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 Oficio
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Patente de Invención ☒ Patente de Modelo de Utilidad

Via Nacional

Via PCT (Fase Nacional) ☒ Capitulo I ☒ Capitulo II

No. Solicitud Internacional PCT/EP2007/011293
Fecha de Presentación Internacional 20/Diciembre/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 56 a 94	17/Junio/2009
Reivindicaciones:	Folios 95 a 99	17/Junio/2009
Prioridad:	EP 06126964.3	22/Diciembre/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.

3. Objeto de la invención

Título de la solicitud: "FORMULACION FARMACEUTICA QUE COMPRENDE UN ANTAGONISTA DE NEUROKININA"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar formulaciones farmacéuticas de N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bis(trifluorometil)-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico de fácil administración y preparación, de mayor biodisponibilidad y menor variabilidad en respuesta a la dosis.

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Para resolver este problema técnico la solicitud en estudio proporciona una dispersión sólida que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico o una sal farmacéuticamente aceptable o solvato del mismo y un vehículo

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 9/14 // 9/16 // 31/55 // 31/165

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de la reivindicación 24 no es patentable de acuerdo con el Art citado.

5. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque no define las características esenciales de la invención puesto que las formulaciones farmacéuticas que comprenden antagonistas de neurocinina 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 2 no es clara cuando reclama una dispersión sólida de acuerdo con la reivindicación 1 que comprende semihidrato de N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico y un vehículo, esta forma de reclamar el segundo componente no es válida pues no define un componente como tal. Se requiere hacer las correcciones necesarias.

La reivindicación 7 no es clara cuando reclama una dispersión sólida donde el vehículo puede comprender uno o más agentes de anti-adhesión, llenadores inertes, agentes tensoactivos, agentes humectantes, modificadores de pH o aditivos. Esta manera de definir este componente de la formulación no es aceptable, puesto que no se define ningún componente como tal. Se recuerda al solicitante que las composiciones se deben definir por características técnicas esenciales como son los ingredientes activos y auxiliares de formulación específicos. Igual observación aplica para la reivindicación 9.

La reivindicación 8 no es clara cuando utiliza el término "por lo menos" el cual no es limitativo ni preciso. Se sugiere sustituirlo por un término preciso o un rango concreto. Igualmente cuando reclama una composición en combinación con por lo menos un excipiente farmacéuticamente aceptable no define ningún componente como tal. Se recuerda al solicitante que las composiciones se deben definir por características técnicas esenciales como son los ingredientes activos y auxiliares de formulación específicos.

La reivindicación 19 no es clara cuando utiliza el término "al menos" el cual no es limitativo ni preciso y no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.

La reivindicación 20 no es clara cuando se utilizan los términos "tales como" y "preferiblemente" los cuales no son limitativos ni precisos y no permiten distinguir la invención del estado de la técnica. Se sugiere sustituirlos por términos precisos o rangos concretos.

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: Diciembre 22 de 2006, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO9807694A	Acylaminoalkenylene-Amide Derivatives as NK1 and NK2 Antagonists	26/Febrero/1998
D2	WO2005039563A2	Use of Neurokinin Antagonists in The Treatment of Urinary Incontinence	06/Mayo/2005
D3	WO2005074891A	Microemulsion Formulations Comprising Particular Substance P Antagonists	18/Agosto/2005
D4	GB2394417A	Solid Dispersion Comprising a Piperidine Substance P Antagonist and a Carrier	28/Abril/2004

D1

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=9807694A1&KC=A1&FT=D&ND=3&date=19980226&DB=worldwide.espacenet.com&locale=en_EP divulga (página 1, páginas 14 a 16, página 45 reivindicación 11) una composición farmacéutica comprendiendo Antagonistas NK1 y NK2.

D2

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2005039563A2&KC=A2&FT=D&ND=3&date=20050506&DB=worldwide.espacenet.com&locale=en_EP divulga (páginas 1, 7 y 8 ; página 16 reivindicación 9) una composición farmacéutica comprendiendo antagonistas de neurocinina

D3

http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2005074891A1&KC=A1&FT=D&ND=3&date=20050818&DB=worldwide.espacenet.com&locale=en_EP divulga (páginas 1 y 2; página 7; página 28) una formulación farmacéutica comprendiendo un antagonista de sustancia P y un proceso para su preparación

D4

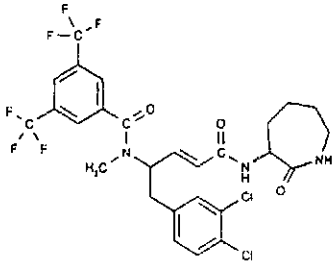
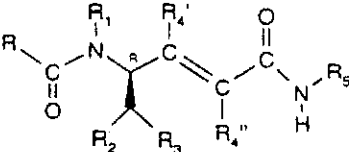
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=GB&NR=2394417A&KC=A&FT=D&ND=4&date=20040428&DB=worldwide.espacenet.com&locale=en_EP divulga (página 1 línea 1 a página 2 línea 4; página 4, líneas 17 a 19; página 6 líneas 24 a 26; página 11 líneas 8 a 16; páginas 15 a 19, ejemplos 1 a 14) una dispersión sólida de un compuesto antagonista de sustancia P y un proceso para su preparación.

7. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una dispersión sólida que comprende N-[(R)-epsilon-
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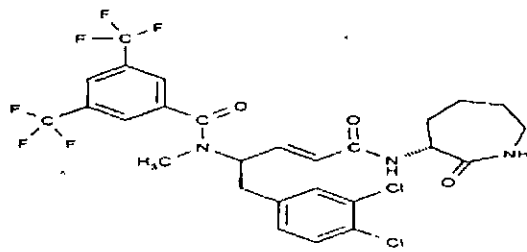
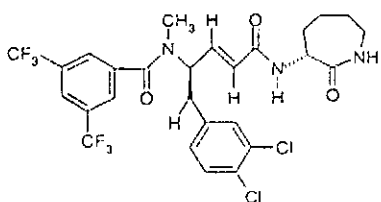
caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico o una sal farmacéuticamente aceptable o solvato del mismo y un vehículo.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D1
Dispersión sólida que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico	Composición farmacéutica que comprende compuestos de formula (I)
	
	R es 3,5 bistrifluorometilfenilo R1 es metilo R2 es hidrógeno R3 es 3,4 diclorofenil R4' y R4'' son hidrógeno R5 es azacicloheptan-2-on-3-il (página 6)
	La composición farmacéutica para administración oral corresponde a grageas, tabletas y cápsulas los cuales se obtienen por combinación del ingrediente activo con vehículos sólidos (página 14)

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual da a conocer una composición farmacéutica dispersa en un vehículo sólido (página 14) comprendiendo el fármaco N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico (página 6)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D1.

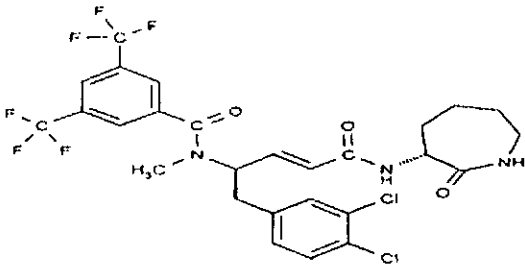
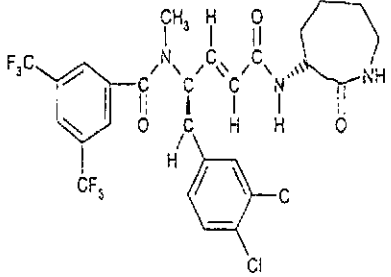
Puesto que las reivindicaciones 2 - 13, 16 - 18 y 23 no presentan características nuevas adicionales tampoco se pueden considerar nuevas

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D2
Dispersión sólida que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico	Composición farmacéutica preparada como se describe en el documento WO 98/07694 (D1) correspondiente a tabletas y cápsulas (página 8) comprendiendo el fármaco de formula (II)
	
	(página 7)

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en D2, el cual da a conocer una composición farmacéutica sólida comprendiendo el fármaco N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico (páginas 7 y 8)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D2.

Puesto que la reivindicación 2 – 13, 16 - 18 y 23 no presentan características nuevas adicionales tampoco se pueden considerar nuevas

Comparación de las características técnicas esenciales, con las del Estado de la Técnica	
Características esenciales	D3
Dispersión sólida que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico 	Composición farmacéutica espontáneamente dispersable que comprende una amida de ácido 5-aril-4-carbonilamino-pent-2-enoico para administración oral (páginas 2 y 3) El principio activo corresponde a un compuesto de fórmula I  (página 7)

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en D3, el cual da a conocer una composición farmacéutica espontáneamente dispersable que comprende como principio activo el compuesto N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D3.

Puesto que las reivindicaciones 2 y 6-9 no mencionan características nuevas adicionales tampoco se pueden considerar nuevas.

En consecuencia las reivindicaciones 1 -13, 16 – 18 y 23 carecen de novedad.

Nivel Inventivo (Art18 D486)

La reivindicación 14 consiste en una composición farmacéutica de acuerdo a las reivindicaciones 8 a 13, en donde la composición farmacéutica es un jarabe/suspensión que comprende un polvo seco, el cual es reconstituido con un líquido acuoso.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica		
SOLICITUD	D1	D3
Composición farmacéutica que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico como principio activo, estearato de magnesio como agente lubricante, almidón de sodio-carboximetilo o crospovidona como agente de desintegración, sílice coloidal como agente de desliz correspondiente a un jarabe/suspensión que comprende un polvo seco, el cual es reconstituido con un líquido acuoso.	Composición farmacéutica que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico como principio activo, estearato de magnesio como agente lubricante, almidón de carboximetilo, como agente de desintegración, sílice coloidal como agente de lubricante (página 15, página 38 ejemplo A) correspondiente a grageas, tabletas y cápsulas	Composición farmacéutica que comprende N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico como principio activo, y diversos aditivos (página 27) correspondiente a una solución oral (página 32, ejemplos 1 a 3)

Los documentos D1 y D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 14 porque composiciones farmacéuticas que comprenden el compuesto N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico (D1 páginas 38 a 40, ejemplos A a E) (D3 página 32, ejemplos 1 a 3)

La diferencia entre la invención, definida en la reivindicación 14 y la composición de D1 consiste en que D1 no divulga específicamente la composición farmacéutica consistente en un jarabe/suspensión que comprende un polvo seco, el cual es reconstituido con un líquido acuoso.

La diferencia entre la invención, definida en la reivindicación 14 y la composición de D3 consiste en que D3 no divulga específicamente los excipientes: estearato de magnesio, almidón carboximetilo, crospovidona y sílice coloidal.

El efecto que logra el incluir una composición farmacéutica consistente en un jarabe/suspensión es proporcionar una composición farmacéutica comprendiendo el compuesto N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico de fácil administración.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar la composición conocida en D1 para proporcionar una composición farmacéutica de fácil administración.

Sin embargo, la utilización de formulaciones líquidas de administración oral que comprenden el compuesto N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-

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metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico, ya está divulgada en el documento D3 que se refiere a soluciones orales que comprenden el principio activo reclamado (página 32, ejemplos 1 a 3)-

Igualmente la preparación de jarabes y suspensiones para administración de fármacos en pacientes pediátricos ya es conocida en el estado de la técnica¹.

En consecuencia, la persona del oficio normalmente versada en la materia, fácilmente utilizaría una composición líquida de administración oral como lo divulga D3 comprendiendo un polvo seco reconstituido con un líquido acuoso comprendiendo hidroxipropilmetilcelulosa como vehículo, estearato de magnesio como agente lubricante, almidón de carboximetilo, como agente de desintegración, sílice coloidal como agente lubricante como lo divulga D1 (página 15) para llegar así al objeto de la reivindicación 14 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicación 15 no presenta características inventivas adicionales tampoco se puede considerar inventiva.

La reivindicación 19 consiste en un procedimiento para hacer una dispersión sólida de acuerdo a cualquiera de las reivindicaciones 1 a 7 que comprende los pasos de a) disolver o suspender N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico o una sal farmacéuticamente aceptable o solvato del mismo y el vehículo en un solvente para formar una solución o suspensión ; y b1) secar la solución o suspensión para dar una dispersión en forma de polvo seco o b2) o granular por aspersión la solución o suspensión en al menos un llenador inerte, excipiente y al menos un agente de anti-adhesión.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica		
SOLICITUD	D1	D4
Preparación de la dispersión sólida mediante los pasos: a)disolver o suspender N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico o una sal farmacéuticamente aceptable o solvato del mismo y el vehículo en un solvente para formar una solución o suspensión ; y b1) secar la solución o suspensión para dar una dispersión en forma de polvo seco o b2) o granular por aspersión la solución o suspensión en al menos un llenador inerte, excipiente y al menos un agente de anti-adhesión.	Preparación de una composición farmacéutica consistente en mezclar el compuesto N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico con el vehículo y los excipientes y posterior granulación (páginas 38 y 39 ejemplos A a C)	Preparación de la dispersión sólida mediante disolución del fármaco antagonista de la sustancia P y el vehículo en una mezcla de etanol y acetona, posterior evaporación hasta obtener una pasta viscosa y final secado hasta obtener un polvo fino (páginas 15 y 16, ejemplos 1 a 6).

Los documentos D1 y D4 se consideran el Estado de la técnica cercano a la invención porque divulgan un proceso para obtener dispersiones de fármacos antagonistas de sustancia P

1. Gennaro R Alfonso. Remington Farmacia 19ª edición 1995, Philadelphia College of Pharmacy and Science. Páginas 2303, 2304, 2323 y 2324 (Ver folios 123 a 126)
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El proceso reclamado difiere del proceso de D1 en que D1 no divulga el proceso de disolución de la mezcla fármaco-vehículo y posterior secado.

El efecto logrado por el hecho del proceso de disolución de la mezcla fármaco-vehículo y posterior secado es proporcionar un proceso de obtención de una dispersión sólida de mayor biodisponibilidad.

Por lo tanto, el Problema técnico objetivo a resolver consiste en “cómo modificar el proceso conocido en D1 para obtener preparaciones farmacéuticas de mayor biodisponibilidad.

Sin embargo, el proceso de disolución de la mezcla fármaco-vehículo y posterior secado, ya está divulgado en el documento D4 que divulga un proceso de disolución de la mezcla de fármaco y vehículo en una mezcla de acetona/etanol y posterior secado (Ver páginas 15 y 16, ejemplos 1 a 6, páginas 17 y 18 ejemplo 10, tabla 3, figura 1).

En consecuencia, la persona del oficio normalmente versada en la materia, utilizaría el proceso de disolución en un solvente y posterior secado tal como lo divulga D4 para producir una dispersión sólida del principio activo de la composición divulgada en D1 (Ver (páginas 38 y 39 ejemplos A a C) para llegar así al objeto de la reivindicación 19 de la solicitud. Por lo cual se considera obvia.

La reivindicación 20 consiste en un procedimiento según la reivindicación 19 en donde en el paso (b2) el llenador inerte se selecciona del grupo que consiste de compuestos solubles en agua o insolubles en agua tales como lactosa, sacarosa, amilosa, dextrosa, manitol e inositol, xilitol, celulosa microcristalina, pero preferiblemente lactosa, manitol o celulosa microcristalina y el agente de anti-adhesión se selecciona del grupo que consiste de Dióxido de Silicio coloidal y Talco.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica		
SOLICITUD	D1	D4
Preparación de la dispersión sólida mediante procedimiento según el cual el llenador inerte se selecciona del grupo que consiste de compuestos solubles en agua o insolubles en agua tales como lactosa, sacarosa, amilosa, dextrosa, manitol e inositol, xilitol, celulosa microcristalina, pero preferiblemente lactosa, manitol o celulosa microcristalina y el agente de anti-adhesión se selecciona del grupo que consiste de Dióxido de Silicio coloidal y Talco.	Preparación de una composición farmacéutica consistente en mezclar el compuesto N-[(R)-epsilon-caprolactam-3-yl]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bistrifluorometil-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enico con el vehículo y los excipientes y posterior granulación (páginas 38 y 39 ejemplos A a C)	Proceso de disolución de la mezcla fármaco-vehículo por en una mezcla de alcohol-acetona y posterior secado por aspersión (página 19 tabla 4 ejemplos 11-14). El material de relleno inerte es lactosa, sacarosa, amilosa, dextrosa, manitol, inositol y celulosa microcristalina (página 6 líneas 24 a 26)

Los documentos D1 y D4 constituyen el estado de la técnica cercano a la invención porque dan a conocer un proceso para obtener dispersiones de fármacos antagonistas

de sustancia P. (D1 páginas 38 y 39 ejemplos A a C) (D4 página 6 líneas 24 a 26, página 19 tabla 4 ejemplos 11-14)

El proceso objeto de esta solicitud se diferencia del proceso mencionado en D1, en que no divulga el proceso de disolución de la mezcla fármaco-vehículo y posterior granulación por aspersión utilizando como agentes de relleno inerte y como agentes de anti-adhesión los excipientes mencionados en la reivindicación 20

El efecto de incluir el proceso de disolución de la mezcla fármaco-vehículo y posterior granulación por aspersión es proporcionar un proceso de obtención de una dispersión sólida de mayor biodisponibilidad.

Por tanto, el Problema Técnico Objetivo consiste en "cómo modificar el proceso conocido según D1 para obtener preparaciones farmacéuticas de mayor biodisponibilidad.

D2 describe el proceso de disolución de la mezcla fármaco-vehículo y posterior aspersión sobre un agente de relleno inerte, el cual corresponde a lactosa, sacarosa, amilosa, dextrosa, manitol, inositol y celulosa microcristalina (Ver página 6 líneas 24 a 26, página 19 tabla 4 ejemplos 11-14).

Igualmente los procesos de secado por aspersión, granulación por aspersión sobre un material de relleno inerte y extrusión por fusión para proporcionar biodisponibilidad, mayor solubilidad y estabilidad a una composición farmacéutica ya son conocidos en el estado de la técnica^{2,3,4}.

La reivindicación es obvia, porque la persona del oficio normalmente versada en la materia fácilmente llevaría a cabo el proceso de disolver la mezcla fármaco-vehículo utilizando como vehículo un derivado de celulosa, un polímero o polivinilpirrolidona según lo divulgado en D4 (Ver página 4, líneas 17 a 19, páginas 15 a 19, ejemplos 1 a 14), y posterior granulación por aspersión utilizando como relleno inerte compuestos seleccionados de lactosa, sacarosa, amilosa, dextrosa, manitol, inositol y celulosa microcristalina (Ver página 6 líneas 24 a 26) y como agentes de anti-adhesión dióxido de silicio coloidal y talco como una selección de excipientes igualmente probables de ser utilizados y teniendo en cuenta como principio activo el compuesto N-[(R)-epsilon-caprolactam-3-il]-amida de ácido (4R)-4-[N'-metil-N'-(3,5-bis(trifluorometil)-benzoil)-amino-4-(3,4-diclorobencil)-but-2-enoico que se divulga en D1 (Ver página 6), llegando de esta forma al proceso objeto de la reivindicación 20.

Por lo cual el proceso de la Reivindicación 20 carece de Nivel Inventivo.

Puesto que las reivindicaciones 21 y 22 no mencionan características inventivas adicionales tampoco se pueden considera inventivas.

2. Gennaro R Alfonso. Remington Farmacia 19ª edición 1995, Philadelphia College of Pharmacy and Science. Páginas 2485, 2488 y 2489. (Ver folios 127 y 128)

3. Breitenbach J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 54(2002) 107-117. Septiembre/2002. (Ver folios 129 a 139)

4. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics. 50(2000) 47-60. Julio/2000. (Ver folios 140 a 153)

En consecuencia las reivindicaciones 14, 15 y 19 – 22 cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

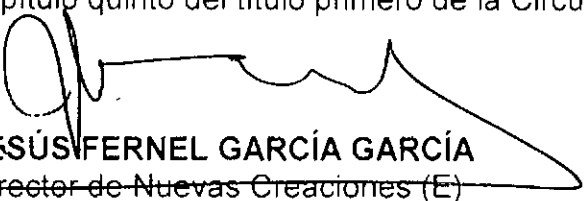
8. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9807694A	1 - 13, 16 – 18, 23	Novedad
		14, 15, 19 - 22	Nivel Inventivo
D2	WO2005039563A2	1 - 13, 16 – 18, 23	Novedad
D3	WO2005074891A	1, 2, 6 - 9	Novedad
		14, 15	Nivel Inventivo
D4	GB2394417A	19-22	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.

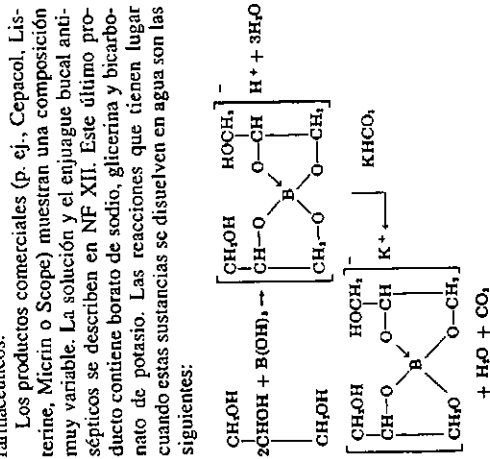

JESÚS FERNEL GARCÍA GARCÍA
 Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha
27 JUL 2012

Elaborado por: Rodolfo Cadena Amaya.
 Revisado por: Gloria Jacqueline Alfonso.

o/c LA

También se emplean colorantes (p. ej., Cepacol, Lisferine, Micrin o Scope) muestran una composición muy variable. La solución y el enjuague bucal antiséptico se describen en NF XII. Este último producto contiene borato de sodio, glicerina y bicarbonato de potasio. Las reacciones que tienen lugar cuando estas sustancias se disuelven en agua son las siguientes:



El enjuague bucal compuesto de cloruro de sodio y el enjuague bucal de sulfato de cinc se describen en BP y PC, respectivamente. El primero de estos enjuagues contiene cloruro de sodio, bicarbonato de sodio, una emulsión concentrada de menta y agua clorofórmica de doble potencia. Las preparaciones compuestas extemporáneas incluyen el alopurinol, con una potencia de aproximadamente 0,1%, preparado a partir de comprimidos en un vehículo suspensor de metilcelulosa al 0,5% edulcorada y aromatizada. Las modificaciones de esta preparación mostraron un grado considerable de estabilidad.

Jugos

Un jugo se prepara con frutas maduras frescas, es acuoso y se utiliza como vehículo en la preparación de jarabes. El jugo fresco recién exprimido se conserva con ácido benzoico y se lo deja reposar a temperatura ambiente durante varios días hasta que las pecuinas naturales sean destruidas por la acción enzimática, proceso que se refleja en la obtención de una solución límpida con alcohol después de la filtración del jugo. Si se dejasen las pecuinas, provocarían precipitación en el jarabe final.

El jugo de cereza (18ª ed., pág. 1320) se describe en la USP XXI, y el jugo de frambuesa en la USP XVIII. El jugo de frambuesa concentrado PC se prepara a partir del jugo clarificado de frambuesa. Se remueve la pecuina en pulpa de frambuesa y se deja reposar la mezcla durante 12 horas. Luego se exprime la pulpa, se clarifica el jugo y se agrega una cantidad suficiente de sucrosa para ajustar el peso entre 1,050 y 1,060 g/mL a 20°C. Luego se concentra el jugo a una sexta parte de su volumen original. Se agre-

ga una cantidad suficiente de ácido sulfuroso o metabisulfito de sodio como conservadores.

En la actualidad las esencias artificiales reemplazan a muchos de los jugos naturales. Si bien estas esencias no poseen el sabor del jugo natural, son más estables y más fáciles de incorporar a la forma farmacéutica final. Recientemente, se utilizaron jugos comestibles, tales como jugos de naranja, manzana, uva y vegetales diversos, en la preparación de productos extemporáneos con colestiramina y nizatidina.

La información relacionada con el jugo de arándano indica que podría ser efectivo en el control de algunas infecciones del tracto urinario y la urolitiasis.

Soluciones nasales

Las soluciones nasales usualmente consisten en soluciones acuosas destinadas a ser introducidas en las fosas nasales en forma de gotas o sprays. Si bien muchas de las drogas se administran por sus efectos simpaticomiméticos locales, como la solución nasal de sulfato de efedrina o clorhidrato de nafazolina USP para reducir la congestión nasal, algunas otras preparaciones oficiales, como la solución nasal de lipresina USP y la solución nasal de ocitocina USP, se administran en forma de sprays por su efecto sistémico en el tratamiento de la diabetes insípida y para producir la bajada de la leche antes de iniciar la lactancia con leche materna, respectivamente. La vía actual para la administración de péptidos y proteínas se limita a la inyección parenteral debido a la inactivación en el tracto gastrointestinal. Por lo tanto, en la actualidad, gran parte de la investigación se centra en la administración intranasal de drogas como análogos de las encefalinas, la hormona liberadora de hormona luteinizante y la insulina. Otras drogas que se absorben poco en el tracto gastrointestinal, por ejemplo, el sulfato de gentamicina, se administran en forma de soluciones nasales para obtener niveles sanguíneos apropiados.

Las soluciones nasales se preparan de un modo que en muchos aspectos son similares a las secreciones nasales para preservar la acción ciliar normal. Por lo tanto, las soluciones nasales acuosas son isotónicas y se amortiguan ligeramente con el fin de mantener un pH de 5,5 a 6,5. Además, en caso de que sea necesario la preparación puede incluir conservadores antimicrobianos similares a los utilizados en las preparaciones oftálmicas y estabilizadores apropiados para las drogas.

Además de las drogas antes mencionadas, las preparaciones nasales comerciales incluyen antibióticos, antihistamínicos y drogas para la profilaxis del asma.

Una fórmula para gotas nasales de efedrina PC es:

Clorhidrato de efedrina	0,5 g
Clorbutanol	0,5 g
Cloruro de sodio	0,5 g
Agua para preparaciones, c.s.p.	100 mL

Los estudios actuales indican que los sprays nasales se depositan principalmente en el ario y se deslizan lentamente hacia la faringe con el paciente en posición vertical. Las gotas se distribuyen de manera más amplia que el spray: tres gotas cubren la mayor parte de las paredes de la cavidad nasal con el paciente en decúbito dorsal y la cabeza inclinada hacia atrás y rotada hacia la derecha y la izquierda. Se ha sugerido que la administración de gotas con los movimientos apropiados por parte del paciente proporciona una cobertura extensiva de las paredes de la cavidad nasal.

Soluciones óticas

Estas soluciones se designan algunas veces con el nombre de preparaciones aurales. Otras preparaciones óticas consisten en suspensiones y ungüentos para aplicación tópica en los oídos.

Las principales clases de drogas utilizadas para la administración tópica en el oído consisten en analgésicos, como benzocaína; antibióticos, como neomicina, y agentes antiinflamatorios, como cortisona. Las preparaciones USP incluyen la solución ótica de antipirina y benzocaína. Las soluciones óticas de sulfato de neomicina y polimixina B y la solución ótica de hidrocortisona contienen buffers y dispersantes apropiados, por lo general en una solución acuosa. Los principales solventes utilizados en estas preparaciones son glicerina o agua. El vehículo viscoso de glicerina permite que la droga permanezca en el oído durante un largo tiempo. La glicerina anhidra es higroscópica y tiende a eliminar la humedad de los tejidos circundantes, reduciendo así la tumefacción. Los líquidos viscosos, como la glicerina o el propilenglicol, se utilizan solos o combinados con un surfactante para contribuir a la eliminación del cerumen (cera ótica). Pueden utilizarse gotas óticas de bicarbonato de sodio BP para eliminar la cera del oído. Esta preparación contiene bicarbonato de sodio (5 g), glicerina (30 mL) y agua purificada (en cantidad suficiente para completar 100 mL).

Para que las preparaciones acuosas tengan tiempo suficiente para actuar es necesario que el paciente

permanezca de costado por algunos minutos para que las gotas no salgan del oído. Las preparaciones óticas se dispensan en un envase que permite la administración de gotas.

Soluciones para irrigación

Estas soluciones se utilizan para lavar o bañar incisiones quirúrgicas, heridas o tejidos corporales. Dado que estos agentes entran en contacto con los tejidos expuestos, es necesario que cumplan requerimientos estrictos para las inyecciones USP, como esterilidad, ausencia de material particulado y los requisitos de la prueba para pirógenos. Estos productos se preparan disolviendo el ingrediente activo en agua para inyección y se envasan en envases monodosis, preferentemente de vidrio Tipo I o Tipo II, o en envases de plástico adecuados y luego se esterilizan. Para detalles acerca de los procedimientos de esterilización véase el capítulo 84. La USP describe numerosas soluciones para irrigación: irrigación con ácido acético para irrigación vesical, irrigación con dimetilsulfóxido para el tratamiento de una cistitis interna, solución de sulfatos de neomicina y polimixina B para el tratamiento de infecciones e irrigación con cloruro de sodio para el lavado de heridas.

Las formulaciones extemporáneas a menudo se preparan utilizando una solución isotónica de cloruro de sodio como solvente. Por ejemplo, la cefazolina o la gentamicina en cloruro de sodio al 0,9% se utilizan como agentes antiinfecciosos, la dinoprostona con lactato Ringer se usa para la irrigación intrauterina continua en el caso de hemorragia posparto grave y el 5-fluorouracilo en cloruro de sodio al 0,9% se utiliza para la irrigación vesical. Se utilizó el alumbre, sea con potasio o con amonio, en agua estéril o en cloruro de sodio al 0,9% como solución para irrigación en casos de hemorragia vesical. La anfotericina en agua estéril se ha empleado para el tratamiento de infecciones localizadas de la vejiga y el tracto urinario. Todas las preparaciones extemporáneas deben cumplir los requerimientos generales mencionados antes para las soluciones de irrigación USP.

Soluciones acuosas edulcoradas y otras soluciones viscosas

Jarabes

Los jarabes son soluciones concentradas de azúcares, como sacarosa, en agua o en otro líquido acuoso. Si se utiliza agua purificada solamente para preparar la solución de sacarosa, la preparación se cono-

ce con los nombres de *jarabe* o *jarabe simple*. Además de la sacarosa pueden agregarse otros polioles, como la glicerina o el sorbitol, para retardar la cristalización de la sacarosa o aumentar la solubilidad de los componentes agregados. A menudo se incluye el alcohol como conservador y también como solvente de las esencias aromatizantes; la incorporación de agentes antimicrobianos puede aumentar la resistencia al ataque microbiano. Si la preparación acuosa contiene alguna sustancia medicinal agregada, el jarabe se designa con el nombre de *jarabe medicado*. Un jarabe *aromatizado* consiste por lo general en un jarabe no medicado que contiene diversas sustancias aromáticas o de sabor agradable y suele utilizarse como vehículo o agente aromatizante en ciertas prescripciones, por ejemplo, jarabe de goma arábica, cereza, cacao y naranja USP XXI.

Los jarabes aromatizados son adecuados como vehículos en compuestos extemporáneos y son aceptados sin inconvenientes por niños y adultos. Dado que estas preparaciones contienen una cantidad infinita de alcohol, o ninguna, son los vehículos de elección para muchas drogas pediátricas. La ausencia de alcohol los convierte en solventes superiores para las sustancias hidrosolubles. Sin embargo, la administración continua de medicamentos a base de sacarosa aparentemente se asocia con un aumento de la incidencia de caries dentales y gingivitis en los niños; en consecuencia, deben considerarse otras formulaciones de la droga, sea no edulcoradas o edulcoradas con sustancias no cariogénicas. El conocimiento del contenido de azúcar en los medicamentos líquidos es importante en el caso de pacientes que deben restringir la ingesta calórica; Bergen elaboró una lista de estos valores calóricos.¹⁰

Los jarabes son muy eficaces para enmascarar el sabor de las drogas amargas o saladas. Se recomendó el jarabe de regalaz para enmascarar el sabor salado de los bromuros, yoduros y cloruros. Esta propiedad se atribuyó a su naturaleza coloidal y a su doble capacidad edulcorante: la dulzura inmediata del azúcar y la dulzura persistente de la glicirina. Este jarabe también sirve para enmascarar el sabor amargo de preparaciones que contengan vitaminas del complejo B. El jarabe de goma arábica USP XXI (pág. 2133), debido a su naturaleza coloidal, es especialmente útil como vehículo para enmascarar el sabor desagradable de numerosos medicamentos. El jarabe de fram-buesa BP es uno de los agentes saborizantes más efectivos y resulta útil sobre todo para enmascarar el sabor de las drogas amargas. Sin embargo, existen muchos factores que deben considerarse para elegir el sabor adecuado. Los datos publicados en la bibliografía a menudo son contradictorios y aparentemente no existen sustitutos para la gama de sabores. La bibliografía sobre este tema fue revisada por Meer,¹¹ y recomendamos consultar esta referencia y el capítulo 80 para obtener mayor información acerca del sabor de los productos farmacéuticos y de la preparación de diversos jarabes oficiales. Una serie de artículos pu-

blicados por Schumacher se refieren para mejorar el sabor de los productos compuestos a granel mediante el uso de agentes saborizantes y edulcorantes.¹²

Para la elaboración de un jarabe es importante seleccionar con sumo cuidado la sacarosa y usar agua purificada desprovista de sustancias extrañas, vasos y recipientes limpios. Esta operación debe ser conducida con cuidado para evitar la contaminación y garantizar la estabilidad del producto.

Es importante que la concentración de sacarosa se aproxime al punto de saturación pero sin llegar a él. En las soluciones diluidas la sacarosa es un excelente medio de cultivo para hongos, levaduras y otros microorganismos, pero en concentraciones del 65% en peso o más, la solución retardará el desarrollo de estos microorganismos. Sin embargo, una solución saturada puede conducir a la cristalización de una fracción de la sacarosa al modificarse la temperatura.

Si se utiliza calor en la preparación de los jarabes es casi inevitable que se produzca la inversión de una pequeña porción de sacarosa. Las soluciones de sacarosa son dextrorrotatorias, pero a medida que avanza la hidrólisis la rotación óptica disminuye y se torna negativa cuando se completa la reacción. Este proceso se conoce con el nombre de *inversión* debido a la formación de *azúcar invertido* (dextrosa más levulosa). La velocidad de la inversión aumenta significativamente en presencia de ácidos; el ion hidrógeno actúa como catalizador en esta reacción hidrolítica. El azúcar invertido es más fácilmente fermentable que la sacarosa y su color es más oscuro. Sin embargo, los dos azúcares reductores presentes en el azúcar invertido contribuyen a retardar la oxidación de otras sustancias.

El *jarabe invertido* se describe en la BP. Este jarabe se prepara hidrolizando la sacarosa con ácido clorhídrico y neutralizando la solución con carbonato de calcio o de sodio. La sacarosa de la solución al 66,7 peso/peso debe estar invertida por lo menos en un 95%. La monografía señala que el jarabe invertido, mezclado en proporciones adecuadas con jarabe, previene la cristalización de sacarosa en la mayoría de las condiciones de almacenamiento.

La levulosa formada durante la inversión es más dulce que la sacarosa y, en consecuencia, el jarabe resultante es más dulce que el jarabe original. La dulzura relativa de la levulosa, la sacarosa y la dextrosa es del orden de 173:100:74. Por lo tanto, el azúcar invertido es $1/100 (173 + 74)/12 = 1,23$ veces más dulce que la sacarosa. La levulosa formada durante la hidrólisis también es responsable del oscurecimiento del jarabe. La levulosa es sensible al calor y se oscurece rápidamente, sobre todo en solución. El calentamiento excesivo del jarabe o de la *sacarosa produce* la caramelización de los mismos. Véase *Caramelo* (18^o ed., pág. 1290). En ocasiones es adecuado utilizar una preparación líquida libre de azúcar; se ha publicado una lista de estas preparaciones.¹³

Preparación. Los jarabes se preparan de diversas maneras, y la selección del método apropiado depen-

de de las características físicas y químicas de las sustancias que forman parte de la preparación.

Solución con calor. Éste es el método habitual para preparar jarabes cuando el componente principal no es volátil ni termolábil y cuando se desea una preparación rápida. La sacarosa por lo común se agrega al agua purificada o a la solución acuosa y se calienta hasta obtener la solución; luego se filtra la solución y se agrega una cantidad suficiente de agua purificada hasta completar el peso o el volumen deseados. Si el jarabe se prepara a partir de una infusión, un extracto obtenido por cocción o una solución acuosa que contiene materiales orgánicos, tales como savia de arc, por lo general es apropiado calentar el jarabe hasta el punto de ebullición para coagular el material aluminoso y separarlo después mediante el filtrado. Si la albúmina u otras impurezas permanecen en el jarabe existe el riesgo de fermentación en un ambiente caluroso. Los sacarómetros son muy útiles en la preparación de jarabes mediante el calor en casos en los que se conozca la densidad del jarabe terminado. Este instrumento puede dejarse flotando en el jarabe mientras hierva y de ese modo puede determinarse el grado exacto de concentración sin esperar que el jarabe se enfríe y tener que recalentarlo para incrementar la concentración. Cuando se obtiene una lectura de la densidad del jarabe caliente debe tenerse en cuenta la variación con respecto de la temperatura oficial (en la USP la densidad se toma a 25°C).

El calentamiento excesivo de los jarabes a temperatura de ebullición es indeseable debido a que invariablemente se produce un cierto grado de inversión de la sacarosa, con una mayor tendencia a la fermentación. Los jarabes no pueden esterilizarse en autoclave sin que se produzca cierto grado de caramelización. Este fenómeno se refleja por una coloración amarillenta o pardusca resultante de la formación de caramelo por la acción del calor sobre la sacarosa.

La fórmula y el procedimiento descritos para el jarabe de goma arábica (pág. 2133) ilustran este método de preparación.

Agitación sin calor. Este proceso se utiliza en casos en los cuales el calor se asociaría con la pérdida de componentes volátiles importantes. Cuando se elaboran cantidades mayores de 2.000 mL la sacarosa debe agregarse a la solución acuosa en un frasco cuyo tamaño sea aproximadamente el doble del recipiente utilizado para el jarabe. Esta precaución posibilita la agitación activa con una solubilización rápida. Es importante tapar el frasco para evitar la contaminación y la pérdida de solución durante el proceso. Mientras no se agita, el frasco debe permanecer acostado. Para la elaboración de jarabes en grandes cantidades se utilizan tanques revestidos de vidrio con agitadores mecánicos especialmente adaptados para la disolución de la sacarosa.

Este método y el descrito anteriormente se utilizan en la preparación de una amplia cantidad de formulaciones que se designan genéricamente con el nombre de jarabes. Por ejemplo, la mayoría de los jarabes antitusivos contienen sacarosa y uno o más componentes activos. Sin embargo, el rotulado de estos productos no incluye la composición exacta. Además, algunos de ellos se encuentran enunciadados en la USP pero no se incluyen instrucciones para su preparación. Por ejemplo, el jarabe de guanifenesina USP (jarabe de gua-

yacolao de glicerilo) es oficial, pero los únicos componentes conocidos son el guayacolato de glicerilo y el etanol (no menos del 3% ni más del 4%).

Por otra parte, el PC incluye un método para la preparación del jarabe de fosfato de codeína. Este jarabe contiene fosfato de codeína (5 g), agua purificada (15 mL), espíritu de cloroformo (25 mL) y una cantidad suficiente de jarabe para completar un volumen de 1.000 mL. Ese jarabe puede utilizarse para aliviar la tos. Otro jarabe utilizado con esta finalidad es el electuario de codeína PC. En realidad esta preparación es un jarabe medicinal que posee propiedades demulcentes, expectorantes o sedantes. A diferencia del jarabe, esta preparación posee un colorante y un saborizante. La fórmula del electuario de codeína PC es la siguiente:

Fosfato de codeína	3 g
Solución de tartrazina compuesta	10 mL
Solución de ácido benzoico	20 mL
Espiritu de cloroformo	20 mL
Agua para preparaciones	20 mL
Jarabe de limón	200 mL
Jarabe, c.s.p.	1.000 mL

Disolver el fosfato de codeína en agua, agregar 500 mL de jarabe y mezclar. Agregar los otros componentes y una cantidad suficiente de jarabe hasta completar 1.000 mL.

Para uso pediátrico, se diluyen 200 mL de esta preparación con una cantidad suficiente de jarabe para completar 1.000 mL. Si el azúcar se encuentra contraindicado puede recurrirse al electuario de codeína para diabéticos:

Fosfato de codeína	3 g
Ácido cítrico monohidrato	5 g
Esencia de limón	1 mL
Solución de tartrazina compuesta	10 mL
Solución de ácido benzoico	20 mL
Espiritu de cloroformo	20 mL
Agua para preparaciones	20 mL
Solución de sorbitol, c.s.p.	1.000 mL

Disolver el fosfato de codeína y el ácido cítrico en agua, agregar 750 mL de la solución de sorbitol y mezclar. Agregar los otros componentes y una cantidad suficiente de solución de sorbitol hasta completar 1.000 mL.

La solución de sorbitol es el agente edulcorante y contiene un 70% peso/peso de los sólidos totales. La solución de sorbitol consiste principalmente en D-sorbitol y su poder edulcorante equivale aproximadamente a la mitad del que tiene el jarabe. En los EE.UU. la FDA prohibió el uso de cloroformo en los productos medicinales y cosméticos debido a casos de carcinogénesis comunicados en animales.

Las formulaciones básicas pueden modificarse fácilmente para elaborar productos comerciales muy publicitados. Evidentemente, en la formulación se deberá omitir la única droga de prescripción (fosfato de codeína o metadona), aunque en ciertos países (como Canadá) se permite que haya una cantidad reducida de fosfato de codeína en los jarabes antitusivos de venta libre. Además de los componentes mencionados o enunciadados en los compendios oficiales

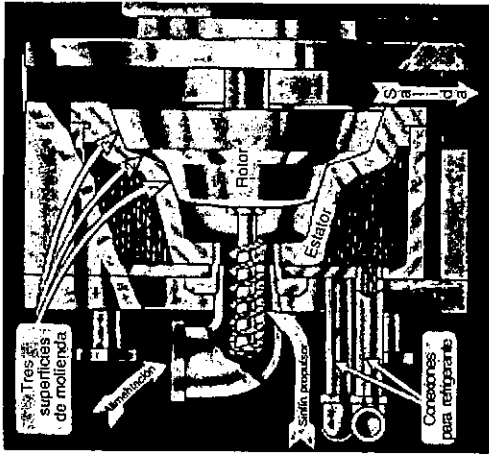


Fig. 86-4. Corte transversal de un molino coloidal (gentileza de Tri-Homo).

Las fases mezcladas de la emulsión granular se someten a homogeneización y se pasan a través de una válvula de molido fino bajo alta presión. Este procedimiento produce una atomización que es incrementada por el impacto recibido por la mezcla atomizada en el momento en que entra en colisión con las superficies metálicas. Estos sistemas operan a presiones de 1.000 a 5.000 psi (66,6 a 333,3 atmósferas) y permiten generar algunas de las dispersiones más finas que pueden obtenerse en una emulsión.

La figura 86-6 ilustra el flujo a través de la válvula homogeneizadora, la cual representa el elemento esencial del homogeneizador de alta presión APV Gaulin. El producto ingresa en el centro de la válvula a alta presión, fluye a través de la región situada entre la válvula y el asiento de ésta a alta velocidad con un rápido descenso de la presión, lo que determina la cavitación; ulteriormente, la mezcla golpea con-

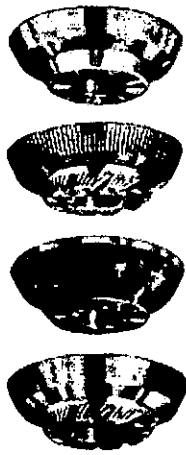


Fig. 86-5. Tipos de rotores utilizados en los molinos coloidales. Los rotores pueden ser lisos (para la mayoría de las emulsiones), estrías (para pomadas y productos muy viscosos) o de piedra vibrada (para las dispersiones de pinturas y de pigmentos) (gentileza de Tri-Homo).

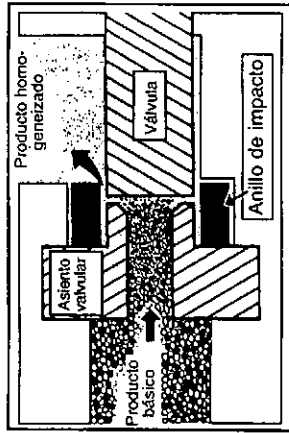


Fig. 86-6. Operación de montaje de la válvula del homogeneizador (gentileza de APV Gaulin).

tra el anillo de impacto, lo que determina un mayor grado de pulverización, y luego es descargada en la forma de producto homogeneizado. Se ha postulado que la circulación y la turbulencia serían las principales responsables de la homogeneización. Se dispone de distintos montajes valvulares, montajes valvulares en dos etapas y equipos con una amplia gama de capacidades.

Los homogeneizadores de dos etapas se construyen de manera que, después del tratamiento en el primer sistema valvular, la emulsión pase directamente a otro sistema en el cual recibe un segundo tratamiento. Una sola homogeneización puede producir una emulsión que si bien posee partículas pequeñas, tienen una tendencia a apelmazarse o a formar aglomeraciones. Las emulsiones de este tipo exhiben una tendencia aumentada a formar crema. Este problema se corrige pasando la emulsión a través de la primera etapa de homogeneización a alta presión (p. ej., 3.000 a 5.000 psi o 200 a 333,3 atmósferas) y luego a través del segundo estado a una presión mucho menor (p. ej., 1.000 psi o 66,6 atmósferas). Este procedimiento rompe toda aglomeración formada en el primer paso.

El sistema Macro Flow-Master Kom-bi-nator emplea varias acciones distintas; cada una de ellas lleva a los componentes un poco más adelante en el proceso de subdivisión de gotitas hasta obtener la homogeneización completa. La máquina está equipada con una bomba que transporta el líquido a través de las diversas etapas del proceso. En la primera etapa, los componentes son forzados, a pasar entre dos rotores especialmente diseñados (engranajes) que impulsan el líquido en direcciones opuestas dentro de una pequeña cámara y de este modo se mezclan por completo. Estos rotores también generan una acción giratoria en la cámara de pasaje siguiente y el líquido es introducido y lanzado en vórtices en remolinos y contracorrientes. La segunda etapa es una acción pulsátil o vibratoria a frecuencia rápida. El producto que sale de esta cámara, atraviesa un pequeño orificio valvular y es impulsado contra la pared de la cámara ho-

mogeneizante. Se aplica una presión menor pero no tanto como la utilizada en otros tipos de homogeneizadores. La presión se controla con exactitud con dispositivos de ajuste que están en la parte frontal de la máquina, y la temperatura se controla haciendo circular refrigerantes a través de los estatores.

En el caso de preparaciones extemporáneas en pequeña escala de emulsiones es especialmente útil el homogeneizador manual, un dispositivo barato provisto por Central Scientific. Es probable que este equipo represente el aparato emulsificante más eficiente que está al alcance del farmacéutico. Las dos fases, previamente mezcladas en un frasco, son bombeadas en forma manual a través del aparato. La recirculación de la emulsión a través del aparato mejora su calidad.

Un homogeneizador no incorpora aire en el producto final. El aire puede deteriorar la emulsión por lo que el agente emulsificante se adsorbe preferentemente a nivel de la interfase aire/agua y a este proceso sigue una precipitación irreversible que se llama *desnaturalización*. Este proceso tiene más probabilidades de ocurrir con el uso de agentes emulsificantes proteicos.

La homogeneización puede arruinar una emulsión si la concentración del agente emulsificante en la formulación es menor que la requerida para compensar el aumento de la superficie producido por el proceso.

El aumento de la temperatura durante la homogeneización no es muy grande. Sin embargo, la temperatura desempeña un papel importante en el proceso de emulsificación. Un aumento de la temperatura se asocia con una disminución de la viscosidad y, en ciertos casos, de la tensión de interfase del aceite con el agua. Sin embargo, existen muchos casos, sobre todo en la fabricación de cremas y pomadas cosméticas, en los cuales los componentes no se emulsificarán adecuadamente si se los procesa a una temperatura demasiado alta. Las emulsiones de este tipo se

Suspensiones

El fisicoquímico define el término "suspensión" como un sistema bifásico que consiste en un sólido finamente dividido disperso en un sólido, un líquido o un gas. El farmacéutico acepta esta definición y puede demostrar que existen una variedad de formas farmacéuticas que entran dentro de esta definición. Sin embargo, hay cierta reticencia a aceptar este concepto en su totalidad y por este motivo se hace hincapié en los sólidos dispersos en líquidos. Además, y dado que existe la necesidad de una terminología más específica, el científico farmacéutico establece una diferencia entre suspensiones, mezclas, magmas, geles y lociones. En un sentido general, todas estas preparaciones son suspensiones.

El estado de subdivisión del sólido insoluble abarca desde partículas que decantan o sedimentan gradualmente durante el reposo hasta partículas de naturaleza coloidal. El límite inferior para el tamaño de las partículas es de aproximadamente 0,1 μ m, y los preparados que se definen farmacéuticamente como suspensiones son las preparaciones que contienen sólidos dispersos con esta magnitud o más.

Las suspensiones poseen diversas aplicaciones en la industria farmacéutica. Estas preparaciones se utilizan para proveer drogas en estado líquido. Muchos pacientes tienen dificultades para deglutir formas farmacéuticas sólidas, y en estos casos una preparación

procesan inicialmente a una temperatura elevada y luego son homogeneizadas a una temperatura no mayor de 40°.

Los homogeneizadores se utilizaron con mayor frecuencia con emulsiones líquidas, pero en la actualidad pueden emplearse con suspensiones, dado que las superficies metálicas están construidas con aleaciones resistentes al uso que toleran bien la acción de las partículas sólidas presentes en las suspensiones.

Dispositivos ultrasónicos. También es posible preparar emulsiones mediante vibraciones ultrasónicas. Un oscilador de alta frecuencia (100 a 500 kHz) se conecta a dos electrodos entre los cuales se coloca una placa de cuarzo piezoeléctrica. La placa de cuarzo y los electrodos se sumergen en un baño de aceite y, cuando el oscilador funciona, se generan ondas de alta frecuencia que fluyen a través del líquido. La emulsificación se logra simplemente sumergiendo un tubo, que contenga los componentes de la emulsión, en este baño de aceite. Se llevaron a cabo numerosos trabajos de investigación sobre la emulsificación ultrasónica, sobre todo en lo que respecta al mecanismo de formación de emulsiones por ese método. Los datos limitados obtenidos hasta el momento, indican que estos dispositivos producen emulsiones estables sólo con líquidos de baja viscosidad. Sin embargo, este método no es práctico para la producción de emulsiones en gran escala.

Los productos comerciales pueden prepararse utilizando equipos ultrasónicos basados en el dispositivo conocido con el nombre de sistema de Pohlman ("Pohlman whistle"). En ese equipo, los líquidos premezclados son forzados a pasar a través de un orificio estrecho e impactan sobre el extremo libre de una barra filosa vibratoria. Se producen ondas ultrasónicas y se forman áreas de compresión y rarefacción. El colapso de las burbujas produce ondas de choque que determinan un efecto de corte produciendo la formación de partículas finas, según la descripción de Scott.²⁷

líquida representa una ventaja; además, la dosis de una preparación líquida puede ajustarse según las necesidades del paciente. Así, si la droga es insoluble o poco soluble, la suspensión puede representar la formulación más apropiada. Si una droga es inestable en un medio acuoso, en la preparación de una suspensión puede utilizarse una forma diferente de la droga, por ejemplo, un éster o una sal insoluble, que no sea soluble en agua.

Para mejorar la estabilidad de un antibiótico como la ampicilina, las formulaciones se efectúan de tal manera que el medio de dispersión (agua) se agrega en el momento de dispensar la preparación para formar una suspensión satisfactoria. Por lo general, el sabor de los productos farmacéuticos puede mejorarse si se los suministra en la forma de suspensión en lugar de una solución; así, el palmitato de cloramfenicol se utiliza en lugar de la forma más soluble, cloramfenicol. Otro medio para reducir la solubilidad de la droga consiste en reemplazar una parte del agua por otro líquido apropiado, como por ejemplo, alcohol o glicerina. Las drogas insolubles pueden formularse en la forma de suspensiones para uso tópico, como la loción de calamina.

Otras preparaciones de suspensiones consisten en suspensiones parenterales, preparaciones oftálmicas o preparaciones medicadas; estas suspensiones se comentan en los capítulos 87, 89 y 90, respectivamente.

Ciertos autores también incluyen a los linimentos y a las nuevas suspensiones de liberación sostenida en la discusión de ese tópico. Los linimentos actualmente se consideran soluciones, aunque varios de los linimentos antiguos en realidad eran suspensiones. Las suspensiones de liberación sostenida representan una clase de preparaciones muy especializadas y como tales se comentan con más detalles en el capítulo 94. Algunas drogas insolubles también se administran en forma de aerosol; un ejemplo consiste en el fosfato de dexametasona suspendido en una mezcla propulsora de fluoroclorocarbonos. Para mayor detalle acerca de los aerosoles véase el capítulo 95.

La formulación y el control de las suspensiones se basan en los principios mencionados en los capítulos 20 y 22. La formulación no consiste simplemente en suspender un sólido en un líquido. Se requiere un conocimiento del comportamiento de las partículas en los líquidos, de los agentes suspensorios y de los agentes soboríferos y de los colorantes para producir una suspensión adecuada.

Las suspensiones bien formuladas deben poseer ciertas propiedades básicas. La fase dispersa debe sedimentar lentamente o no sedimentar y redispersarse con rapidez al agitar. Las partículas no deben aglomerarse al sedimentar y la viscosidad debe permitir que la preparación pueda verse fácilmente. Al igual que en el caso de otras formulaciones, la estabilidad química de la suspensión es un factor esencial.

den usarse para controlar la ionización de conservadores o agentes de viscosidad iónicos o para mantener el pH de las suspensiones dentro de un rango adecuado. En las preparaciones orales la fase externa generalmente consiste en agua; sin embargo, puede considerarse el uso de otros líquidos polares, como el alcohol o la glicerina, para controlar la solubilidad, la estabilidad y el sabor. La selección de la fase externa se basa en las características de sabor, viscosidad, densidad y estabilidad. Pueden usarse líquidos no polares, como los hidrocarburos alifáticos y los ésteres grasos, si la preparación está destinada al uso externo.

Como lo comentamos antes, deben incorporarse conservadores adecuados para reducir el riesgo de contaminación microbiana. La suspensión debe ser aceptable para el paciente en lo que respecta al sabor, al color y a las cualidades estéticas (elegancia); los dos últimos factores tienen particular importancia en preparaciones destinadas al uso externo.

Preparación

La preparación de suspensiones implica varios pasos; el primero consiste en obtener partículas del tamaño apropiado (micrométrico). Las preparaciones orales no deben ser aerosoles, las preparaciones tópicas deben ser suaves al tacto y las preparaciones inyectables no deben provocar irritación tisular. El tamaño y la distribución de las partículas también deben considerarse en términos de biodisponibilidad o, alternativamente, para controlar la velocidad de liberación. Las partículas muy pequeñas (menos de 1 µm) serán más solubles que las más grandes, lo que puede generar problemas con la disolución y luego la formación de partículas de mayor tamaño.

La *molienda* define el proceso mecánico destinado a reducir el tamaño de las partículas, el cual puede realizarse mediante diversos tipos de máquinas, como lo señaló Parrot.²² El molino de percusión triturará los polvos a través del impacto de martillos rotatorios y permite obtener partículas que después pasan a través de un tamiz de una malla que oscila entre 4 y 325. Un molino a bolas contiene numerosas bolas de acero en un contenedor que gira; estas bolas reducen el tamaño de las partículas hasta una malla 20-200 mediante atrición e impacto. Un molino de energía líquida produce partículas de 1-30 µm mediante una violenta turbulencia en aire que circula a alta velocidad. Los molinos a rodillo poseen dos o más rodillos que rotan a distintas velocidades y reducen las partículas a un tamaño de malla 20-200 mediante una acción de compresión y de corte.

En pequeña escala, en el ámbito de una farmacia, las partículas deben humidificarse por completo con una pequeña cantidad de solvente miscible en agua, por ejemplo, glicerina o alcohol, para reducir la tensión a nivel de la interfase líquido/aire. Luego se agrega el agente suspensor en el medio acuoso. De

manera alternativa, el agente suspensor seco puede triturarse con las partículas de droga utilizando una pequeña cantidad de glicerina o alcohol y completando el volumen con agua diluyente.

En gran escala, las partículas de droga se tratan con una pequeña cantidad de agua que contiene el agente humidificante y se dejan reposar durante varias horas para liberar el aire atrapado. Simultáneamente, el agente suspensor debe ser disuelto o disperso en la fracción principal de la fase externa y la mezcla se deja reposar hasta la hidratación completa. Posteriormente, las partículas de droga humidificadas se agregan lentamente a la porción principal del agente suspensor disuelto. Otros excipientes, como los electrolitos o los buffers, deben agregarse con sumo cuidado para evitar variaciones de la carga de las partículas. Luego se agregan los agentes conservadores, saborizantes y colorantes. Una vez efectuados todos los agregados necesarios, se debe recurrir al tratamiento con homogeneizadores o dispositivos ultrasónicos para reducir el tamaño de las partículas aglomeradas, como lo señaló Nash.²³

Generalmente se utilizan equipos como los molinos coloidales o los homogeneizadores en las suspensiones con molido y humidificación finales para reducir las aglomeraciones de partículas y formar una preparación adecuada (figs. 86-4, 86-5 y 86-6).

Calidad

La calidad de la suspensión puede determinarse de distintas maneras, entre ellas la fotomicroscopia, para establecer la configuración, el tamaño y la floculación de las partículas. Puede usarse el contador Coulter para determinar la distribución del tamaño de las partículas. La estabilidad física, es decir, el grado de sedimentación o floculación, puede establecerse mediante el uso de probetas graduadas. La viscosidad del producto final y del agente suspensor disuelto en el medio líquido puede determinarse mediante instrumentos para humedad, tales como el viscosímetro de Brookfield. Las mediciones de la densidad son útiles para determinar el grado de atrapamiento de aire. Evidentemente, deben realizarse pruebas microbiológicas y pruebas de envejecimiento para determinar la eficiencia del conservador y las características de la formulación en lo que respecta a la estabilidad y el tiempo útil.

Suspensión a partir de comprimidos

En ocasiones es necesario preparar una formulación líquida de una droga para cumplir ciertos requerimientos del paciente, como la incapacidad de ingerir una forma farmacéutica sólida o preparar un producto para una vía de administración distinta o con una concentración diferente. La droga pura debe utilizarse para preparar la forma farmacéutica en lugar

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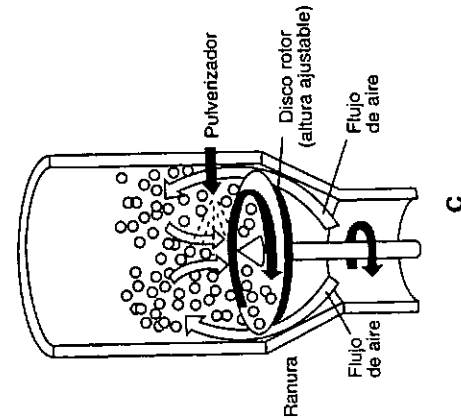
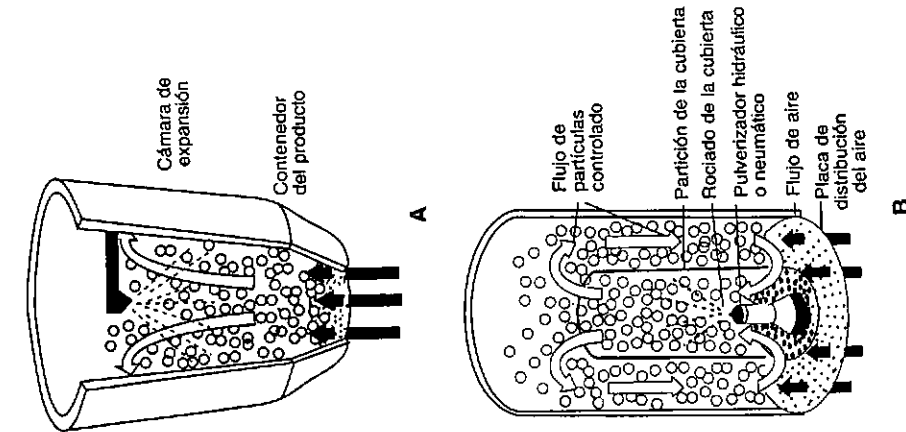


Fig. 92-12. Tres versiones de granulación en lecho fluido y secado. A. Método de secado por rociado superior en una cubertura de granulación con lecho fluido convencional; B. método de rociado inferior utilizado en las columnas de aire suspendido Wurster; C. método de rociado tangencial utilizado en las cuberturas/granuladoras. (Cortesía, Astor Publ., adaptación de la referencia 31.)

Después del secado, se reduce el tamaño de las partículas de la granulación, haciéndolas pasar por un tamiz de malla más pequeña. Después del tamizado en seco, el tamaño de los gránulos tiende a ser más uniforme. Para las granulaciones secas el tamiz a elegir depende del diámetro del punzón. Se sugieren los siguientes tamaños:

- comprimidos de hasta 1/4 pulgadas o 0,47 cm de diámetro, utilícese malla 20;
- comprimidos entre 1/8 y 1/4 o 0,55 a 0,8 cm de diámetro, utilícese malla 16;
- comprimidos entre 1/8 y 1/4 o 0,87 a 1,03 cm de diámetro, utilícese malla 14;
- comprimidos de 1/4 pulgadas o 1,11 cm de diámetro o mayores, utilícese malla 12.

Para pequeñas cantidades de granulación pueden usarse tamices manuales y el material se hace atravesar con la ayuda de espátulas de acero inoxidable.

malla 60 o 100 para eliminar los grumos pequeños y aumentar el poder de cobertura del lubricante. Como se requiere que cada gránulo esté cubierto por el lubricante, éste se mezcla con la granulación de manera muy suave, preferentemente mediante una mezcladora con acción oscilante. Es conveniente una acción suave para mantener el tamaño uniforme del gránulo. Se ha sugerido que no es deseable un polvo demasiado fino debido a que no podría llenar la matriz de manera uniforme y, en consecuencia, habría variaciones en peso y densidad. Los polvos finos habitualmente designados "finos" también se esparcirían alrededor del punzón superior y del punzón inferior, lo que haría necesaria la limpieza más frecuente de la máquina. No obstante, los formuladores buscan tradicionalmente un contenido de finos del 10-20% en los comprimidos. La presencia de algunos finos es imprescindible para el llenado apropiado de la cavidad matriz. En el presente, aún se utilizan con éxito concentraciones más altas de finos en la elaboración de los comprimidos. La mayoría de los investigadores coinciden en que no existen límites generales para la cantidad de finos que pueda estar presente en una granulación, pero deben ser determinados para cada fórmula específica.

Muchos formuladores creían (y algunos aún lo creen) que el mezclado excesivo aumentaba la cantidad de finos y, en consecuencia, se producía un atrapamiento de aire en la fórmula. Se pensó que la causa del cascado y de la laminación de los comprimidos asociados con el mezclado excesivo de los lubricantes se debía a estas bolsas de aire. La mayoría de los científicos reconoce en el presente que una explicación más razonable tiene que ver con la función de los lubricantes mismos. Dado que el lubricante por naturaleza tiende a transformar las superficies menos susceptibles a la adhesión, el mezclado excesivo evita la unión entre los gránulos que tiene lugar durante la compactación.

Granulación en lecho fluido

Un nuevo método para la granulación se logra a partir de la tecnología de secado en lecho fluido. El concepto es rociar una solución granulante en las partículas suspendidas, que luego deberán secarse con rapidez en el aire suspendido. El beneficio principal de este sistema es que la granulación y el secado del lote se producen en un lapso breve. Las dos firmas principales que desarrollaron esta tecnología son *Glatt* y *Aeromatic*. Los diseños de estos sistemas son básicamente los mismos para ambas compañías (véase fig. 92-12). Con este método, las partículas de un material inerte o de la droga activa se suspenden en una columna vertical con una corriente de aire ascendente; mientras las partículas están suspendidas, los materiales granulantes comunes se rocían en la columna. Hay una formación gradual de partículas bajo un juego controlado de condiciones que producen una granulación del comprimido, que está listo para

la compresión luego del agregado del lubricante. Existe una ventaja obvia dada por el granulado y el secado, que tienen lugar en una sola pieza del equipo. Debe destacarse, sin embargo, que muchas de las mezcladoras descritas antes suplementadas con una camisa de vapor y vacío pueden proporcionar la misma ventaja.

En estos sistemas se rocía una solución granulante o solvente en el interior o sobre el lecho de las partículas suspendidas. La velocidad en el agregado del aglutinante, la temperatura en el lecho de las partículas, la temperatura del aire, el volumen y la humedad del aire ejercen un papel importante en la calidad y el rendimiento del producto final. Muchos científicos creen que este método es una extensión del método de granulación húmeda, ya que incorpora muchos de sus conceptos. Sin embargo, cualquiera que ha desarrollado una formulación en un sistema de lecho fluido sabe que los numerosos parámetros de operación involucrados hacen que esto sea algo más complejo.³¹ Además de su empleo para la preparación de granulaciones para comprimidos, esta técnica ha sido propuesta para la cobertura de las partículas sólidas como una manera de mejorar las propiedades de flujo de las partículas pequeñas. Los investigadores observaron que, en general, las granulaciones de lecho fluido producen partículas menos densas que los métodos convencionales y que esta característica puede afectar el comportamiento posterior frente a la compactación. Un proceso de granulación en lecho fluido a gran escala fue descrito para el *Tylenol* (*McNeil*). Los métodos para la preparación de comprimidos compactados han sido publicados en la bibliografía.³²

En la planta de *Merck Sharp & Dohme*, ubicada en Elkhon, VA, el proceso de elaboración completo basado en el método de granulación húmeda es controlado en forma computarizada. Por medio de una computadora, el sistema pesa los ingredientes, los aglutina, los granula, los seca y los lubrica para preparar una granulación uniforme con tamaño de partícula especificado y distribución por tamaño. La computadora dirige la compresión del material para que los comprimidos tengan especificaciones exactas para el espesor, el peso y la dureza. Después de la compresión, los comprimidos se recubren con una película de base acuosa. La computadora controla y monitorea el flujo de todos los materiales. Esta planta es la primera en la elaboración de productos farmacéuticos con instalaciones totalmente automatizadas. Véase la figura 92-13.

Si bien en las instalaciones de Merck la tecnología abarca el proceso completo de la producción, hay muchas otras industrias que tienen partes de la operación (como revestimiento, compresión o proceso de granulación en lecho fluido) con un alto grado de sofisticación y automatización. Ésta es la tendencia del futuro. Los fabricantes de equipos trabajan en estrecha colaboración con las compañías farmacéuticas individuales para diseñar sistemas especializados y exclusivos.

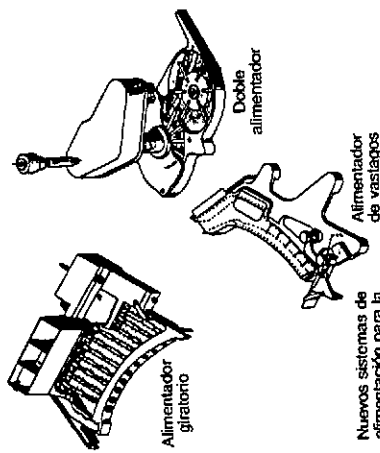


Fig. 92-14. Dispositivos de alimentación diseñados para promover el flujo de las granulaciones en las máquinas de alta velocidad. (Cortés, Stokes/Pennwalt.)

En época reciente, muchas compañías revirieron su optimismo con respecto a algunos sistemas de compresión directa. Algunas formulaciones hechas por este método no han sido tan "vendidas" como los productos granulados húmedos más antiguos. Las variaciones en la materia prima, en especial en las drogas, provocaron que muchas compañías se encontraran con formulaciones escasamente compactables. El interés en la compresión directa también estimula la investigación básica sobre la fluidez de los polvos con presencia de aditivos o sin ella. Las fórmulas para la compresión directa están incluidas en la sección de fórmulas que se encuentra en la página 2500.

Procesos afines con la granulación

Esferonización. La esferonización, una forma de granulación, se refiere a la formación de partículas esféricas a partir de las granulaciones húmedas. Dado que las partículas son redondas, tienen buenas propiedades de fluidez cuando se secan. Pueden ser formuladas para que contengan suficiente cantidad de aglutinante para impartir cohesividad en la elaboración de comprimidos. Los equipos de esferonización, como el Manumerizer (Lawa) y el CF-Granulator (Vector) están disponibles comercialmente. Una granulación húmeda, que contiene la droga, el diluyente (si se necesita) y el aglutinante, se hace pasar primero a través de una máquina extrusora para formar segmentos cilíndricos en bastones que oscilan en diámetro de 0.5 a 12 mm. El diámetro del segmento y el tamaño de la partícula esférica final dependen del tamaño del tamiz del extrusor. Después de la extrusión, los segmentos son puestos en el Manumerizer, donde toman la forma de esferas por fuerzas centrífuga y de fricción sobre una placa rotativa (véase fig. 92-15). Los gránulos luego son secados por los



Fig. 92-15. El interior de una Manumerizer Q1-400. (Cortés, Lawa.)

métodos convencionales, mezclados con los lubricantes adecuados y compactados en comprimidos, o utilizados como material para llenar cápsulas. Se demostró que la celulosa microcristalina es un diluyente y aglutinante efectivo para las granulaciones a ser esferonizadas.^{15,16} Las ventajas del proceso incluyen la producción de gránulos regulares en forma, tamaño y características de superficie, baja friabilidad —lo que da por resultado que sean menos finos y tengan menos polvillo— y la capacidad para regular el tamaño de las esferas dentro de una estrecha distribución de tamaño de partículas.

Las esferas también pueden ser producidas por las técnicas de granulación en lecho fluido y por otros equipos especializados, como el CF-Granulator (Vector). Estos procesos, no obstante, deben comenzar con cristales o semillas, seguidos del armado. Los resultados exactos, como la densidad de las esferas, son diferentes para los diversos métodos y podrían ser importantes en el rendimiento del producto. Esta metodología puede ser producida en lotes o de manera continua.

Secado por rociado. Varios aditivos adecuados para la realización de comprimidos por compresión directa han sido preparados por el proceso de secado por rociado. El método consiste en unir un líquido altamente dispersado y un volumen suficiente de aire caliente para producir la evaporación y el secado de las gotitas del líquido. El líquido de alimentación puede ser una solución, suspensión, emulsión, gel o pasta, con la precaución de que se lo pueda bombear y que se pueda atomizar. Como se muestra en la figura 92-16, el líquido de alimentación se rocía en una corriente de aire caliente filtrado. El aire suministra el calor para la evaporación y conduce el producto seco al colector; luego es eliminado con la humedad. Como las gotitas del líquido presentan una gran superficie para el aire caliente, el calor local y los coeficientes de transferencia son altos.

Las partículas de polvo secadas por rociado son homogéneas, aproximadamente esféricas, casi uniformes en tamaño y, con frecuencia, huecas. Esta di-

tima característica produce una densidad de masa baja con una rápida velocidad de disolución. Debido a que son esféricas y de tamaño uniforme, las partículas poseen buena capacidad para moverse de manera libre y continua. El diseño y el funcionamiento de la secadora por rociado puede variar muchas características del producto final, como el tamaño de las partículas y la distribución del tamaño, volumen y densidad de las partículas, porosidad, contenido de humedad, fluidez y friabilidad. Entre los materiales secados por rociado disponibles para fórmulas de compresión directa se encuentran la lactosa, el manitol y la harina. Otra aplicación del proceso en la elaboración de comprimidos es el secado por rociado de la combinación de los aditivos de los comprimidos, como el diluyente, el desintegrante y el aglutinante. El material secado por rociado luego se mezcla con el componente activo o la droga, se lubrica y comprime directamente en comprimidos.

Dado que la atomización del líquido de alimentación produce una gran superficie, la humedad se evapora con rapidez. La evaporación mantiene el producto frío, por lo que el método es aplicable para los materiales sensibles al calor. Entre las sustancias de uso farmacéutico sensibles al calor que son secadas con éxito por rociado figuran aminoácidos, antibióticos como la aureomicina, la bacitracina, la penicilina y la estreptomicina, ácido ascórbico, extractos de cáscara sagrada, extractos de hígado, pepsina y enzimas similares, hidrolizados de proteínas y tiamina.¹⁷

Con frecuencia el secado por rociado es más económico que otros procesos, ya que produce un polvo seco directamente a partir de un líquido y elimina otros pasos del procesamiento, como cristalización, precipitación, filtrado o secado, reducción del tamaño y clasificación de las partículas. La eliminación de estos pasos reduce la mano de obra, los costos del equipamiento, las necesidades de espacio físico y la posible contaminación del producto. El concentrado del factor intrínseco obtenido a partir de mucosa de cerdo, preparado anteriormente por Lederle, utilizaba un proceso de precipitación salina, seguido de liofilización. A partir del secado por rociado es posible elaborar un producto de alta calidad por un proceso continuo. Las partículas esféricas del producto facilitan su mezcla posterior con la vitamina B₁₂. Se encuentran eficiencias similares en los procesos que producen trisilicato de magnesio y carbonato sódico de dihidroxiálumino; ambas sustancias químicas son muy empleadas en las preparaciones de antiácidos.

Mediante los equipos de secado por rociado también pueden encapsularse las sustancias químicas. El proceso es útil para recubrir un material sobre otro con el objeto de proteger la sustancia interior o para controlar la velocidad de su liberación. La sustancia a recubrir puede ser líquida o sólida, pero debe ser insoluble en una solución del material que lo va a recubrir. Las vitaminas solubles en aceite, A y D, pueden cubrirse con materiales como la goma arábiga para evitar su deterioro. Los aceites saborizantes y los sa-

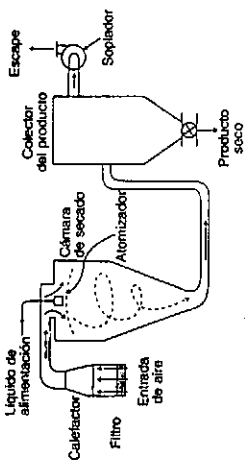


Fig. 92-16. Típico sistema de secado por rociado. (Cortés, Bowen Eng.)

bores sintéticos son cubiertos para producir los llamados sabores secos.

Congelamiento por rociado. También llamado enfriamiento por rociado, es una técnica similar al secado por rociado. Consiste en fundir sólidos y reducirlos a perlas o polvo rociando los materiales fundidos en una corriente de aire u otro gas. Se utiliza el mismo equipo básico que para el secado por rociado, aunque no se necesita la fuente de calor. Se utiliza el aire ambiental o refrigerado según el punto de congelamiento del producto. Por ejemplo, los monoglicéridos y los materiales similares son congelados por rociado con aire a 10°C. Un sistema cerrado de serpentina con refrigeración enfría y recicla el aire. Por medio de este proceso es posible disolver o suspender las drogas en una cera fundida y congelada por rociado; el material resultante se puede adaptar para una forma de liberación prolongada de la droga.

Entre los carbohidratos utilizados en los comprimidos compactados sólo el manitol posee alta estabilidad al calor. El manitol funde a 167°C, asimismo puede fundirse y congelarse por rociado solo o en combinación con otros carbohidratos. Drogas elegidas mostraron ser solubles en estas mezclas fundidas; por otra parte, los materiales resultantes del congelamiento por rociado poseen excelentes características de fluidez y compresión.

Máquinas para la elaboración de comprimidos

Como se mencionó, la unidad básica mecánica para la compresión de los comprimidos involucra la operación de dos punzones de acero dentro de una cavidad con matriz de acero. El comprimido se forma por la presión que los punzones ejercen sobre la granulación dentro de la cavidad matriz o celda. El comprimido adquiere el tamaño y la forma de los punzones y de la matriz utilizados. Véanse las figuras 92-17 y 92-18. Si bien los comprimidos redondos son los más utilizados, pueden emplearse formas ovales, capsulares, cuadradas, triangulares u otras irregulares. La curvatura de las caras de los punzones determina la forma de los comprimidos. Los diámetros,



Review article

Melt extrusion: from process to drug delivery technology

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Abstract

Starting from the plastic industry, today melt extrusion has found its place in the array of pharmaceutical manufacturing operations. This article reviews the process technology with regard to the set up and specific elements of the extruder as well as its application. Melt extrusion processes are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. As a specific area the manufacture of solid dispersions, in particular, solid molecular dispersions using the melt extrusion process is reviewed. Melt extrusion is considered to be an efficient technology in this field with particular advantages over solvent processes like co-precipitation. Potential drawbacks like the influence of heat stress and shear forces on the drug active have been overcome in a number of examples with drugs of different chemical structure. Examples of suitable excipients and recent findings like self-emulsifying preparations are presented. The article concludes with a number of published examples of melt extrudates applying the principle of solid molecular dispersions. Improved bioavailability was achieved again demonstrating the value of the technology as a drug delivery tool. © 2002 Published by Elsevier Science B.V.

Keywords: Melt extrusion; Solid dispersion; Solid molecular dispersion; Extruder; Bioavailability; Solubility

1. Introduction

Industrial application of the extrusion process dates back to the 1930's [1]. One can therefore consider the extrusion process as being a well elaborated manufacturing technology with a plethora of different technical solutions already available in other fields. Extrusion is a process of converting a raw material into a product of uniform shape and density by forcing it through die under controlled conditions [2]. Extrusion may be operated as a continuous process, which affords a consistent product flow ideally at relatively high throughput rates.

An extruder consists of two distinct parts: a conveying system which transports the material and sometimes imparts a degree of distributive mixing, and a die system which forms the materials into the required shape. Extrusion may be broadly classified into molten systems under temperature control or semisolid viscous systems. In molten extrusion, heat is applied to the material in order to control its viscosity, to enable it to flow through the die. Semisolid systems are multiphase concentrated dispersions containing a high proportion of solid mixed with a liquid phase [3].

Solid molecular dispersions of drugs in a matrix fit the

molten systems especially as the fusion method in polymeric matrices has been applied to achieve such specific distributions of drugs. Generally, solid dispersions of drugs with poor solubility revealed remarkably higher bioavailability [4,5]. Less drug material may be applied and potentially a lower degree of variability in bioavailability are obvious advantages [6]. With the recent advent of high throughput screening and the growing specificity for given receptors poorly soluble drugs present a frequent and growing challenge to formulation scientists [7,8].

Solid dispersions of drugs therefore fulfill the prerequisites of drug delivery systems being designed to:

- increase the active agent bioavailability,
- reduce side effects,
- increase the duration of the drug action in the body.

At the same time, extrusion represents an efficient manufacturing technology required to disperse drugs in a melt up to a true molecular solution of the active agent in the matrix. It is a striking example of a technology transfer establishing a new technology life cycle curve.

The most relevant technologies for the manufacture of solid dispersions are hot spin mixing [9], embeddings by means of spray drying [10], co-evaporation, co-precipitation [11], freeze-drying [12] and roll-mixing or co-milling [13,14].

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An indication that life cycle management is a key driver for the melt extrusion technology is the remarkable amount of publications in the patent literature.

2. Melt extrusion: the process technology

2.1. General remarks

With regard to pharmaceuticals, most systems extruded today consist of particles dispersed in a matrix. Although consideration is given to the manufacture of pure thermoplastics, the main emphasis is still on paste extrusions [15]. These differ in the fact that a connective matrix is present between solid particles. The relative position of solid and liquid can change during the various stages of the extrusion process, and hence produce effects different from those associated with single-phase systems like a molecular distribution of a drug in a polymeric matrix. In the latter, the matrix acts as a real solvent for the drug. Ideally, such systems are supposed to have a single-phase over a wide range of solubility of the drug in the polymeric matrix.

The various types of extruders have a common feature of forcing the extrudate from a wider cross-section through the restriction of the die. The theoretical approach to understand the system, is therefore, generally associated with dividing the process of flow into four sections:

- feeding of the extruder,
- conveying of mass and entry into the die,
- flow through the die,
- exit from the die and down-stream processing.

These four sections drive considerations of different aspects like flow of powder, shear force, residence time and pressure, cooling rate and shaping.

Generally, the extruder consists of at least one rotating screw inside a stationary cylindrical barrel. The barrel is often manufactured in sections, which are bolted or clamped together. An end-plate die, connected to the end of the barrel, determines the shape of the extruded product (see Fig. 4).

Sometimes as much as 80% of the heat required to melt or fuse the material is supplied by the heat generated by friction as the material is sheared between the rotating screws and the wall of the barrel. Additional heat may be supplied by electric or liquid heaters mounted on the barrel. It is important to realize that residence time and pressure in the die area might have a significant impact on the impurity profile of the product [16].

Most commercial extruders have a modular design, providing a choice of screws or interchangeable sections which alter the configuration of the feed, transition, and metering zones. This makes it possible to modify the process to meet particular requirements, for example, from a standard to a high shear extrusion. Modified screw designs allow the extruder to perform a mixing role in addition to

extrusion, so that the material can be blended into the extrudate or even dissolved (Fig. 1). The various screw and die designs available and practical considerations of thermoplastic extrusion are reviewed by Whelan and Dunning [17].

The extrusion channel is conventionally divided into three sections: feed zone, transition zone, and metering zone (Fig. 4). The starting material is fed from a hopper directly into the feed section, which has deeper flights or flights of greater pitch (Fig. 2). This geometry enables the feed material to fall easily into the screw for conveying along the barrel. Pitch and helix angle determine the throughput at constant rotation speed of the screws. The material is transported as a solid plug to the transition zone where it is mixed, compressed, melted, and plasticized. Compression is developed by decreasing the thread pitch but maintaining a constant flight depth or by decreasing flight depth while maintaining a constant thread pitch [18]. Both methods result in increased pressure as the material moves along the barrel. The melt moves by circulation in a helical path by means of transverse flow, drag flow, pressure flow, and leakage; the latter two mechanisms reverse the flow of material along the barrel. The space between screw diameter and width of the barrel is normally in the range of 0.1–0.2 mm.

The material reaches the metering zone in the form of a homogeneous plastic melt suitable for extrusion. For an extrudate of uniform thickness, flow must be consistent and without stagnant zones right up to the die entrance. The function of the metering zone is to reduce pulsating flow and ensure a uniform delivery rate through the die cavity.

The twin-screw extruder has two agitator assemblies mounted on parallel shafts (Fig. 3). These shafts are driven through a splitter/reducer gearbox and rotate together with the same direction of rotation (co-rotating) or in the opposite sense and are often fully intermeshing. In such case, each agitator element wipes both the surface of the corresponding element on the adjacent shaft, and the internal surfaces of the mixing chamber. The agitators are said to be self-wiping, an arrangement that eliminates stagnation areas within the mixing chamber and ensures a narrow and well-defined residence time distribution. If the agitators are chosen not to intermesh, the arrangement comes close to a single-screw set up. In general, co-rotating shafts have better mixing capabilities as the surfaces of the screws move towards each other. This leads to a sharp change in mass flow between the screw surfaces [19]. As the screws rotate, the flight of one screw element wipes the flank of the adjacent screw, causing material to transfer from one screw to the other. In this manner the material is transported along the extruder barrel.

The twin-screw extruder is characterized by the following descriptive features:

Short residence time: The residence time in the twin-screw extruder in a typical extrusion process is of the order of up to 2 min.

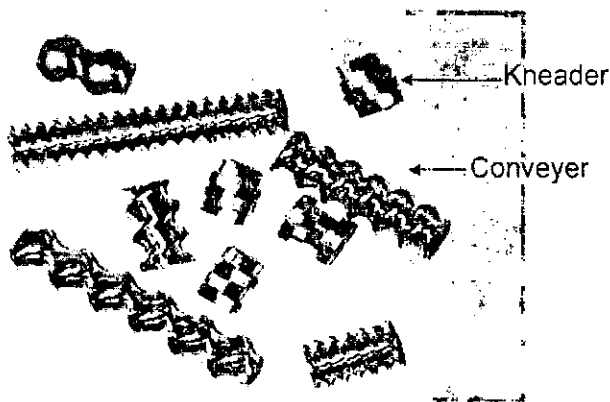


Fig. 1. Screw and kneading elements.

Self wiping screw profile: The self wiping screw profile i.e. the flight of one screw wipes the root of the screw on the shaft next to it, ensures near complete emptying of the equipment and minimises product wastage on shutdown.
Minimum inventory: Continuous operation of the equipment coupled with the low volume of the mixing chamber lead to reduced inventories of work in progress. This is important when processing valuable or potentially hazardous materials.
Versatility: Operating parameters can be changed easily

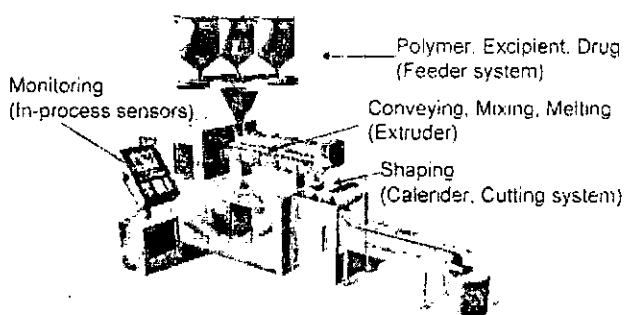


Fig. 3. Schematic presentation of a twin-screw extruder set-up.

and continuously to change extrusion rate or mixing action. The segmented screw elements allow agitator designs to be easily optimized to suit a particular application. Die plates can also be easily exchanged to alter the extrudate diameter and hence the spheroid diameter. This allows processing of many different formulations on a single machine, leading to good equipment utilization. Polymers with a wide range of viscoelastic and melt viscosities can be processed and even fine powders can be directly fed into the system (Fig. 3).

Typical twin-screw laboratory scale machines have a diameter of 16–18 mm and a length of four to ten times

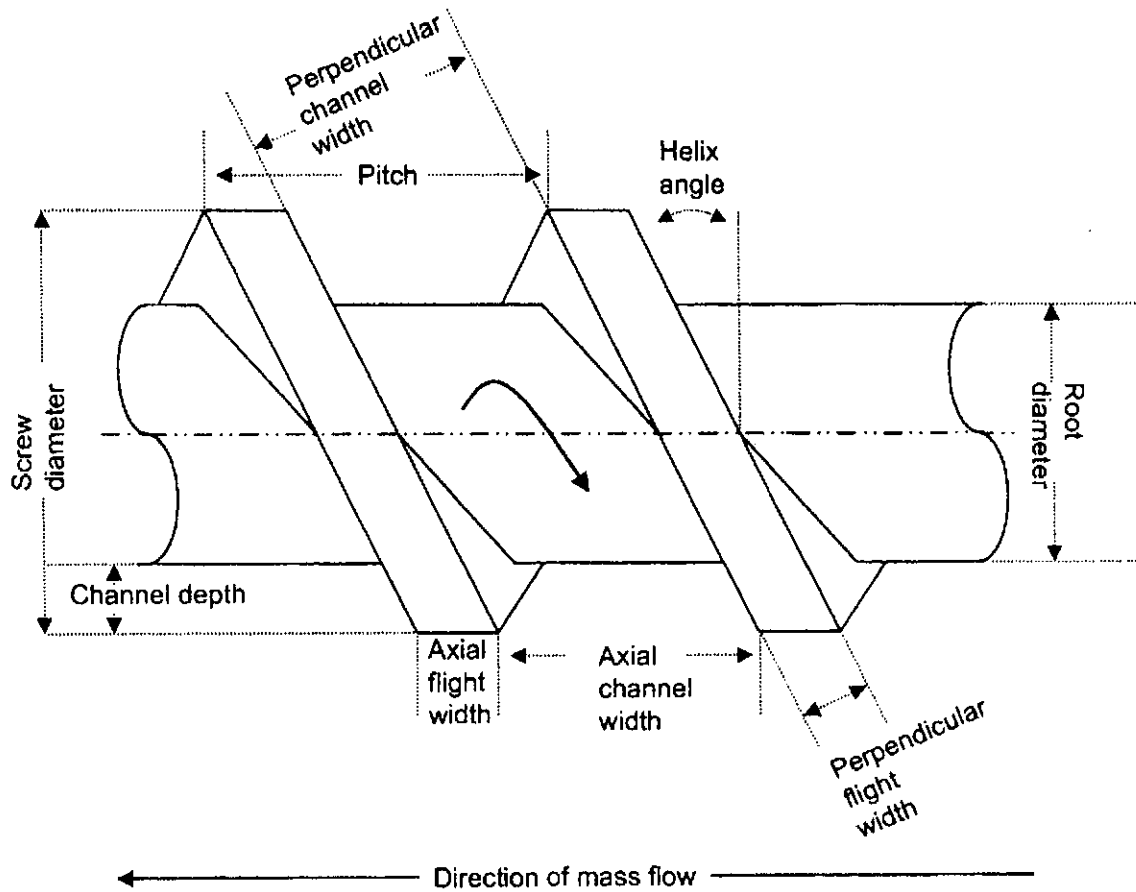


Fig. 2. Extrusion screw geometry.

the diameter. A typical throughput for such type of equipment is 0.5–3 kg/h.

As the residence time in the extruder is rather short and the temperature of all the barrels are independent and can be accurately controlled from low temperatures (30°C) to high temperatures (250°C) degradation by heat can be minimized. In addition oxygen and moisture may be excluded almost completely – an advantage for components sensitive towards oxidation and hydrolysis.

Extrusion processing requires close monitoring and understanding of the various parameters: viscosity, variation of viscosity with shear rate and temperature, elasticity, extensional flow, and slippage of the material over hot metal surfaces. Today extruders allow in process monitoring and control of parameters, such as the temperature in the extruder, head and die as well as pressures in extruder and die (Fig. 4) [20].

In particular, the molecular weight of polymeric matrices, their respective glass transition temperature and the sensitivity of the matrix or the drug towards heat and shear force create a basic set of data that qualify materials for the extrusion process. Additionally, miscibility can experimentally be determined with differential scanning calorimetry (DSC) and hot stage microscopy (HSM). In order to determine the miscibility of drug and excipient to predict if glass solutions are likely to form when drug and excipient are melt extruded, estimation of drug/excipient miscibility has been investigated. Melt extrusion of miscible components resulted in solid solution formation, whereas extrusion of an 'immiscible' component led to amorphous drug dispersed in crystalline excipient. In conclusion, combining calculation of solubility parameters with thermal analysis of drug/excipient miscibility has been successfully applied to predict formation of glass solutions with melt extrusion [21]. The challenge to determine the solubility of a drug in a polymeric matrix still needs to be addressed more adequately. A screening system based on a dimeric moiety

of polyvinylpyrrolidone (PVP) has been presented which is capable of comparing the solubility in the liquid to that in the solid, in this case the polymer [22].

2.2. Industrial applications

2.2.1. General

Extrusion technology is extensively applied in the plastic and rubber industries, where it is one of the most important fabrication processes. Examples of products made from extruded polymers include pipes, hoses, insulated wires and cables, plastic and rubber sheeting, and polystyrene tiles. Plastics that are commonly processed by extrusion include acrylics (polymethacrylates, polyacrylates) and copolymers of acronitrile, celkulosics (cellulose acetate, propionate, and acetate butyrate), polyethylene (low and high density), polypropylene, polystyrene, vinyl plastics, polycarbonates, and nylons.

The process often is referred to as profile or line extrusion in which the shape of the extrudate like a tube is determined by the die. The extruded profile proceeds horizontally to the cutoff equipment, which controls its length. Profiles may be further processed, for example, as in film extrusion, blow molding, or injection molding [23].

In film extrusion, the polymer melt is extruded through a long slit die onto highly polished cooled rolls which form and wind the finished sheet. This is known as cast film. Plastic packaging film is also formed by blow extrusion, where tubular film is produced by the melt, usually vertically, through an annular-shaped slit die. The extruded tube is inflated by air to form a large cylinder. Blow molding refers to a process where the plastic is heated to a melted or viscous state and a section of molten polymer tubing is extruded usually downward from the die head into an open mold. The mold is closed around it, sealing it at one end. Compressed air is blown into the open end of the tube, expanding the viscous plastic to the walls of the cavity, thus

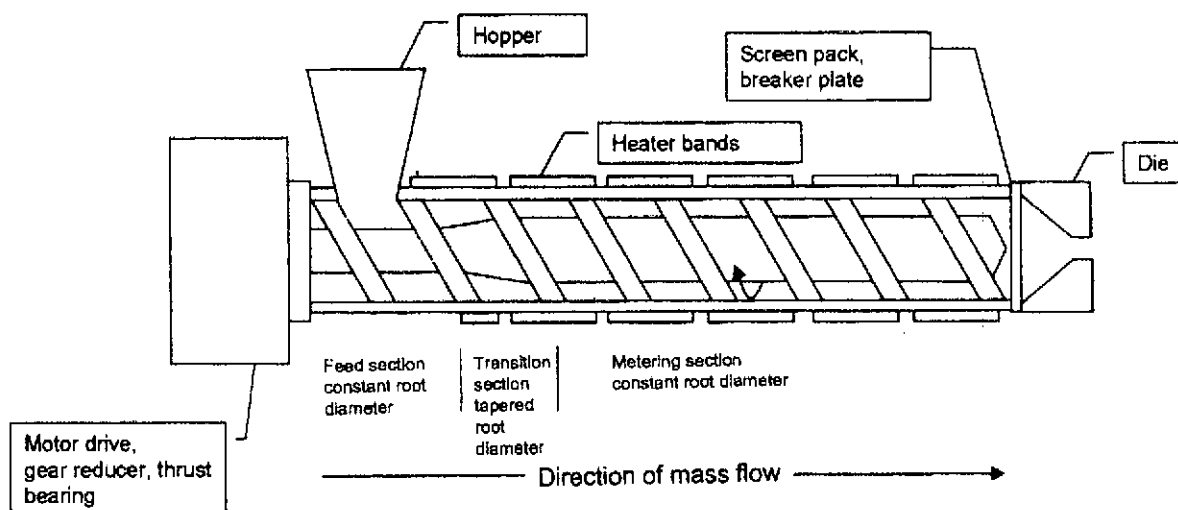


Fig. 4. Component parts of a single-screw extruder.

forming the desired shape of the container. During injection molding the molten plastic is not extruded but rather injected into a cavity mold at high pressure. The material cools in the cavity and solidifies. The mold is then opened and the article is removed.

Injection molding, has been used to manufacture tablets [24] and sustained release preparations [25]. In terms of feasibility, fast drug release, and economics, injection molding was considered suitable for drug solid dispersion or solution manufacture [26]. Injection molding has been exploited for its potential to manufacture sophisticated bi-layer tubular systems for customized release profiles [27].

In the food industry extrusion has been utilized since 1930s for pasta production. A widely used versatile technique combines cooking and extrusion in a so-called extrusion cooker [28].

In the animal feed industry, extrusion is most commonly applied as a means of producing pelletized feeds [29]. The manufacture of implants by extrusion or injection molding is another field of application in the veterinary field.

The need to formulate drugs with poor solubility is not only limited to the pharmaceutical field. Fast dispersing PVP melt extrudates of poorly soluble active agents as molecular dispersions are marketed in the crop protection field [30].

2.2.2. Application in the pharmaceutical industry

The most important application of extrusion in the pharmaceutical industry is in the preparation of granules or pellets of uniform size, shape, and density, containing one or more drugs [31]. The process involves a preliminary stage in which dry powders, drug, and excipients are mixed by conventional blenders, followed by addition of a liquid phase and further mixing to ensure homogeneous distribution. The wet powder mass is extruded through cylindrical dies or perforated screens with circular holes, of typically 0.5–2.0 mm diameter, to form cylindrical extrudates [32]. In the large-scale manufacture of suppositories and pessaries extrusion rather refers to forcing the material through a capillary die [33,34].

Melt extrusion for the manufacture of pellets [35] had revealed the potential for controlled release of polymer-embedded drugs and limitations. Pioneering work in the field employing the melt extrusion process as a manufacturing tool was performed by Doelker [36]. Typically, a co-rotating twin-screw configuration is used in most of the published studies. The equipment for the manufacture of solid dispersions has been described more precisely by Nakamichi [37,38].

The second core element of the integrated technological system is the device to shape on-line the thermoplastic strand leaving the extruder [39]:

(a) Calendering, in which the molten strand is forced between two calender rollers, thus producing films, flakes or sheets which may already contain single tablet cores.

(b) Pellet-forming, which may, for example, be a rotating knife cutting spaghetti-like extruded strands.

2.2.3. Regulatory aspects

Oral pharmaceutical products from the melt extrusion process have been approved in the USA, European and Asian countries. The process technology lends itself to comprehensive documentation, thus satisfying regulatory authorities. It is a major advantage that extrusion is a mature engineering technology. As a process it provides many parameters, such as feeding rate, segmental temperatures and pressure or applied vacuum, which can be monitored on-line with local meters and sensors. Such data contribute to the comprehensive documentation and the quality of production lots and may finally simplify quality control.

3. The drug delivery technology

3.1. Introduction

Melt extrusion may be applied to disperse drugs in a given matrix down to the molecular level, e.g. to form a true solution. It is the convenience of the technology that gives new hope to the glass or solid solution approach as a delivery system for poorly soluble drugs. The use of melts in order to obtain solid molecular dispersions, e.g. glass or solid solutions, is well known to the expert and the essential advantage of a melt process in this domain is its solvent-free formation of such dispersions [40]. Since with solvent processes there are various problems relating to their use (environmental pollution, explosion-proofing and residual organic solvent) and measures to counteract these problems are desirable [41].

The melt extrusion process is capable of handling active agents of different particle sizes as well as amorphous solids or other polymorphic forms leading to the same product. Basically, solid dispersion systems can be divided into six different categories (Fig. 5) [42].

Sekiguchi and Obi were first to report the melting or fusion method [43]. In 1974 solid dispersions of drugs were described as: "... a relatively new field of pharmaceutical technique and its principles play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs" [44].

When we look at the market of pharmaceutical products today solid dispersion systems, in particular, solid molecular dispersions are still found to be neglected. Only a few ever made it to the market including a griseofulvin–polyethyleneglycol-dispersion (Gris-PEG[®] marketed by Wander), Cesamet[®] a nabilone-PVP (polyvinyl pyrrolidone) preparation (marketed by Lilly) [45] as well as a formulation of troglitazone (Rezulin[®]) marketed by Parke-Davis which had to be withdrawn from market for toxicology related issues of the drug. Several implants containing

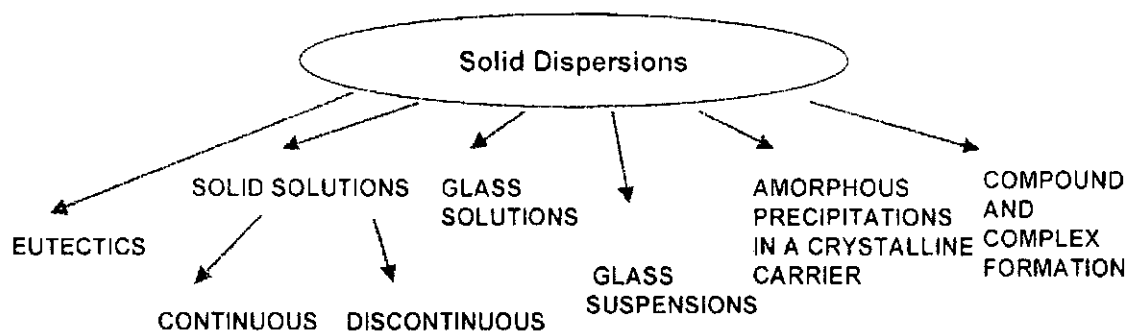


Fig. 5. Categories of solid dispersions.

LHRH agonists for parenteral use have become commercially available, such as goserelin (Zoladex[®]) or buserelin (Depot-Profact[®]) embeddings in poly(lactide-co-glycolide) (PLGA) [46].

The troglitazone formulation in PVP was actually manufactured by melt extrusion [47]. Melt extrusion technology has proven to be a suitable method for the production of controlled release reservoir systems consisting of polyethylene vinylacetate (EVA) co-polymers. Based on this technology, two controlled release systems Implanon[®] and NuvaRing[®], have been developed [48].

Problems limiting the commercial application of solid dispersions involve mainly the method of preparation, reproducibility of physicochemical properties, formulation into dosage forms, the scale up of manufacturing processes, and the physical and chemical stability of drug and vehicle [49].

A matter of uncertainty rarely addressed is the analytical differentiation of amorphous embeddings in crystalline carriers compared to a true solid solution, where the drug is molecularly dispersed in the carrier. The same holds true for the amorphous embedding in a glassy carrier compared to a glass solution. The term solid molecular dispersion differentiates from amorphous embeddings [50]. Solid molecular dispersion summarizes solid and glass solution irrespective of the nature, e.g. the molecular weight, of the solvent or solute.

Two major factors that stabilize solid molecular dispersions are intermolecular interactions [51–53] between the drug and the carrier and the viscosity of the carrier [54]. Glass transition temperature has long been seen as the predominant factor governing the physical stability of solid dispersions. However, this concept only holds for true solid molecular dispersions above their saturation limit. Within solid amorphous dispersions, the mobility of the active molecule is already given in the amorphous phase of the active itself possibly leading to recrystallization processes [55]. In the meantime investigations have shown that direct linear correlations between glass transition temperature and recrystallization tendency are rarely given. The solubilizing and stabilizing effects of the carrier systems' intermolecular interactions are often of far greater importance for physicochemical stability [56–59].

The mechanisms of drug release from solid dispersions in water-soluble polymers has been reviewed recently [60]. Because of surface activity of carriers used, complete dissolution of drug from melt extruded solid dispersions can be obtained without the need for further pulverization, sieving and mixing with excipients [61]. The effect of the molecular weight of the matrix polymers on the dissolution profile has been described with special respect to solid dispersions and solid molecular dispersions [62].

These findings contribute to the field of melt extrusion as the molecular weight and other characteristics of a polymeric carrier such as crystallinity and hydrogen bonding, vice versa pre-determine the manufacturing conditions in the extrusion process.

3.2. Application of melt extrusion as drug delivery technology

The breakthrough was achieved by the availability of a great variety of pharmaceutically approved carrier systems [63]. Such carrier systems include PVP [64] or its co-polymers [65], poly(ethylene-co-vinylacetate) [66], polyethylene glycol (PEG) [67], cellulose-ethers [68], and acrylates [69]. The properties of polyethylene oxide (PEO) as a drug carrier in melt extrusion with the aim to obtain chlorpheniramine maleate matrix tablets was examined by McGinity [70]. Amongst the different classes of biodegradable polymers, the thermoplastic aliphatic poly(esters) like poly(lactide) (PLA), poly(glycolide) (PGA), and the copolymer of lactide and glycolide, poly(lactide-co-glycolide) (PLGA) have been used in extrusion. Starch and starch derivatives have been applied along with [71] low molecular weight excipients like sugars and sugar alcohols and waxes [72]. The basic prerequisite for the use in melt extrusion is the thermoplasticity of the polymers or that of the respective formulations.

Long residence time and high glass transition temperature (T_g) resulting in high process temperatures have often been described as potential drawbacks of the melt extrusion process. The comparison of the influence of two different implant manufacturing techniques, extrusion and injection molding, on the *in vitro* degradation of the polymeric matrix

of polylactic acid (PLA) was studied. Both kinds of implants were loaded with a somatostatin analogue. It was shown that both molecular weight and polydispersity decreased after extrusion or injection molding. This decrease was more pronounced with the latter technique possibly due to an increased residence time [73]. Repka et al. showed that a thermally labile drug, hydrocortisone, could be successfully incorporated into hydroxypropylcellulose (HPC) films produced by melt extrusion [74].

Apart from distinct dosage forms or tailored release profiles melt extrusion offers the chance to circumvent the problem of polymorphic forms with different solubilities, the possibility to start from different particle sizes and a possible reduction of tablet size. Examples have shown that more favorable polymorphic forms may be stabilized on incorporation into PVP [75,76]. Melt extrusion with pharmaceutical actives having a low melting point has also been described. Under such conditions the extrusion process may serve as an agglomeration step [77]. An example for a change in morphology, continuously introduced in the melt extrusion process, applied to alter the release characteristics has been presented by Gurny et al. [78]. In order to influence the release of an extrudate a 200 µm thick layer on the extrudate surface was introduced while extruding.

In addition, implants [79,80], stents [81], oral dosage forms [82], bioadhesive ophthalmic inserts [83], topical films [84], and effervescent tablets [85] have been developed using the melt extrusion process.

3.3. Solid dispersions with melt extrusion technology

Melt extrusion is a significant step forward to cover the technology related issues and makes the solid molecular dispersion approach a viable option. The viability of melt extrusion technology for the production of thin, flexible, acrylic films for topical drug delivery has been investigated by Aitken-Nichol et al. ([86]). Lidocaine HCl was able to plasticize the acrylic polymer and the drug was completely dispersed at the molecular level in the extruded films. Solubilized drug molecules were shown to plasticize the polymer by increasing the average polymer chain spacing [86].

A contraceptive vaginal ring containing etonogestrel and ethinyl estradiol has been prepared by melt extrusion. Coaxial fibers have been produced with varying steroid concentrations in the polymer and the release has been studied. The powder mixtures were blended in a twin-screw extruder. The polymer melted and the steroids completely dissolved in the polymer. After leaving the extruder, the strands were cooled to room temperature and granulated using a strand granulator. For the preparation of the coaxial fibers, a co-extrusion installation was used. The installation consisted of two single-screw extruders that are connected to a spinning block. The two extruders were used to melt the core and membrane polymer at temperatures above 110°C. The molten polymers were delivered to two gear pumps, which assure an accurate flow of both polymers to the spin-

neret. Subsequently, the membrane and core polymers were combined in a spinneret, thereby forming the coaxial fiber [87].

A floating sustained release dosage form composed of nifedipine hydrochloride and hydroxypropylmethylcellulose acetate succinate was prepared using a twin-screw extruder. By adjusting the position of the high-pressure screw elements in the immediate vicinity of the die outlet, and by controlling the barrel temperature, a puffed dosage form with very small and uniform pores were obtained. It was shown that the puffed dosage form, consisting of enteric polymer prepared using the twin-screw extruder, was very useful as a floating dosage form that was retained for a long period in the stomach [88].

Sustained release formulations of isosorbide nitrates with polyvinylacetate have been developed using melt extrusion as manufacturing process. The *in vitro* release profiles indicate that even at low amounts (w/w) of the polymer the sustaining action of the polymer is sufficient to delay the release [89]. Formulations and dosage forms for poorly soluble drugs applying melt extrusion technology have been evaluated in a number of cases.

Underlining the economic importance of the melt extrusion process Ghebre-Sellassie [90] examined the use of different polymers revealing that hydroxypropyl cellulose may be a better water-soluble polymer compared to PVP for poorly soluble drugs. X-ray powder diffraction studies suggested that the drug substance mostly existed in the crystalline state truly representing a crystalline solid dispersion. Extrusion as a way of manufacture is mentioned and a variety of examples using melt processes are given [90].

A number of glass solutions of poorly soluble drugs have been developed using the melt extrusion process with a drug load ranging from 30 to 60% with real time stability up to 9 years. During this time period no crystallization could be detected by means of X-ray powder diffraction or differential scanning calorimetry [91]. It seems obvious, that stability of solid molecular dispersions is achieved when the solubility of a given drug in the carrier is not exceeded. By definition such systems are thermodynamically stable as their stability is related to the solubility of the active and not to the viscosity of the matrix as in supersaturated systems which are kinetically stabilized.

Glass solutions of a lipophilic drug substance by melt extrusion technology which on dissolution forms nanoparticles and thereby increases the dissolution kinetics have been presented recently [92]. PVP or a vinylpyrrolidone–vinylacetate copolymer have been studied together with different surfactants.

17-Estradiol hemihydrate as a poorly water-soluble drug was improved with respect to its solubility and dissolution rate by melt extrusion. Different compositions of excipients such as PEG 6000, PVP or a vinylpyrrolidone–vinylacetate-copolymer were used as polymers and Sucroester[®] WE15 or Gelucire[®] 44/14 as additives. The solid dispersions resulted in a significant increase in dissolution rate when compared

to the pure drug or to the physical mixtures. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17-Estradiol, 50% PVP and 40% Gelucire™ 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets [93].

Amorphous polysaccharide matrices determining the release rate of melt extruded dispersions have been examined by Rein et al. [94]. Carbohydrate based glassy matrices which are stable in the glassy state at ambient temperatures may be prepared by the use of aqueous plasticizers with melt extrusion. Such glassy matrices are useful for the encapsulation of drugs and flavoring agents [95].

Foster et al. melt extruded indomethacin, lacidipine and tolbutamide with PVP. Indomethacin samples remained amorphous on storage as demonstrated by X-ray powder diffraction (XRPD) and temperature modulated differential scanning calorimetry (TMDSC). For lacidipine and tolbutamide low crystallinity levels were detected which, at estimated 7% crystallinity, decreased the dissolution rate significantly. The presence of significant hydrogen bonding (as indicated by the deviation of the experimental from the theoretical glass T_g values) may decrease uptake of moisture and restrict plasticization of the matrix. However, lacidipine recrystallized even when T_g was well above the storage temperature [96].

Along with literature describing the in vitro performance of solid dispersions a number of melt extruded solid dispersions have been examined in humans.

The antiretroviral agent loviride has been melt extruded to a solid molecular dispersion in HPMC and showed remarkably lower food-effect compared to capsules [97].

Further, the extrusion process has been applied in order to combine a sparingly water-soluble drug compound, a cyclodextrin, and a physiologically tolerable water-soluble organic polymer [98].

Antifungal compositions of itraconazole were prepared as solid dispersions from the melt extrusion process. In a limited number of volunteers the melt extruded tablet gave an area under the curve (AUC) of itraconazole in the fasted state that was 2.3 times the area under the curve of the marketed reference capsule [99].

Melt extruded dispersions of ibuprofen were compared to the lysinate salt of ibuprofen in healthy volunteers. Bioequivalence was demonstrated with the relevant parameters AUC and C_{max} . Also, the t_{max} as a measure for onset proved to be equivalent with 0.5 h for test and reference [100].

4. Conclusions and outlook

Melt extrusion technology today represents an efficient pathway for the manufacture of drug delivery systems. Resulting products are mainly found amongst semi-solid and solid preparations. The potential of the technology is reflected in the wide scope of different dosage forms cover-

ing oral, parenteral and topical applications. In addition, the physical state of the drug in the melt extruded formulations reaches from simple crystalline embeddings, mainly in the field of sustained release applications, to amorphous or molecularly dissolved stages. Compared to solvent processes aiming at solid molecular dispersions melt extrusion offers a promising alternative. The possible use of a broad selection of excipients from high molecular weight polymers to low molecular weight additives like sugar alcohols, waxes or surfactants opens a field of numerous combinations for formulation research.

Drawbacks of the technology are often related to high energy input mainly related to shear forces and temperature. This is where process engineering comes into play. The design of screw assemblies and extruder dies are two major areas, which have significant impact on the degradation of drugs and excipients. As the residence time is rather short compared to conventional processes like sterilization, even drugs known to be sensitive to elevated temperatures have been processed successfully. In addition the exposure to oxygen in the extrusion channel is limited.

Work in the field is increasing and the literature published reveals interesting new aspects like in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt, and nanoparticles released from molecular dispersions manufactured by melt extrusion.

Unlike other delivery systems, most of which consist of a random dispersion of a drug in a matrix, extrusion technology may be used to place exact amounts of active drug in well-defined layers of micrometer range thickness. In addition, the processing of the polymer determines not only the design of the device but it influences its morphology, namely its microporous structure, polymeric chain orientation and crystallinity to a high degree.

Further, it remains to be seen whether the intense interaction in the melt can be used to form complexes with rather sensitive molecules like peptides and proteins in order to stabilize such structures.

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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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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 solvent (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

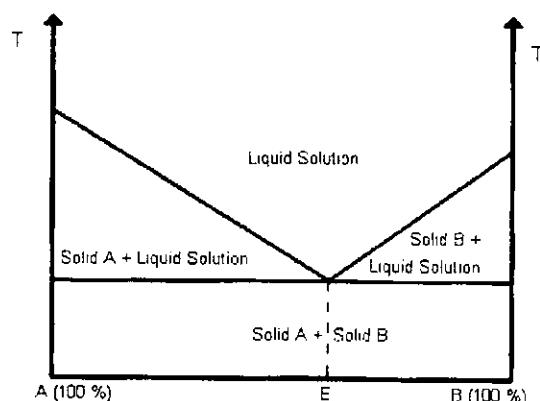


Fig. 1. Phase diagram for a eutectic system (reproduced with modifications from Ref. [8]).

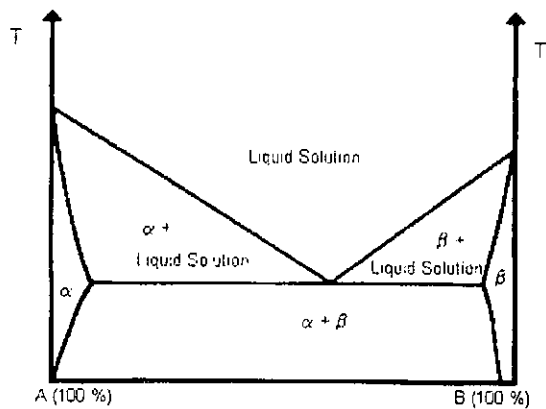


Fig. 2. Phase diagram for a discontinuous solid solution (reproduced with modifications from Ref. [8]).

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

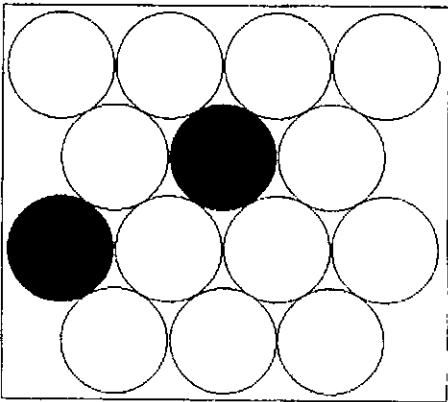


Fig. 3. Substitutional crystalline solid solution (reproduced with modifications from Ref. [13]).

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.

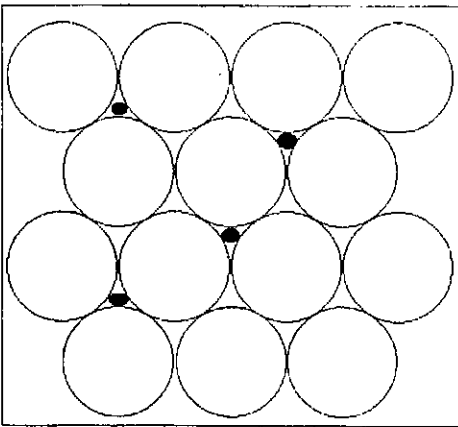


Fig. 4. Interstitial crystalline solid solution (reproduced with modifications from Ref. [13]).

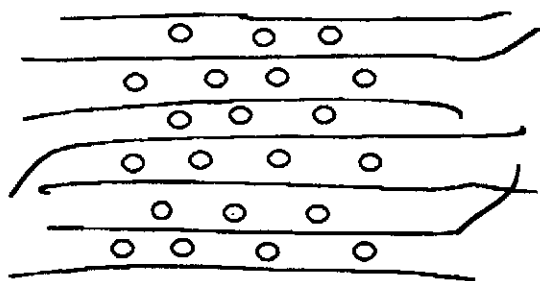


Fig. 5. Interstitial solid solutions of small molecules in the crystalline parts of a polymer (reproduced with modifications from Ref. [15]).

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

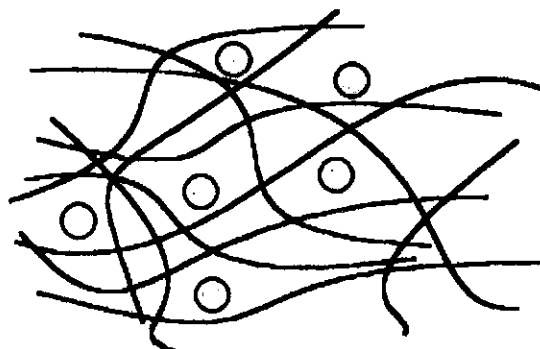


Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

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 Nakamura [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.

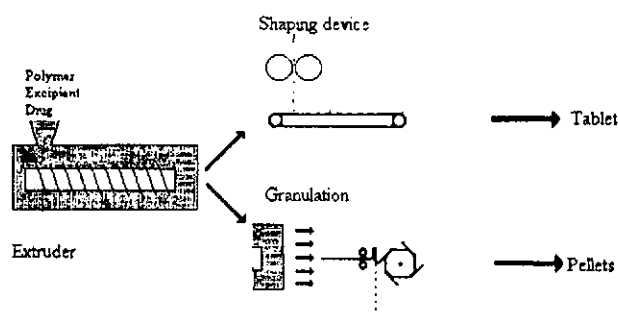


Fig. 7. Scheme of a hot melt extruder (reproduced with modifications from Ref. [37]).

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], urso-deoxycholic 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 Kearney 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 hydroxypropyl-methylcellulose 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) Hydroxypropyl-methylcellulose (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 IIO-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 IIO-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 spironolactone 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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