified wood cellulose) is a white, fibrous, inert, neutral material that can be used alone or in combination with starch as a disintegrating agent for aspirin, penicillin, and other drugs that are pH- and moisture-sensitive. Its fibrous nature endows it with good wicking properties and is more effective when used in combination with clays such as kaolin, bentonite, or Veegum. This combination is especially effective in tablet formulations possibly having a high moisture content (such as ammonium chloride, sodium salicylate, and vitamins).

Alginic acid is a polymer derived from seaweed comprising D-mannuronic and L-glucuronic units. Its affinity for water and high sorption capacity make it an excellent disintegrant. It is insoluble in water, slightly acid in reaction, and should be used only in acidic or neutral granulations. It can be used with aspirin and other analgesic drugs. If used with alkaline salts or salts of organic acids, it tends to form soluble or insoluble alginates that have gelling properties and delay disintegration. It can be successfully used with ascorbic acid, multivitamin formulations, and acid salts of organic bases.

Explotab (sodium starch glycolate) is a partially substituted carboxymethyl starch consisting of granules that absorb water rapidly and swell. The mechanism by which this action takes place involves accelerated absorption of water leading to an enormous increase in volume of granules. This results in rapid and uniform tablet disintegration. Explotab is official in the N.F. XVI.

ranging from 5 to 35% of the final tablet weight. The major benefits derived from addition of PEG to tablet granulations include prolonging disintegration time and improving the tablet surface texture in instances where the addition of certain medicaments to the formulation might result in a tablet with a rough or pitted surface. The inclusion of varying percentages of PEG 6000 or 8000 to a formulation aids in increasing the attainable hardness of many directly compressible tablet vehicles as well as improving the compressibility of some marginally acceptable granulations. Also, the PEG 6000 or 8000 does not have any discernible flavor or mouth-feel characteristics of its own. Polyethylene glycol, being inert, is compatible with most medicaments that may be incorporated in the tablet formulation. This material can be added to a powder mixture before wet-granulating, added with flavors and lubricants after the granulation is dried, or added to a direct-compression vehicle prior to mixing.

The quantity of PEG added to direct-compression tablet bases is determined by the physical characteristics of each individual vehicle. Some formulations possess a slow disintegration profile of their own and compress to a hardness sufficient to give the desired 5- to 10-min dwell time in the oral cavity. This desired, slow, *in vivo* disintegration is not possible with some bases because of the rapid disintegration characteristics of the tablet components. Addition of PEG (20–30%) will, in many instances, slow disintegration (erosion) to the desired time interval [43]. Incorporation of PEG in tablets containing medicament in the 30+ percentage range may improve particle cohesive forces, compression characteristics, and tablet hardness values in those instances where addition of the medicament results in a poor or marginally acceptable product.

Addition of polyethylene glycol to a wet-granulated tablet base will also aid binding and improve the organoleptic quality of the product, but its use in this type of granulation is mostly relegated to the latter function, as tablet disintegration can be controlled by the incorporation of different binders or binder concentrations. The resulting tablet will have a soft, wet, and spongy consistency, difficult to compress, susceptible to picking and binding, as well as possessing an exceptionally long (20–30 min) *in vivo* disintegration time if the quantity of PEG added to a wet-granulated vehicle is excessive. Polyethylene glycol is best added externally with flavor and lubricants when incorporated in a wet granulation tablet base.

Other Fillers

Other fillers suitable for inclusion into compressed lozenge tablet base include dicalcium phosphate (*Emcompress* [89]), calcium sulfate (*powder or Compactrol* [90]), calcium carbonate, and lactose [44]. These materials, when added in varying percentages, aid in the densification of the granulation to improve flow and die fill characteristics. Dicalcium phosphate, Compactrol, and lactose can be used in either wet granulations or direct-compression vehicles, while powdered calcium sulfate and calcium carbonate are most suitable for wet-granulated tablet bases.

Microcrystalline cellulose (*Avicel*) is another filler suitable for incorporation into both wet and direct-compression granulations, as an aid in improving marginal compression characteristics of a formulation. Avicel is available in a variety of particle sizes as well as in anhydrous form, and is suitable for moisture-sensitive medicaments or for materials that are sticky or hygroscopic [45]. Some disadvantages of microcrystalline cellulose

in lozenge tablet base include (a) diminution of granulation flow characteristics when this material is incorporated in concentrations above 20%; (b) decrease in lozenge disintegration time due to the exceptional disintegration properties of Avicel; (c) production of a particulate disintegration instead of a smooth erosion of the lozenge; (d) reduction in organoleptic appeal due to the starchy, fibrous, and drying mouth-feel imparted to the lozenge as it dissolves in the oral cavity. Avicel added in concentrations of less than 20% can improve the compression of marginally compressible tablet granulations without imparting many of the above-mentioned negative characteristics to the product. A summary of tablet vehicle components is presented in Table 7.

Binders

The function of a binder in a wet-granulated tablet base is to hold together as discrete granules the particulate matter that forms as a result of the granulating procedure. The binder is also the major contributor to final tablet hardness, since the type and concentration of binder present will enhance the intragranular forces in each individual granule as well as the intergranular forces, which are the bonding forces between granules [31].

When preparing a tablet granulation, if the intragranular force is greater than the intergranular force, the tablet will break, leaving an irregular and rough surface on the fracture line; but if the intergranular force or forces are greater, the fracture will be smooth. When compressing quantities of active ingredients into direct-compression vehicles, the intergranular forces must be maintained at a level sufficient to produce tablets with acceptable hardness and compression characteristics of their own. As these materials are added to a direct-compression tablet base, the level and efficiency of the intergranular forces of the tablet base are reduced, resulting in a lessening of tablet hardness, compression, and, in some instances, flow characteristics. At a certain critical concentration (different for each medicament in each individual tablet vehicle), the compression quality or attainable hardness values fall out of the acceptable range. Additional binder is required when this situation occurs, to form particles possessing sufficient intergranular force to produce a tablet within the required hardness and compression parameters.

Remedial actions required to improve direct-compression granulations may include (a) the addition of more tablet base to lower medicament concentration; (b) the incorporation of adjunct materials designed to improve the compression quality (e.g., PEG 6000 or 8000). A major disadvantage of adding more tablet vehicle is an increase in final tablet size and weight. The alternative, if neither of the above approaches proves acceptable, may be conversion to the preparation of a wet-granulated tablet base.

Since the compressed-tablet lozenge weight is in the range of 1.5–4.0 g, medicament concentration usually will not exceed 20%, a level that is suitable for compression into most directly compressible granulations. Use of wet granulation is reserved for improvement of organoleptic quality of the tablet, prolonging disintegration time, or the preference of the formulator for the wet granulation method of tablet base preparation.

Binders that are most effective in the wet granulation of compressed-tablet lozenges include acacia, corn syrup, sugar syrup, gelatin, polyvinylpyrrolidone, tragacanth, and methylcellulose. These ingredients are effective in increasing the intergranular forces while at the same time helping to improve the demulcent and surface texture characteristics of the lozenge when it is dissolving in the oral cavity.