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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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REF: EXPEDIENTE 10-054-915

TÍTULO SOLICITADO: “UN SISTEMA INTRAUTERINO PARA LA RETENCION DE UN COMPUESTO BIOLOGICAMENTE ACTIVO QUE COMPRENDE, UN DEPOSITO DEL COMPUESTO, UNA ESTRUCTURA QUE DEFINE UN ESPACIO INTERIOR PARA RECIBIR EL DEPOSITO Y UNO O MAS ELEMENTOS DE RETENCION”

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PRIORIDAD: EP 07120191.7 DE 07/11/2007

SOLICITANTE: N.V. ORGANON

APODERADO: LUZ CLEMENCIA DE PAEZ.

TRÁMITE: REMISIÓN DE INFORMACIÓN.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, conocido apoderado de la sociedad **LAFRANCOL S.A.S.** en el trámite de la referencia, y con el propósito de coadyuvar en la decisión sobre la misma habrá de adoptarse próximamente, de manera respetuosa me permito presentar argumentos adicionales para demostrar que la solicitud en cuestión incumple los requisitos aplicables, y no merece, por ello, recibir el beneficio patentario.

I. COMPLEMENTO DE INFORMACIÓN.

Con el propósito de reiterar que la solicitud trámite carece de los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486, me permito plantear los siguientes argumentos adicionales.

En primer lugar, es importante señalar que el capítulo reivindicatorio modificado presentado el 11 de abril de 2014, corresponde a un cambio de forma, que por esa condición, no logra superar los argumentos planteados en contra por el suscrito, ni aquellos formulados por el examinador técnico. De esta manera al revisar dicho nuevo capítulo reivindicatorio, persiste la carencia de nivel inventivo, pues se mantienen las mismas características técnicas:

Reivindicación 1 anterior	Nueva Reivindicación 1
Un sistema intrauterino (1) para la retención de un compuesto biológicamente activo dentro del útero de un mamífero hembra, el sistema comprende: un depósito (22) que comprende un compuesto y un polímero EVA, en donde el polímero EVA controla una velocidad de liberación del compuesto dentro del útero y en donde el depósito tiene forma sustancialmente estable y no se erosiona durante el uso; una estructura (16) que define un espacio interior (20) para recibir el depósito, la estructura tiene una estructura abierta que permite el acceso de al menos 50% de una superficie externa del depósito; y al menos un elemento de retención (6) para retener la estructura dentro del útero.	Un sistema intrauterino (1) para la retención de un compuesto biológicamente activo dentro del útero de un mamífero hembra el sistema comprende: un depósito (22) que comprende un compuesto y un polímero EVA, en donde el polímero EVA controla una velocidad de liberación del compuesto dentro del útero y en donde el depósito tiene forma estable y no se erosiona durante el uso; una estructura (16) que define un espacio interior (20) para recibir el depósito, la estructura tiene una estructura abierta que permite el acceso de al menos 50% de una superficie externa del depósito; y al menos un elemento de retención (6) para retener la estructura dentro del útero.

Como se puede ver en la tabla anterior, la reivindicación principal no presenta cambio alguno que le permita superar las objeciones referentes a concisión (Art 30 D 486, Art 22 PCT) o nivel inventivo (Art18 D486).

Es de notar que los defectos de las reivindicaciones 1, 2, 5, 8, 9, 10 y 15 permanecen en la versión modificada del grupo de reivindicaciones, conservando resultados a alcanzar y palabras que restan claridad a la materia reclamada y por tanto haciendo caso omiso a los requerimientos presentados por el despacho de la SIC.

Ventajas y resultados a obtener

El solicitante, en relación con la objeción del Examinador en cuanto a la reclamación de ventajas y resultados a obtener, menciona (Reiv. 1, 2 y 8):

b- i) Haciendo referencia a las objeciones respecto a expresiones en las reivindicaciones que reclaman resultados a alcanzar, me permito llamar la atención del Examinador sobre el hecho que un parámetro y un resultado a alcanzar son características aceptadas según el Manual Andino de Patentes (MAP) y el Instructivo Examen de Solicitudes de Patentes de Invención y Modelos de Utilidad de la SIC, en donde se establece que un resultado a alcanzar no es una característica técnica de la invención, pero puede aparecer en la reivindicación acompañado de las características técnicas que definen la invención^{1,2}.

La problemática frente a la concesión de este tipo de reivindicaciones (con ventajas y resultados a alcanzar) es que abarcan las tecnologías conocidas y las futuras, pues los “resultados a alcanzar” pueden ser logrados, indefinidamente, por otros medios.

En este caso particular, conceder esta reivindicación impediría usar formulaciones de la farmacia clásica como lo son las formulaciones de liberación modificada, por los expertos en farmacia e investigadores de este tipo de tecnologías.

Se desea indicar que existen varios tipos de formulaciones capaces de modificar la liberación del fármaco: **prolongada, retardada y pulsátil**, incluso son reguladas a nivel sanitario por monografías de las farmacopeas aceptadas:

Formas farmacéuticas de liberación modificada. Preparaciones en las que la velocidad y el lugar de liberación de la sustancia o sustancias activas es diferente del de la forma farmacéutica de liberación convencional administrada por la misma vía. Esta modificación deliberada se consigue por una formulación particular o por un método de fabricación especial. Las formas farmacéuticas de liberación modificada incluyen formas farmacéuticas de liberación **prolongada**, de liberación **retardada** y de liberación **pulsátil**.

REAL FARMACOPEA ESPAÑOLA, 2.a edición, p. 579

Se tiene que las formulaciones para controlar la velocidad de liberación de un fármaco son conocidas para medicamentos hormonales del tipo anticonceptivo y para otros como metronidazol (ES 2 174 930, fecha de publicación 04.12.1996):

⁵⁴ Título: Composiciones de metronidazol de liberación modificada y métodos para preparar y utilizar las mismas.

⁵ Campo de la invención

Esta invención se refiere generalmente a composiciones farmacéuticas que contienen metronidazol y, particularmente, a composiciones de metronidazol de liberación modificada que, cuando se toman una vez al día, liberan una cantidad terapéuticamente efectiva de metronidazol durante un periodo de 24 horas.

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En las farmacopeas se encuentran formas sólidas para liberación como comprimidos vaginales, óvulos, cápsulas vaginales, tampones medicamentosos y otros. Las cuales deben demostrar la capacidad de liberación mediante ensayos **disolución**.

A partir de lo reclamado, se puede concluir que el **depósito (22)** es como un comprimido que desde las normas regulatorias debe cumplir con ensayos como de del disolución o disgregación, como se ve a continuación:

Comprimidos vaginales

DEFINICIÓN

Los comprimidos vaginales son preparaciones sólidas unidosis. En general, se ajustan a las definiciones de los comprimidos no recubiertos o peliculares que se dan en la monografía *Comprimidos (0478)*.

PRODUCCIÓN

Se lleva a cabo un ensayo adecuado para demostrar la liberación apropiada del o los principios activos por los comprimidos vaginales destinados a una acción local prolongada.

ENSAYOS

Disgregación. A menos que estén destinados a una acción local prolongada, los comprimidos vaginales satisfacen el ensayo de disgregación de los supositorios y óvulos (método especial para comprimidos vaginales, 2.9.2). Examinar el estado de los comprimidos después de 30 min, salvo excepción justificada y autorizada.

REAL FARMACOPEA ESPAÑOLA, 2.a edición, p. 617

Con lo anterior, lo que se pretende es dejar claro que se están reclamando **características y formas farmacéuticas** ya conocidas, que acaparan la comercialización y uso de otros DIU que liberen de forma prolongada **cualquier tipo de fármaco**, pues nótese que en la reivindicación 1 no limita el compuesto biológico: ni a los compuestos evaluados, ni a una extrapolación razonable de los mismos.

Términos imprecisos

Frente a la objeción del Examinador, el solicitante menciona:

ii) Con el ánimo de facilitar el trámite de la presente solicitud, los términos “sustancialmente” (Reivindicación 1) y “parte sustancial” (Reivindicación 15), han sido eliminados del Capítulo Reivindicatorio Modificado adjunto, y específicamente para el caso de la expresión “parte sustancial”, este término se ha reemplazado por el rango “al menos 50%”.

Con relación a lo anterior, se tiene que a pesar de haber corregido esos defectos en el nuevo capítulo reivindicatorio, no se puede considerar que el actual total cumplimiento de la norma pues un porcentaje sigue siendo un valor relativo y su implementación en los rangos de al menos 50% no supone un efecto técnico demostrado.

Reclamación de compuestos farmacológicos

Frente a este aspecto, el solicitante menciona:

iii) Finalmente, en relación con la objeción de que se están reclamando compuestos farmacológicos y características de copolímeros EVA en las Reivindicaciones 1 y 9, quisiera aclarar al Examinador que dichos elementos corresponden a características específicas del depósito (que es un elemento estructural), es decir, se está indicando el tipo de material del depósito que es un elemento estructural. Como se mencionó en el punto 2(b)(ii) anterior, el inventor tiene el derecho de reclamar protección para la totalidad de un concepto inventivo desarrollado sin importar la amplitud de éste, siempre y cuando encuentre soporte en el Capítulo Descriptivo y se conserve el principio de unidad de invención. Adicionalmente, dichas características únicamente están limitando el espectro de protección a la que el solicitante tiene derecho las cuales son totalmente aceptables a la luz de los lineamientos de la Guía de Examinación de Patentes de Invención y el Manual Andino de Patentes.

Se observa que en el caso de invenciones de ingeniería mecánica, ni la novedad y el nivel inventivo deberían estar en función del material que se utiliza (con efecto biológico o no), lo cual parece no ser tenido en cuenta por el solicitante, quien alega que los **compuestos** y las características de los **copolímeros EVA** “*son características específicas del depósito*”.

Se anota pues que si fuera vital definir el DEPÓSITO mediante el polímero EVA y CUALQUIER compuesto con actividad biológica entonces estaríamos reconociendo que se trata de una composición farmacéutica.

En cualquier caso, vale la pena destacar que estas matrices (**depósito**) ya eran conocidas en el estado de la técnica en sistemas de liberación controlada como Implanon® y Nuvaring®:

1. Introduction

Extrusion technology has proven to be an elegant method for the production of controlled release reservoir systems. Based on this technology, Organon developed two controlled release systems, i.e.,

Implanon® and NuvaRing® [1,2]. Both products are made of polyethylene vinylacetate (EVA) copolymers. Implanon® is an implant and is designed to release a progestagen for a period of three years. NuvaRing® is a contraceptive vaginal ring, designed to release both a progestagen and an estrogen for a period of 21 days.

The concept of these systems comprises a coaxial fiber, wherein a drug is dispersed or dissolved in a core polymer. The release from these coaxial fibers depends directly on the concentration gradient over

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Contrario a lo mencionado por el Solicitante, estas características **no están limitando** el espectro de protección sino que aumentan la materia protegida y le restan claridad a lo reclamado.

La concesión de este tipo de reivindicaciones pueden afectar no solo el mercado sino la investigación misma por parte de inventores nacionales al restringir elementos como el depósito (o matriz, núcleo, comprimido o composición farmacéutica), los compuestos (no definidos), o un (cualquier) sistema de retención dentro del útero.

A continuación se muestra un esquema de la reivindicación 1 en el cual se indican los defectos que la misma exhibe a pesar de la modificación realizada:

Por favor nótese que según la reivindicación 1, el depósito (22) es definido como un sistema de entrega de fármaco (SENF), es decir, una forma farmacéutica sólida, tableta, comprimido, cápsula granulado, polvo o supositorio, capaz de modificar la velocidad de liberación del compuesto según las necesidades.

Se desea anotar que en el campo técnico de farmacia varias tecnologías se emplean con el fin de modificar la velocidad de liberación de fármacos como:

Formas farmacéuticas de liberación prolongada
Formas farmacéuticas de liberación retardada
Formas farmacéuticas de liberación modificada
Formas farmacéuticas de liberación pulsátil

Son componentes de una forma farmacéutica para uso vaginal. Por favor notar que NO especifica el compuesto activo, el polímero, ni las cantidades de las mismas para alcanzar el resultado reclamado

(Ver anexo)

1. Un sistema intrauterino (1) para la retención de un compuesto biológicamente activo dentro del útero de un mamífero hembra el sistema comprende:

un depósito (22) que comprende un compuesto y un polímero EVA, en donde el polímero EVA controla una velocidad de liberación del compuesto dentro del útero y en donde el depósito tiene forma estable y no se erosiona durante el uso;

una estructura (16) que define un espacio interior (20) para recibir el depósito, la estructura tiene una estructura abierta que permite el acceso de al menos 50% de una superficie externa del depósito; y

al menos un elemento de retención (6) para retener la estructura dentro del

útero

Abarca cualquier tipo de estructura que retenga un DIU dentro del útero, no sólo los brazos de la T

Abarca cualquier depósito (comprimido vaginal) estable y que no se erosione, lo cual es parte de las normas de calidad de este tipo de dispositivos según las Farmacopeas (Ver anexo)

Comentarios sobre el Nivel inventivo – D1

Frente a las objeciones realizadas por el Examinador, el solicitante menciona que D1 no revelaba que el depósito pudiera estar exhibido en al menos 50%, ni el mismo diseño interior de la recepción del depósito, pues D1 incluye resortes:

23 a 25). Contrario a la presente invención donde el depósito no requiere de medios para empujar el suministro de la sustancia sólida y mucho menos tiene que encontrarse en una posición específica dentro del armazón para poder liberar su medicación. La dosis terapéutica del

presente invento se ubica en la totalidad del espacio interno del armazón en donde por lo menos el 50% de dicha dosis tiene contacto con la superficie exterior del depósito para liberar la medicación. A continuación se muestra un esquema donde se ilustra esta característica de la

(...)

reclama la presente invención. Es decir, no habría motivación para modificar el diseño de los huecos de D1 para utilizar un depósito que no se erosione y tenga una forma estable, pues el diseño específico del dispositivo de D1 requiere que la tableta que se encuentra ubicada en las perforaciones se erosione y colapse para así dar paso a la tableta que se encuentra ubicada adyacentemente a esta mediante la activación del mecanismo con resorte; si esta erosión no ocurre dicho mecanismo nunca podría activarse, luego no pueden ser hechas de polímero de EVA.

Se considera pertinente D1 porque enseña:

- diseño de DIU que contuviera formas farmacéuticas solidas en su interior para su disolución en la cavidad intrauterina
- el cual consta de orificios para la liberación del fármaco, *lo cual parece ser la característica técnica esencial del dispositivo reclamado*.

Y aunque D1 no revelaba los mismos orificios, estos no suponen un adelanto inesperado o sorprendente en el campo técnico pues como se verá a continuación un experto en la materia al enfrentar el problema planteado: *“la necesidad de desarrollar un sistema de dispositivo intrauterino capaz de almacenar una dosis de agente farmacológico y de dosificarlo eficientemente manteniendo un flujo constante durante un tiempo prolongado, además de ser compacto evitando lesiones sobre el cuello uterino del sistema reproductor femenino”*, a partir de D1 lograría llegar al DIU acá reclamado.

Factor clave a considerar: Superficie o frente de disolución

Se anota que la liberación del fármaco depende entre otros de la superficie de la forma farmacéutica expuesta al medio acuoso de liberación (en este caso: espacio

intrauterino), el esquema siguiente presenta cómo una forma farmacéutica al exponerse en el medio acuoso empieza a humedecerse y a liberar el fármaco:

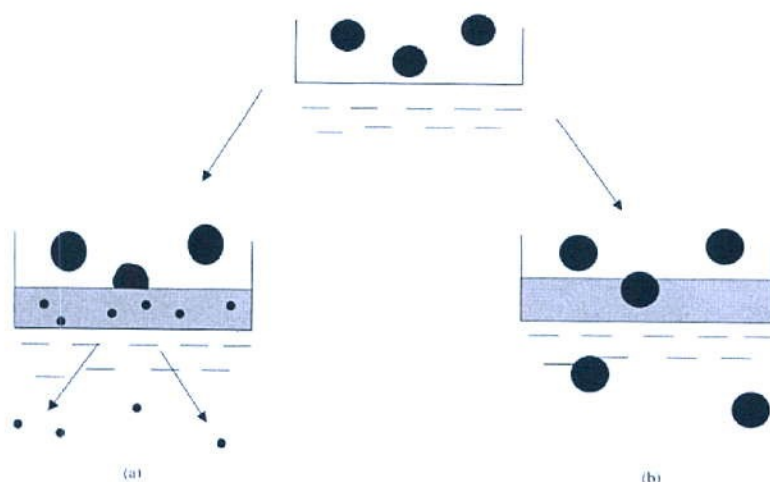


Fig. 4. Schematic diagram showing the fate of drug particles during the dissolution process. (a) Carrier-controlled dissolution, whereby the drug dissolves into the concentrated carrier layer prior to release and (b) drug-controlled dissolution whereby the drug is released effectively intact into the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

Duncan Q.M Craig, The mechanisms of drug release from solid dispersions in water-soluble polymers, International Journal of Pharmaceutics Volume 231, Issue 2, 14 January 2002, Pages 131–144

Entonces, a mayor superficie expuesta, más partículas de fármaco se liberan, adicionalmente, el grado de liberación también depende del polímero¹ con el cual se fabrica la matriz:

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

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

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

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

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

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

¹ Otras referencias que se discutirán más adelante ya revelaban el uso de polímeros EVA para estas matrices.

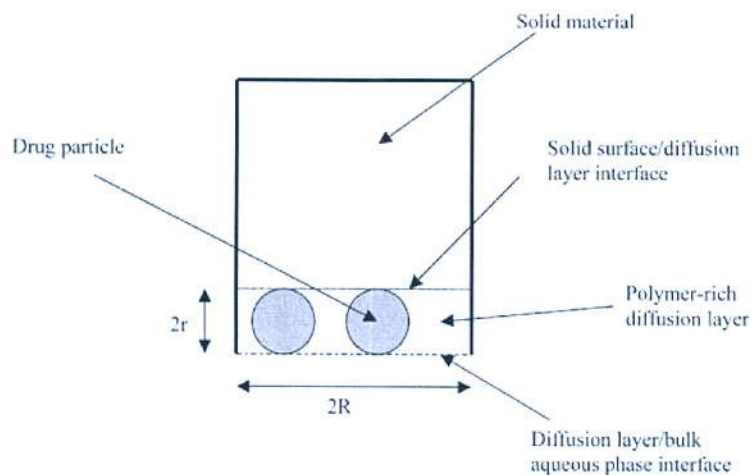


Fig. 5. Schematic representation of the structure of solid dispersions with reference to the model derived for drug-controlled dissolution.

Duncan Q.M Craig, The mechanisms of drug release from solid dispersions in water-soluble polymers, International Journal of Pharmaceutics Volume 231, Issue 2, 14 January 2002, Pages 131–144

En suma, la liberación de fármaco depende de varios factores, entre ellos la superficie de disolución, por tanto, para una persona experta que en la búsqueda de la solución del problema planteado hubiera sido **obvio**:

1. Aumentar la ventana de exposición del DEPÓSITO al espacio intrauterino, e
2. Incrementar la superficie del DEPÓSITO (p.ej. cilindro o tira).

Teniendo en cuenta la forma de este tipo de dispositivos, un experto medio con el ánimo de resolver el mencionado problema técnico, realizaría un diseño en el cual la mayoría del cuerpo de la T quedara expuesto. De esta forma, no nos encontramos frente a un DIU con efectos sorprendentes o inesperados gracias a sus orificios, pues lo reclamado es obvio a partir de las enseñanzas D1 y del conocimiento del experto en la materia.

De la composición del depósito

En otro aspecto de la invención, el solicitante hace hincapié en el tema del polímero EVA que está en el núcleo de matriz que a su vez contiene el medicamento (reivindicaciones 7 a 9):

Depósito que comprende

- I. Un núcleo de matriz de polímero,
- II. donde el polímero es EVA
- III. que comprende > 10% de vinil acetato
- IV. diámetro de 1 a 3 mm
- V. membrana que comprende polímero EVA de < 40% de vinil acetato
- VI. un compuesto esteroidal progesténico (ver Reiv. 9)

Frente a esto, se observa que J.A.H. *van Laarhoven et al.*, en su estudio de las propiedades de liberación de un dispositivo de liberación controlada, ya revelaba el uso de polímeros EVA de 9 y 28% junto con etonogestrel, un compuesto esteroidal progesténico:

2. Materials and methods

2.1. Materials

The steroid used in this study, etonogestrel, was obtained from Diosynth. The melting temperature of etonogestrel is 199 °C. Two types of polyethylene vinylacetate polymers were used in this study. "EVA 28" contains 28% vinylacetate and is used as core material in the coaxial fibers because of the higher solubility and permeability. "EVA 9" contains 9% vinylacetate and is applied in the membrane because of the lower solubility and permeability properties. The crystallinity of both polymers is about 20 and 38%, respectively [3–5]. Both EVA 28 and EVA 9 are random copolymers and have a melting temperature of, respectively, 80 and 100 °C.

The molecular weights are given in Table 1.

Por lo tanto, se tiene que las características de la composición del depósito ya habían sido reveladas previamente.

Comentarios sobre el Nivel inventivo – D2

Menciona el solicitante;

De acuerdo a lo anterior, no hay ninguna descripción en D2 de que el acceso se proporciona a al menos el 50% del recipiente, tales dimensiones no pueden ser simplemente tomadas de dibujos y la función técnica alcanzada no puede ser también derivada de estos. Según D2, no hay ninguna sugerencia diferente a que, únicamente un área mínima de material Silastic se encuentra expuesta para permitir la liberación gradual de la medicación y su posterior rellenado. Debido a que la

En este aspecto, este documento disponible para un experto en la materia sugiere una imagen que trasmite una idea muy similar sino igual a la reclamada por el solicitante. De este dibujo, es muy claro que el cuerpo de la T además de retener en si mismo un forma farmacéutica, posee ranuras para la liberación del fármaco, el tema del porcentaje de exposición – como bien lo dice el solicitante – es algo subjetivo pero el dibujo es bastante claro al sugerir cortes sobre la T.

Continúa el solicitante:

intrauterino en una estructura abierta. Adicionalmente, el contenedor de D2 está destinado para ser rellenado; lo cual no queda elaro el argumento del Examinador, cuando establece que podría lograrse la característica de obtener una forma estable, si lo que requiere es una expansión del contenedor de látex. En este sentido, el contenedor de D2 no puede ser considerado como un depósito de forma estable.

En esta región se aprovecha la argumentación para conectar lo mencionado por el Examinador en el Oficio, pues la palabra “estable” en este caso no es contundente para describir lo que el solicitante quiere decir, al parecer estable sería rígido o indeformable.

De cualquier manera, retornado al requisito de nivel inventivo, en este caso la persona versada en la materia tendría que pensar en las propiedades fisicoquímicas de liberación del fármaco en las condiciones acá planteadas (procesos de pre-formulación y formulación), de lo cual resulta que la ampliación de la ventana de exposición del fármaco y la forma cilíndrica o alargada del depósito (núcleo o matriz) son obvias para una persona versada en la materia.

Combinación D1, D2 y D3

Menciona el solicitante

biológicamente activo dentro del útero de un mamífero hembra. En conclusión, las enseñanzas de D1 a D3 no le permitirían a la persona medianamente versada en la materia a estar motivada a desarrollar un dispositivo intrauterino que comprende un depósito con un compuesto y un polímero de EVA, y un armazón que tiene una estructura abierta longitudinalmente a lo largo de todo el dispositivo.

Se observa que estos documentos efectivamente sugieren a la persona medianamente versada en la materia la forma de llegar a la materia reclamada, pues sus imágenes y divulgaciones enseñan y sugieren información clave para el técnico medianamente versado en la materia pues revelan plenamente las características esenciales reclamadas a lo largo de todo el capítulo reivindicatorio, como el depósito (22), la estructura (16) con espacio (20) y el elemento de retención.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

II. PRUEBAS.

Ruego que se tengan como pruebas de este escrito, los documentos mencionados en el texto del mismo, todos ellos aportados por el suscrito y obrante en el expediente.

2. J.A.H. van Laarhoven, M.A.B. Kruft, H. Vromans, Effect of supersaturation and crystallization phenomena on the release properties of a controlled release device based on EVA copolymer; Journal of Controlled Release 82 (2002) 309–317.
3. Duncan Q.M Craig, The mechanisms of drug release from solid dispersions in water-soluble polymers, International Journal of Pharmaceutics, Volume 231, Issue 2, 14 Enero 2002, P 131–144

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P. 44.655 del C. S de la J.

FORMAS FARMACÉUTICAS

FORMAS FARMACÉUTICAS

Glosario	579	Preparaciones líquidas para aplicación cutánea	593
Barras	580	Preparaciones líquidas de aplicación cutánea para uso veterinario	594
Cápsulas	580	Preparaciones líquidas para uso oral	596
Comprimidos	582	Preparaciones nasales	598
Dispositivos intrarruminales	585	Preparaciones oftálmicas	600
Espumas medicamentosas	586	Preparaciones óticas	603
Gomas de mascar medicamentosas	587	Preparaciones para inhalación	604
Granulados	588	Preparaciones para irrigación	609
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GLOSARIO

El siguiente texto proporciona definiciones y explicaciones de expresiones que pueden encontrarse o utilizarse en las monografías generales de formas farmacéuticas, pero que no están definidas en ellas. En ciertos casos, se hace referencia a otras expresiones equivalentes que pueden encontrarse en otras publicaciones o contextos.

Este glosario se incluye a título informativo.

Término estándar. Ha sido establecido por la Comisión de la Farmacopea Europea para describir la forma farmacéutica de un medicamento, la vía de administración y el envase utilizado y se proporciona en una publicación separada como Términos Estándar.

Principio activo. Cualquier componente de un medicamento destinado a proporcionar una actividad farmacológica u otro efecto directo en la diagnosis, tratamiento o prevención de enfermedades, o a actuar sobre la estructura o función de un organismo humano o animal por medios farmacológicos. Un medicamento puede contener más de un principio activo. Términos equivalentes: ingrediente activo, sustancia farmacéutica, sustancia medicinal.

Excipiente. Cualquier componente, distinto del principio o principios activos, presente en un medicamento o utilizado en su fabricación. La función de un excipiente es servir como soporte (vehículo o base) o como componente del soporte del principio o principios activos contribuyendo así a propiedades tales como estabilidad, perfil biofarmacéutico, aspecto y aceptación por el paciente, y para facilitar su fabricación. En general, en la formulación de una especialidad farmacéutica se utiliza más de un excipiente.

Vehículo. Soporte, compuesto por uno o más excipientes, de la sustancia o sustancias activas en una preparación líquida.

Base. Soporte, compuesto por uno o más excipientes, de la sustancia o sustancias activas en preparaciones semi-sólidas y sólidas.

Formas farmacéuticas de liberación convencional. Preparaciones en las que la liberación de la sustancia o sustancias activas no está deliberadamente modificada por un diseño de formulación particular ni por un método de fabricación especial. En el caso de una forma farmacéutica sólida, el perfil de disolución de la sustancia activa depende esencialmente de sus propiedades intrínsecas. Término equivalente: forma farmacéutica de liberación inmediata.

Formas farmacéuticas de liberación modificada. Preparaciones en las que la velocidad y el lugar de liberación de la sustancia o sustancias activas es diferente del de la forma farmacéutica de liberación convencional administrada por la misma vía. Esta modificación deliberada se consigue por una formulación particular o por un método de fabricación especial. Las formas farmacéuticas de liberación modificada incluyen formas farmacéuticas de liberación prolongada, de liberación retardada y de liberación pulsátil.

Formas farmacéuticas de liberación prolongada. Formas farmacéuticas de liberación modificadas para garantizar una liberación más lenta de la sustancia o sustancias activas que la de una forma farmacéutica de liberación convencional administrada por la misma vía. La liberación prolongada se consigue por una formulación particular y un método de fabricación especial. Término equivalente: forma farmacéutica de liberación ampliada.

Formas farmacéuticas de liberación retardada. Formas farmacéuticas de liberación modificadas para retrasar la liberación de la sustancia o sustancias activas. La liberación retardada se consigue por una formulación particular y por un método de fabricación especial. Las formas farmacéuticas de liberación retardada incluyen preparaciones gastro-resistentes como se definen en las monografías generales de formas farmacéuticas sólidas para administración oral.

Formas farmacéuticas de liberación pulsátil. Formas farmacéuticas de liberación modificadas para garantizar una

dos para la fabricación de envases (3.1 y subsecciones) y para Envases (3.2 y subsecciones).

Se pueden distinguir varios tipos de preparaciones vaginales:

- óvulos,
- comprimidos vaginales,
- cápsulas vaginales,
- disoluciones, emulsiones y suspensiones vaginales,
- comprimidos para disoluciones y suspensiones vaginales,
- preparaciones vaginales semisólidas,
- espumas vaginales,
- tampones vaginales medicamentosos.

PRODUCCIÓN

Durante la fabricación, envasado, conservación y distribución de las preparaciones vaginales se toman las medidas necesarias para asegurar su calidad microbiológica; en el texto *Calidad microbiológica de las preparaciones farmacéuticas* (5.1.4) se dan recomendaciones a este respecto.

ENSAYOS

Uniformidad de contenido (2.9.6). Salvo indicación contraria o excepción justificada y autorizada, las preparaciones sólidas unidosis cuyo contenido de principio activo sea inferior a 2 mg, o menor del 2 por ciento de la masa total, satisfacen el ensayo A (comprimidos vaginales) o el ensayo B (óvulos, cápsulas vaginales) para la uniformidad de contenido de preparaciones presentadas en dosis únicas. Si la preparación contiene más de un principio activo, el ensayo sólo se aplicará a los que se encuentren en las condiciones anteriormente indicadas.

Uniformidad de masa (2.9.5). Las preparaciones sólidas vaginales unidosis satisfacen el ensayo de uniformidad de masa de preparaciones en dosis únicas. Si se prescribe un ensayo de uniformidad de contenido para todos los principios activos, no se exige el ensayo de uniformidad de masa.

Masa o volumen extraíble (2.9.28). Las preparaciones vaginales líquidas o semisólidas suministradas en envases unidosis satisfacen el ensayo.

Disolución. En el caso de preparaciones sólidas presentadas en dosis única se puede llevar a cabo un ensayo apropiado para demostrar que la liberación del principio o principios activos es satisfactoria, por ejemplo, uno de los ensayos descritos en el texto *Ensayo de disolución para formas sólidas orales* (2.9.3).

En los casos en que se prescribe un ensayo de disolución, puede no exigirse un ensayo de disgregación.

Óvulos

DEFINICIÓN

Los óvulos son preparaciones sólidas unidosis. Son de formas variables, pero generalmente ovoides, con un volumen y consistencia adaptados a la administración por vía vaginal. Contienen uno o más principios activos dispersados o

disueltos en una base apropiada que puede ser soluble o dispersable en agua o puede fundirse a la temperatura del cuerpo. Si es necesario, pueden añadirse excipientes tales como diluyentes, adsorbentes, agentes tensioactivos, lubricantes, conservantes antimicrobianos y colorantes autorizados por la Autoridad competente.

PRODUCCIÓN

Los óvulos se preparan normalmente por moldeado. Cuando proceda durante la fabricación de óvulos, se toman las medidas necesarias para garantizar un tamaño de las partículas del principio o de los principios activos adecuadamente controlado. Si es necesario, el principio o los principios activos se trituran previamente y se pasan por un tamiz adecuado.

Cuando se preparan por moldeado, la masa medicamentosa, suficientemente licuada por calentamiento, se vierte en moldes apropiados. El óvulo solidifica por enfriamiento. Se utilizan diversos excipientes para este procedimiento, tal como grasa dura, macrogoles, manteca de cacao, y diversas mezclas gelatinosas que consisten, por ejemplo, en gelatina, agua y glicerol.

Se lleva a cabo un ensayo adecuado para demostrar la liberación apropiada del o los principios activos por los óvulos destinados a una acción local prolongada.

Cuando proceda, se efectúa la determinación de la resistencia a la fractura de los óvulos (2.9.24).

ENSAYOS

Disgregación. A menos que estén destinados a una acción local prolongada, los óvulos satisfacen el ensayo de disgregación de supositorios y óvulos (2.9.2). Examinar el estado de los óvulos después de 60 min, salvo excepción justificada y autorizada.

CONSERVACIÓN

En envase bien cerrado.

Comprimidos vaginales

DEFINICIÓN

Los comprimidos vaginales son preparaciones sólidas unidosis. En general, se ajustan a las definiciones de los comprimidos no recubiertos o pelliculares que se dan en la monografía *Comprimidos* (0478).

PRODUCCIÓN

Se lleva a cabo un ensayo adecuado para demostrar la liberación apropiada del o los principios activos por los comprimidos vaginales destinados a una acción local prolongada.

ENSAYOS

Disgregación. A menos que estén destinados a una acción local prolongada, los comprimidos vaginales satisfacen el ensayo de disgregación de los supositorios y óvulos (método especial para comprimidos vaginales, 2.9.2). Examinar el estado de los comprimidos después de 30 min, salvo excepción justificada y autorizada.

Cápsulas vaginales

DEFINICIÓN

Las cápsulas vaginales (óvulos encapsulados) son preparaciones sólidas unidas. En general son similares a las cápsulas blandas, de las que difieren solamente en su forma y tamaño. Las cápsulas vaginales son de formas variables, pero generalmente son ovoides, lisas y de aspecto exterior uniforme.

PRODUCCIÓN

Se lleva a cabo un ensayo adecuado para demostrar la liberación apropiada del o de los principios activos por las cápsulas vaginales destinadas a una acción local prolongada.

ENSAYOS

Disgregación. A menos que estén destinadas a una acción local prolongada, las cápsulas vaginales satisfacen el ensayo de disgregación de supositorios y óvulos (2.9.2). Examinar el estado de las cápsulas vaginales después de 30 min, salvo excepción justificada y autorizada.

Disoluciones, emulsiones y suspensiones vaginales

DEFINICIÓN

Las disoluciones, emulsiones y suspensiones vaginales son preparaciones líquidas destinadas a efecto local, a irrigación o a fines de diagnóstico. Pueden contener excipientes, por ejemplo, para ajustar la viscosidad de la preparación, ajustar o estabilizar el pH, incrementar la solubilidad del principio o principios activos o estabilizar la preparación. Los excipientes no perjudican la acción medicamentosa deseada ni, a las concentraciones elegidas, provocan irritación local indebida.

Las emulsiones vaginales pueden presentar signos de separación de fases pero se reconstituyen fácilmente por agitación. Las suspensiones vaginales pueden presentar un sedimento, que es rápidamente dispersable por agitación dando una suspensión lo bastante estable para permitir que se administre una preparación homogénea.

Se suministran en envase unidos. El recipiente está adaptado para suministrar la preparación a la vagina o lleva un aplicador apropiado.

PRODUCCIÓN

Durante la fabricación de las suspensiones vaginales, se toman medidas que garanticen un tamaño de las partículas adecuadamente controlado para el uso destinado.

Comprimidos para disoluciones y suspensiones vaginales

DEFINICIÓN

Los comprimidos destinados a la preparación de disoluciones y suspensiones vaginales son preparaciones unidas que se

disuelven o dispersan en agua en el momento de su administración. Pueden contener excipientes para facilitar la disolución o dispersión o impedir la aglomeración.

Además del ensayo de disgregación, los comprimidos para disoluciones o suspensiones vaginales satisfacen la definición de *Comprimidos* (0478).

Después de la disolución o dispersión, la preparación satisface, según el caso, los requisitos de las disoluciones o suspensiones vaginales.

ENSAYOS

Disgregación. Los comprimidos para disoluciones o suspensiones vaginales se disgregan en 3 min cuando se examinan de acuerdo con el ensayo de desintegración de comprimidos y cápsulas (2.9.1), pero empleando *agua R* de 15 °C a 25 °C.

ETIQUETADO

La etiqueta indica:

- el método de preparación de la disolución o suspensión vaginal,
- las condiciones y duración de la conservación de la disolución o suspensión después de su reconstitución.

Preparaciones vaginales semisólidas

DEFINICIÓN

Las preparaciones vaginales semisólidas son pomadas, cremas o geles.

Se envasan en recipientes unidos. El envase lleva un aplicador adecuado.

Las preparaciones vaginales semisólidas satisfacen los requisitos de la monografía *Preparaciones semisólidas para aplicación cutánea* (0132).

Espumas vaginales

DEFINICIÓN

Las espumas vaginales satisfacen los requisitos de la monografía *Espumas medicamentosas* (1105).

Tampones vaginales medicamentosos

DEFINICIÓN

Los tampones vaginales medicamentosos son preparaciones sólidas unidas destinadas a ser introducidos en la vagina durante un período de tiempo limitado.

Satisfacen los requisitos de la monografía *Tampones medicamentosos* (1155).

Effect of supersaturation and crystallization phenomena on the release properties of a controlled release device based on EVA copolymer

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Abstract

This study describes the influence of steroid concentration, manufacturing and storage on the release properties of etonogestrel from polyethylene vinylacetate (EVA) based coaxial fibers. Coaxial fibers were manufactured by extrusion technology. As a consequence of the high extrusion temperatures large amounts of etonogestrel dissolve in the polymeric melt. Since the release from the coaxial fibers is directly proportional to the concentration gradient over the membrane, the amount of dissolved drug that recrystallizes upon cooling is of crucial importance. Therefore crystallization kinetics were studied using thermal analysis and hot stage microscopy. It was found that if the amount of etonogestrel is below a critical nucleation concentration at room temperature, the dissolved steroid remains in a supersaturated state. If on the other hand the amount of dissolved steroid is just above the critical nucleation concentration, the supersaturated steroid recrystallizes very slowly. It is concluded that the release of etonogestrel from an extruded coaxial fiber is a result of a complicated set of parameters, where, respectively process conditions, concentration of etonogestrel and both time and temperature of storage are of importance.

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Keywords: Drug delivery; Controlled release; Supersaturation; Solubility; Crystallization; Polyethylene vinylacetate

1. Introduction

Extrusion technology has proven to be an elegant method for the production of controlled release reservoir systems. Based on this technology, Organon developed two controlled release systems, i.e.,

Implanon[®] and NuvaRing[®] [1,2]. Both products are made of polyethylene vinylacetate (EVA) copolymers. Implanon[®] is an implant and is designed to release a progestagen for a period of three years. NuvaRing[®] is a contraceptive vaginal ring, designed to release both a progestagen and an estrogen for a period of 21 days.

The concept of these systems comprises a coaxial fiber, wherein a drug is dispersed or dissolved in a core polymer. The release from these coaxial fibers depends directly on the concentration gradient over

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the rate limiting membrane. When the drug is present in a concentration that exceeds solubility, it is the saturated concentration that determines the gradient. It is therefore essential to know the amount of dissolved drug and to investigate factors that may influence the solubility of a drug in the polymeric matrix.

In this paper it is demonstrated that the solubility of drug in the polymer is influenced by the temperature of the extrusion process. Typical extrusion temperatures are far below the melting point of the drug but significantly above room temperature (usually between 110 and 150 °C). Upon cooling of the extruded fibers, dissolved steroid may either recrystallize or remain soluble, resulting in a super-saturated state. Since the amount of dissolved steroid is directly correlated to the release properties, it is important to understand the crystallization behavior after the extrusion process. In this paper both the crystallization behavior of etonogestrel in EVA and its consequences on the release properties were investigated.

2. Materials and methods

2.1. Materials

The steroid used in this study, etonogestrel, was obtained from Diosynth. The melting temperature of etonogestrel is 199 °C. Two types of polyethylene vinylacetate polymers were used in this study. "EVA 28" contains 28% vinylacetate and is used as core material in the coaxial fibers because of the higher solubility and permeability. "EVA 9" contains 9% vinylacetate and is applied in the membrane because of the lower solubility and permeability properties. The crystallinity of both polymers is about 20 and 38%, respectively [3–5]. Both EVA 28 and EVA 9 are random copolymers and have a melting temperature of, respectively, 80 and 100 °C.

The molecular weights are given in Table 1.

2.2. Methods

2.2.1. Solubility in polymeric films (at low temperatures)

The interfacial partitioning of a drug molecule

Table 1
Molecular weights of EVA 28 and EVA 9

	M_w	M_n	M_w/M_n
EVA 28	50 000	14 700	3.4
EVA 9	83 500	15 500	5.4

between a solution and a polymer is related to the solubilities in the solution (C_s) and in the polymer (C_p) as defined by the partition coefficient $K=C_s/C_p$ [6,7]. By keeping the solution saturated, the polymer will also become saturated.

In order to determine the solubility of etonogestrel at low temperatures, films (200 μ m) of EVA 28 were cut in pieces of 5×5 cm and subsequently immersed in saturated aqueous steroid solutions at 25 and 37 °C. In order to keep the solution saturated, an excess of crystalline steroid was added. After 6 weeks of storage, equilibrium was reached and the films were analyzed for the content of steroid. The samples were extracted with methanol for 20 h at a temperature of 70 °C and subsequently the concentration of steroid was assessed by high-performance liquid chromatography (HPLC).

HPLC conditions were as follows: column: Novapak C₁₈ 150×3.9 mm, column temperature: 30 °C, mobile phase: acetonitrile–water (30:70, v/v) solution, flow-rate: 1.5 ml/min, injection volume: 10 μ l, detection: UV at 205 nm, apparatus: HP 1090, runtime: 13 min.

2.2.2. Solubility in molten polymer (at elevated temperatures)

Micronized etonogestrel was mixed thoroughly with ground EVA 28 in small transparent containers in varying concentrations and were subsequently stored in an oven at distinct temperatures (90 to 180 °C). The molten mass was stirred regularly with a spatula. In order to determine the solubility, the samples were visually inspected in course of time until no further change was observed. A clear state (absence of crystals) was interpreted as a fully dissolved state.

By increasing the temperature in distinct steps the steroid in all containers was finally dissolved. Subsequently all samples were cooled down to room temperature and were stored for 2 months at 20 °C. During storage the samples were frequently visually

examined in order to study the recrystallization behavior of etonogestrel and to determine the lowest concentration at room temperature at which the steroid still seems to crystallize.

2.2.3. Blend extrusion

5 wt.% etonogestrel was mixed with 95 wt.% EVA 28 in a Berstorff ZE25 twin screw blend extruder. The extrudate was prepared under various process conditions. In order to prevent the dissolved steroid from recrystallization in the polymeric matrix, the extrudate was temporarily stored at -50°C .

2.2.4. Hot stage microscopy

Hot stage microscopy was used to study the crystallization behavior of etonogestrel in EVA 28. The equipment consisted of a Jenaval light microscope and a Linkam hot plate heating/cooling system. Small coupes were cut from the extrudate described in paragraph 2.2.3 and examined with transmission light microscopy at various temperatures.

2.2.5. Scanning electron microscopy

In order to study how the supersaturated steroid was crystallized in the solid structure of EVA 28, extrudate that was produced at 105°C and 160°C was also examined with scanning electron microscopy. After storage at 20°C during 1 month, coupes were cut at a temperature of -20°C . In order to locate the position of the crystals on the surface of the coupe, the steroid crystals were removed by etching the surface of the coupes with methanol for 30 s. Subsequently the surface of the coupe was examined with scanning electron microscopy.

2.2.6. Differential scanning calorimetry (DSC)

A Perkin-Elmer differential scanning calorimetry (DSC7) apparatus was used for thermal analysis of the extrudate described in paragraph 2.2.3. Open aluminum pans ($30\text{ }\mu\text{l}$) were applied. The heating rate was set at $5^{\circ}\text{C}/\text{min}$. Dry nitrogen was used as a purge gas and a cryogenic cooler was used to cool below room temperature.

2.2.7. Manufacturing of coaxial fibers

Coaxial fibers with a diameter of 4 mm were produced with varying steroid concentrations (2, 3.5,

5, 10 and 20 wt.%). EVA 28 and EVA 9 were used, respectively, as core and membrane polymer. The thickness of the membrane was adjusted to $110\text{ }\mu\text{m}$. In order to prepare a coaxial fiber, a steroid loaded core granulate was manufactured by mixing micronized steroid and ground EVA 28 in the desired ratios. Subsequently, the powder mixtures were blended in a twin screw blend extruder (Berstorff ZE25) at a temperature of 150°C . After leaving the blend extruder the strands were cooled to room temperature and granulated using a Scheer strand granulator, thereby forming steroid loaded pellets with diameter of about 2.5 mm and a length of about 3 mm.

The co-extrusion installation (Plastik Maschinenbau) consists of two single screw extruders that are connected to a spinning block. The maximum extrusion temperature of the extruders was set to 145°C . The molten polymers are delivered to two gear pumps, which assure an accurate flow of both polymers to the spinneret. The thickness of the membrane polymer is determined by the ratio between rotation speed of both pumps. Subsequently, the membrane and core polymers are combined in a spinneret, thereby forming the coaxial fiber. The temperature of the spinneret was set to 110°C .

A water bath was positioned below the spinneret in order to cool the fiber to room temperature. The outer diameter of the fiber was measured on-line using a Mitutoyo laser scan micrometer. Subsequently the fibers were stored at -50°C , to maintain the physical state of the fibers immediately after extrusion. In order to investigate the influence of storage conditions on the degree of supersaturation, part of the fibers were also stored at 20, 30 and 40°C .

2.2.8. Determination of the in-vitro release rate

An automated release control system was used to measure the in-vitro release rate of the coaxial fibers. The coaxial fibers were cut into pieces of 157 mm and the ends were sealed with Loctite[®] acrylate glue, which is impermeable for steroids. The samples were immersed in 200 ml water of 37°C under continuous stirring (750 rpm). The steroid concentration of the release medium was determined daily by UV spectroscopy. In order to maintain sink conditions the water in the containers was refreshed daily by an auto-sampler.

In the literature [8] the following model is derived

to predict the release rate from a cylindrical reservoir system:

$$\frac{dM_i}{dt} = \frac{2LDK\Delta C}{\ln(r_o/r_i)} \quad (1)$$

where: dM_i/dt is the release rate (kg/s); L is the length of the cylinder (m); D is the diffusion coefficient membrane (m^2/s); K is the partition coefficient between membrane and core; ΔC is the concentration gradient over the membrane (kg/m^3); r_o is the outer radius (m); r_i is the inner radius (= outer radius – membrane thickness) (m).

3. Results and discussion

3.1. Solubility in EVA 28

Fig. 1 depicts the solubility of etonogestrel as a function of temperature. In this graph, data obtained from the film saturation method at low temperatures are combined with data obtained at higher temperatures in molten polymer. Surprisingly, the results appear to be reasonable in line with each other, despite the fact that different approaches were applied and a phase transition (solid-melt) is present between the two data sets.

As can be seen, the solubility of etonogestrel at typical extrusion temperatures (110–150 °C) is about 10 times higher than at room temperature. This

means that a considerable amount of steroid will dissolve during the extrusion process. When rapid cooling prevents the recrystallization of the excess, a supersaturated solution will result. The stability of the supersaturated solutions was investigated by assessing the transparency of samples containing various amounts of dissolved steroid after 2 months of storage at 20 °C. Below a concentration of about 2 wt.% etonogestrel, no crystallization was observed and the samples remained transparent. In Fig. 1 it is shown that the saturation solubility at room temperature is only 0.35 wt.%. This suggests that the 2% dissolved etonogestrel represents a supersaturated state at room temperature.

3.2. Solubility and recrystallization as a function of process parameters

Extrudate containing 5 wt.% etonogestrel and 95 wt.% EVA 28 was prepared by blend extrusion at various process conditions. As a result of the process conditions the amount of dissolved etonogestrel varied from partly dissolved (90 °C) to completely dissolved (160 °C). At room temperature crystallization phenomena were observed within 1 day for the extrudate that was prepared at 160 °C. After another 2 days no significant changes could be observed.

It was found that the formation of crystals progressed considerably faster when the extrudate was stored at higher temperatures, most probably because of the increased mobility of the polymeric chains and steroid. While the recrystallization time at 20 °C was approximately 3 days, the recrystallization time at 70 °C was only 1.5 min.

This rapid process enables the measurement of the heat of crystallization by differential scanning calorimetry. Thin couples were cut from the extrudate and were measured by DSC from 30 to 90 °C with a rate of 5 °C/min. Hot stage microscopy was carried out using the same temperature program in order to visualize the thermodynamic effects observed with DSC.

Because the polymer itself also has a complex melting curve, it appeared not possible to measure the small crystallization heat of steroid in the polymer directly. Therefore it was tried to determine the crystallization heat of steroid in the polymeric matrix by subtracting the melting curve of placebo EVA 28

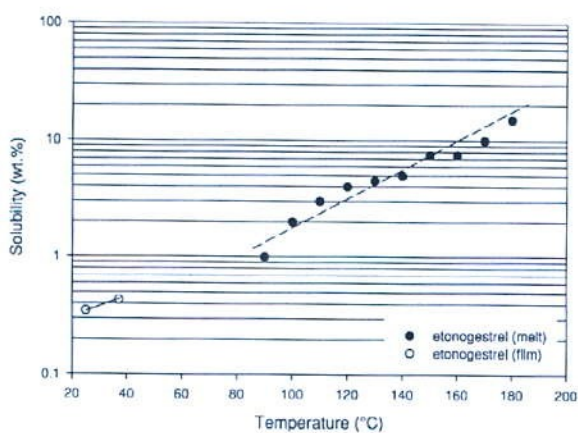


Fig. 1. The solubility of etonogestrel in EVA 28 at both extrusion and ambient temperatures.

(no crystallization of etonogestrel). In order to be used as a reference curve for all measurements, the sample was pretreated above its melting point during 2 min and cooled down quickly. This reference curve was normalized and subtracted from the curves of the steroid loaded samples. The resulting curve showed an exothermic peak at approximately 55 to 72 °C (Fig. 2). Hot stage microscopy revealed that this peak is a result of crystallization of the steroid (see inserted photographs).

It appeared that the area of this peak varied with the amount of etonogestrel dissolved.

Except for this peak the shape of the DSC curve was found to be constant for all samples.

The crystallization heat of etonogestrel in the extrudate (produced at 160 °C) in which all steroid (5 wt.%) was dissolved, was approximately 2 J/g extrudate (determined from the area under the curve in Fig. 2). Since the solubility of etonogestrel in EVA 28 at 70 °C can be estimated as approximately 0.7 wt.% (Fig. 1), it is possible to deduce the solubility of etonogestrel in supersaturated extrudate produced under other process conditions.

Fig. 3 depicts the amount of dissolved etonogestrel at zero time in EVA 28 extrudate prepared with the blend extruder at various extrusion conditions. It can be seen that the amount of dissolved steroid is

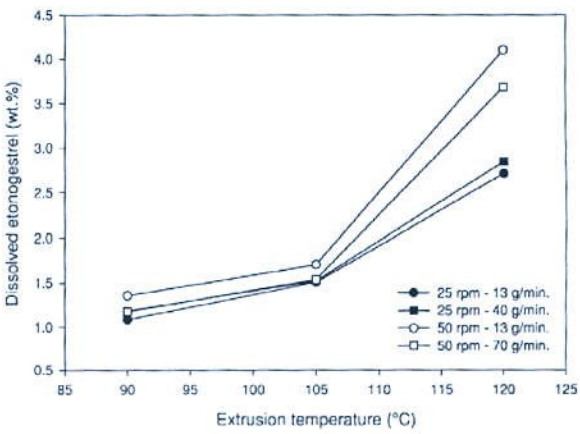


Fig. 3. The influence of the process conditions on the amount of dissolved etonogestrel in EVA 28 during blend extrusion at various screw speed and throughput rates.

influenced by the process conditions. By increasing the rotation speed of the screws, the amount of shear will increase and as a consequence more etonogestrel will dissolve.

The extrudate depicted in Fig. 3 was stored at room temperature and the amount of dissolved etonogestrel was determined after different storage times. Fig. 4 shows results of the thermoanalytical measurements, where the amount of etonogestrel in

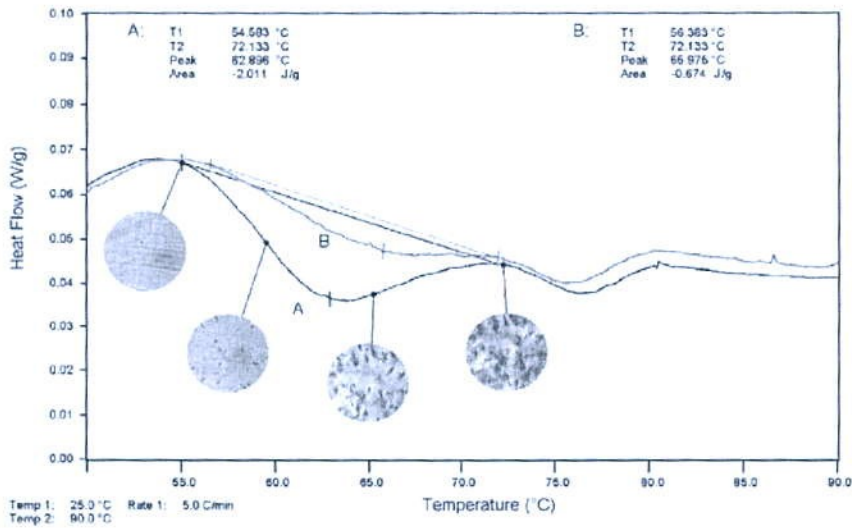


Fig. 2. Crystallization of etonogestrel in extrudate containing 5% etonogestrel and 95% EVA 28. Samples were prepared at different extrusion temperatures (A: 160 °C and B: 105 °C). In this figure observations done with hot stage microscopy are combined with DSC measurements.

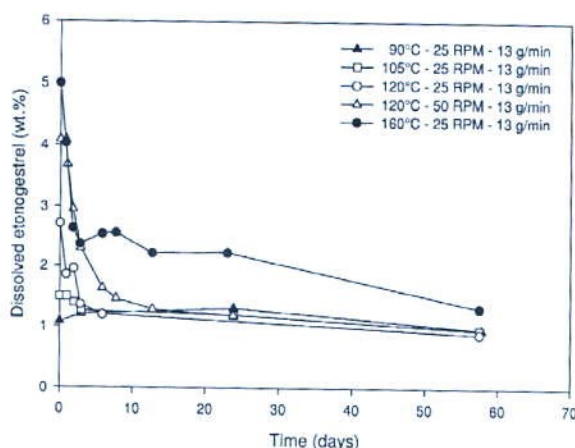


Fig. 4. The amount of dissolved etonogestrel in extrudate containing 5% etonogestrel and 95% EVA 28 upon storage at 20 °C. The extrudate was prepared under various extrusion conditions.

solution is plotted as a function of storage time. As already was indicated before, most of the supersaturated steroid recrystallizes in the first few days. However a remaining amount of dissolved etonogestrel of approximately 1 wt.% was found for all extrudate.

This suggests that the amount of dissolved etonogestrel remains above the saturation solubility of 0.35% at 20 °C that was found in saturated flat films. If the degree of supersaturation at room temperature is defined as:

$$\text{degree of supersaturation} = \frac{\text{concentration of dissolved steroid}}{\text{saturation solubility}} \quad (2)$$

then the degree of supersaturation is approximately 3 (1 wt.% divided by 0.35 wt.%).

3.3. The influence of supersaturation and recrystallization on the release properties

According to Eq. (1) the release rate from the coaxial fiber is directly proportional to the concentration, i.e., the amount of dissolved steroid. As a consequence the degree of supersaturation is directly reflected in the in-vitro release.

Fig. 5 depicts the in-vitro release for a coaxial fiber containing 2 wt.% etonogestrel (completely

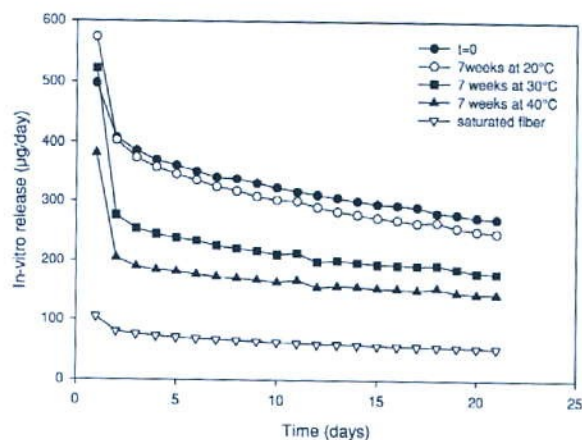


Fig. 5. The in-vitro release of etonogestrel at 37 °C from coaxial fibers containing 2 wt.% steroid upon storage at various temperatures. The in-vitro release of a fiber containing 0.35 wt.% etonogestrel (based on the saturation solubility at 25 °C) has also been plotted.

dissolved during extrusion) upon storage during 7 weeks at, respectively, 20, 30 and 40 °C. It can be seen that the corresponding release from the coaxial fibers is dependent on both storage time and temperature. This is a logical result of the proceeding crystallization of the steroid. It is also obvious from the figure that all fibers exhibit a higher release than the one containing 0.35 wt.% etonogestrel. Since this represents the saturation solubility at 25 °C, it seems to be likely that fibers remain to a certain degree supersaturated.

Similar experiments were performed with fibers containing different concentrations of etonogestrel. Microscopic examination on freshly prepared fibers confirmed that the steroid was dissolved in the fibers with concentrations up to 5 wt.%. The fibers containing 10 and 20 wt.% were opalescent, indicating that only a part of the etonogestrel was dissolved.

The degree of supersaturation of several fibers has been calculated by dividing the average (day 2–21) release by that of a saturated fiber. Fig. 6 shows both the average release and the degree of supersaturation upon storage at, respectively 20, 30 and 40 °C versus the steroid concentration in the core. The release data of the fibers with a steroid content lower than 2 wt.% were obtained from Ref. [9]. The average release from a saturated fiber is approximately 63 µg/day.

As can be seen, the release from the coaxial fiber

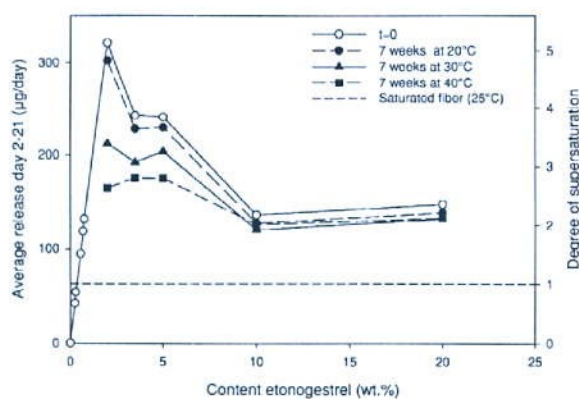


Fig. 6. The influence of the core concentration on the average release at 37 °C upon storage under various conditions.

increases with increasing steroid content in the core. However, when the amount of dissolved steroid is higher than a certain threshold, further increase in steroid concentration results in a decrease in release. This is attributed to crystallization. Apparently, there exists a critical nucleation concentration, where the dissolved steroid recrystallizes in the polymeric matrix. By increasing the steroid content in the core even more, the average release levels off to about 140 µg/day. Obviously crystallization is facilitated in the presence of a large amount of steroid crystals. However it can be seen that the release is still not equal to release of a saturated fiber. This suggests that the amount of dissolved etonogestrel is still in a supersaturated state (degree of supersaturation=2).

In the fibers containing 5 wt.% of steroid almost all etonogestrel dissolves during extrusion at 145 °C. For these fibers a theoretical release of about 880 µg/day is expected directly after extrusion. As can be seen the release on "t=0" is only 240 µg/day. Obviously, recrystallization already occurs during the release measurement at 37 °C.

After 7 weeks storage at 20 °C the fiber had become opalescent indicating recrystallization of etonogestrel. However it can be seen that the average release has not changed significantly and therefore etonogestrel is still in a supersaturated state (degree of supersaturation=3.5). This value is well in agreement with the result found earlier with the DSC measurement on the extrudate containing 5 wt.% etonogestrel.

3.4. Crystallization in polymer

In order to study how the supersaturated steroid has crystallized in the solid structure of the polymer, the extrudate containing 5 wt.% etonogestrel and prepared at 105 and 160 °C was also examined with scanning electron microscopy. In order to allow the steroid to crystallize, the extrudate was first stored at 20 °C during 1 month. Subsequently couples were cut from the extrudate.

The couples that were examined with scanning electron microscopy were first pretreated. The steroid on the surface of the couple was removed by etching the surface with methanol for about 30 s. In this way the steroid on the surface was dissolved and as a consequence the position of the steroid crystals can be seen more easily.

In Fig. 7 the presence of steroid crystals can be seen in the extrudate that was produced at 105 °C. At this temperature only a small fraction of the steroid was initially dissolved upon extrusion. Scanning electron microscopy (Fig. 7b) reveals the original position of the steroid crystals that were not dissolved during the extrusion process.

Fig. 8 shows the presence of steroid crystals in the extrudate that was produced at an extrusion temperature of 160 °C. Initially all steroid was dissolved as a consequence of the higher extrusion temperature. Therefore all crystals that can be seen with transmission microscopy (Fig. 8a) are associated with recrystallized steroid.

While a large amount of recrystallized steroid crystals can be seen with transmission light microscopy, scanning electron microscopy only reveals a few small indentations (Fig. 8b). Therefore it can be concluded from this picture that the steroid can only recrystallize in the amorphous domains of the polymer or by pressing the polymeric matrix aside. Most probably the recrystallization of steroid in this case is severely hindered by the polymeric matrix. As a consequence it is expected that not all supersaturated steroid will recrystallize.

4. Conclusion

The solubility of etonogestrel in polyethylene vinylacetate copolymers is much higher at elevated

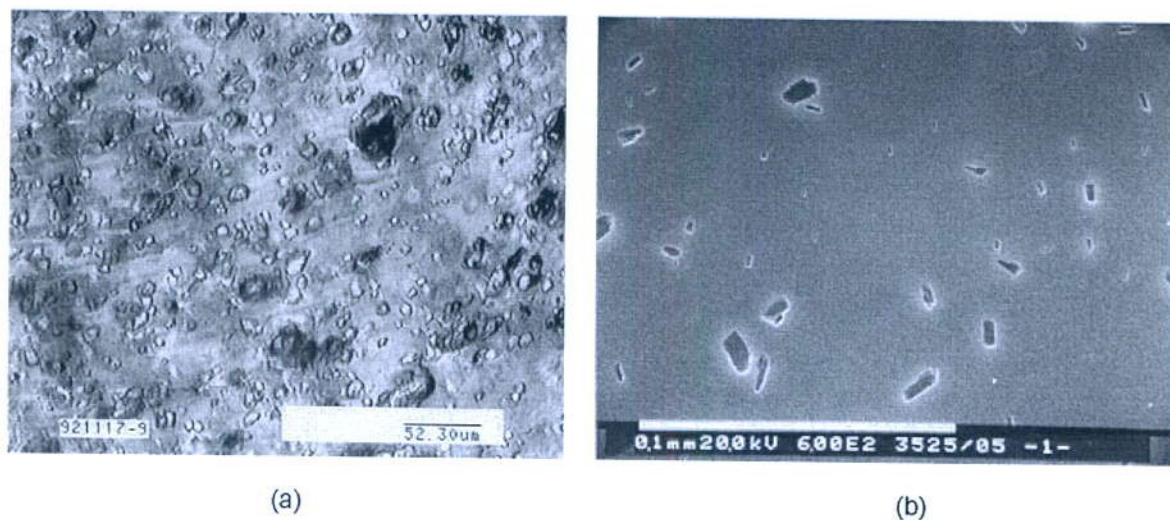


Fig. 7. The presence of etonogestrel crystals in the polymeric matrix after 1 month storage at 20 °C in a 5 wt.% steroid/EVA 28 mixture, prepared at extrusion temperature of 105 °C (a, transmission light microscopy; b, scanning electron microscopy).

temperature than at room temperature. Therefore considerable amounts of steroid dissolve in the polymeric melt during the manufacturing of the coaxial fibers.

If the amount of steroid in the core is completely dissolved during the extrusion process and at the same time is lower than the critical nucleation concentration, the steroid will remain in a dissolved

(supersaturated) state. The in-vitro release will be proportional to the amount of dissolved steroid. If on the other hand the amount of dissolved steroid is larger than the nucleation solubility, the major part of the dissolved steroid will crystallize gradually. The rate and the amount of steroid that will crystallize are influenced by the steroid concentration and the storage temperature. This means that the corre-

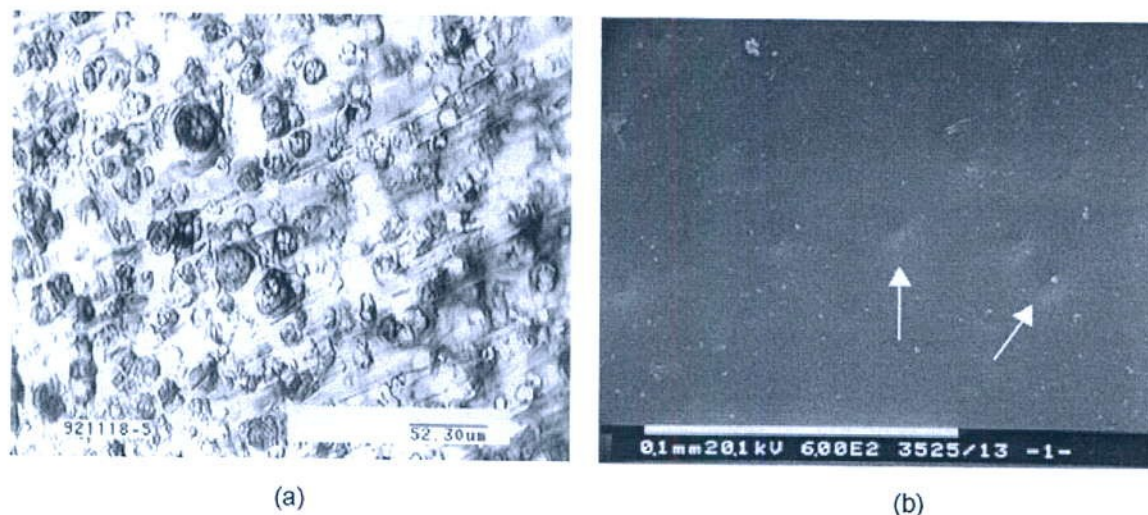


Fig. 8. The presence of recrystallized etonogestrel crystals in the polymeric matrix after storage at 20 °C for 1 month in a 5 wt.% steroid/EVA 28 mixture, prepared at extrusion temperature of 160 °C (a, transmission light microscopy; b, scanning electron microscopy).

sponding release from the coaxial fibers is dependent on the storage time and temperature.

The results indicate that the concentration of dissolved steroid remains higher than the solubility value measured at room temperature.

In conclusion, the release of etonogestrel from an extruded coaxial fiber is a result of a complicated set of parameters, where process conditions, concentration of etonogestrel and finally time and temperature of storage are of importance.

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Review

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

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Abstract

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

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

1. Introduction

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

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

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

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

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

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

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

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

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

2. Proposed structures of solid dispersions

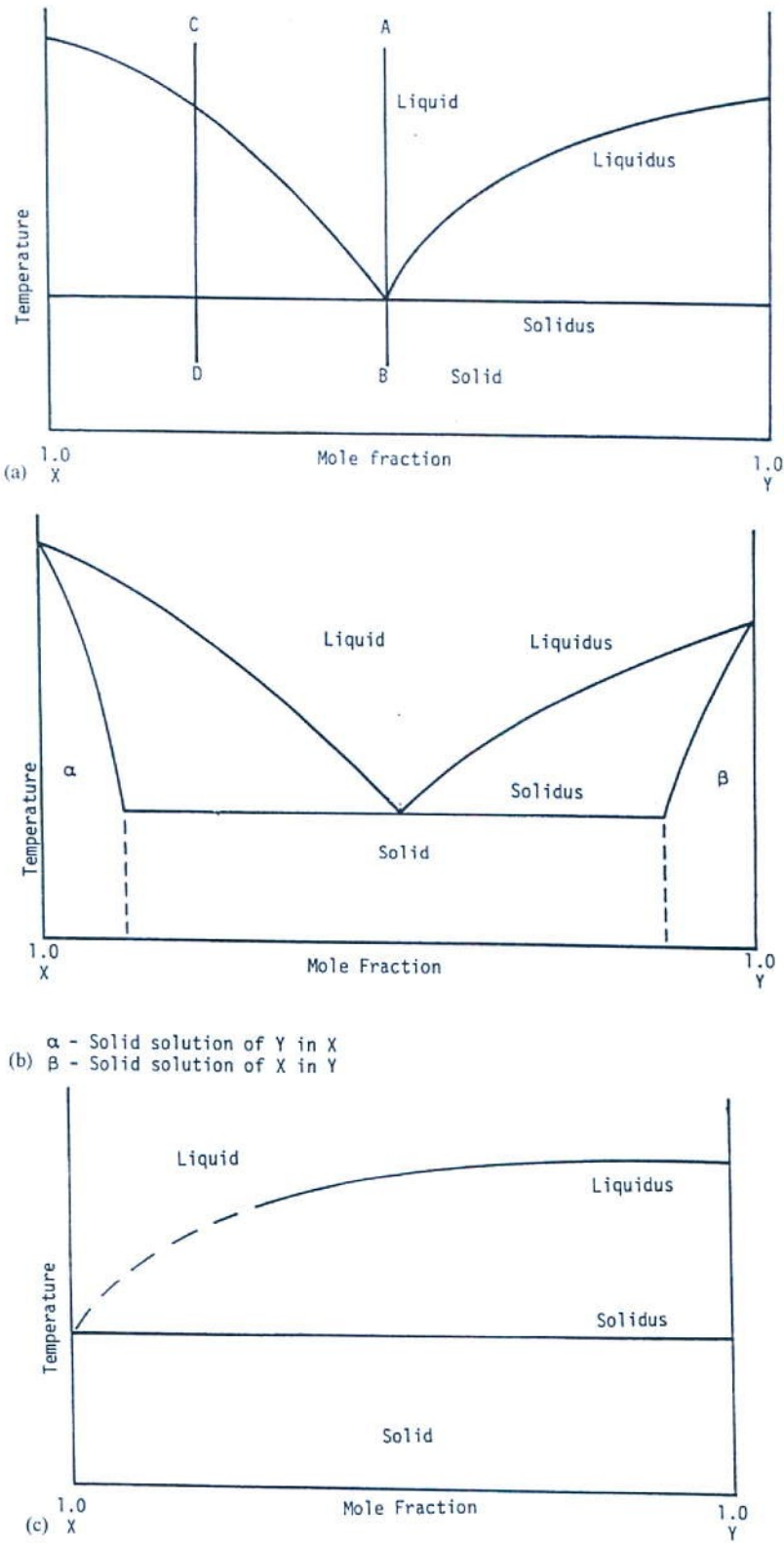
Before discussing the dissolution properties of the dispersions, it is clearly essential to have some consideration of the solid-state properties of these systems. The dispersions have traditionally been formed by heating mixes of the drug and carrier to the molten state (although whether this molten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

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

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

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

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



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

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

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

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

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

3. Drug release from solid dispersions

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

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

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

3.1. Particle size reduction and reduced agglomeration

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

3.2. Increased solubility or dissolution rate of the drug

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

polymorphic form may also be considered under this category.

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

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

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

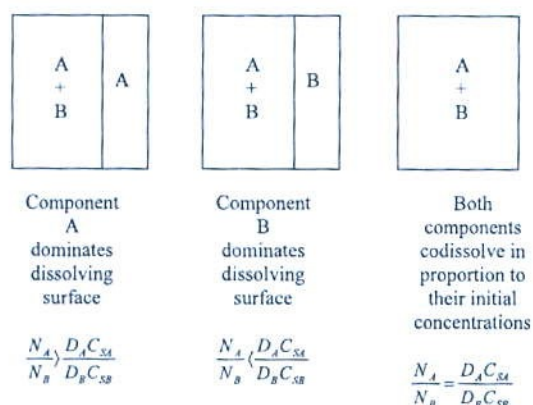


Fig. 2. Schematic representation of the dissolution model for a two component system (after Higuchi et al., 1965). See text for explanation of symbols.

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

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

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

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

and

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

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

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

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

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

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

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

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

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

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

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

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

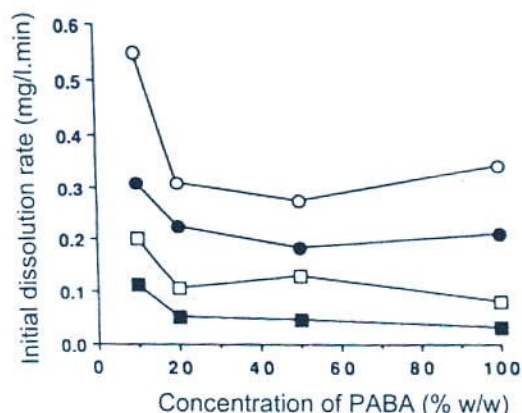


Fig. 3. Relationship between initial intrinsic dissolution rate and concentration of *para*-aminobenzoic acid (PABA) in PEG 4000 solid dispersions. (○) Methyl PABA; (●) ethyl PABA; (□) propyl PABA; (■) butyl PABA (reproduced with permission from Sjökvist-Saers and Craig, 1992).

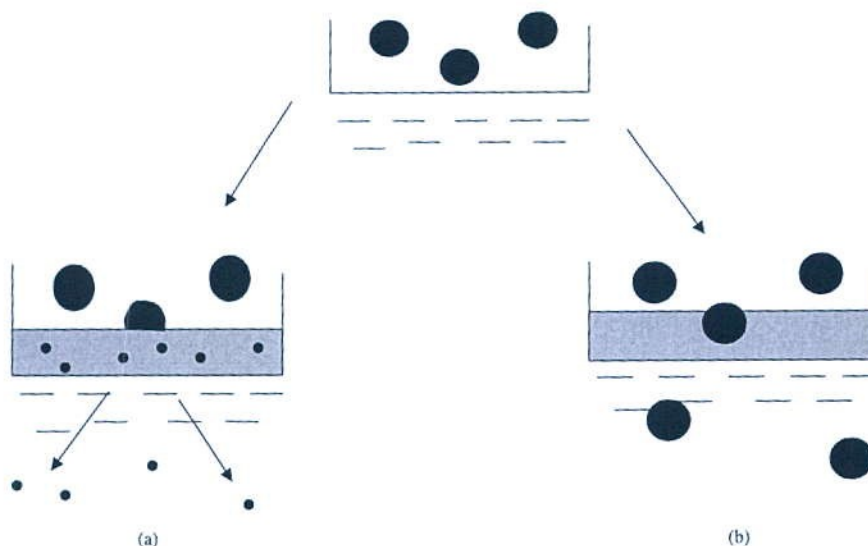


Fig. 4. Schematic diagram showing the fate of drug particles during the dissolution process. (a) Carrier-controlled dissolution, whereby the drug dissolves into the concentrated carrier layer prior to release and (b) drug-controlled dissolution whereby the drug is released effectively intact into the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

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

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

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

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

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

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

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

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

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

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

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

5. Mathematical modelling of drug-controlled dissolution

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

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

$$G_T(t) = \sum^N G_p'(t) \approx G_p(t)N(t) \quad (7)$$

where G_p' is the dissolution rate at time t of the individual particles. In the first instance it is necessary to calculate the time dependence of the particle release process by considering the time required for sufficient polymer to dissolve in order to release a particle. This is achieved by considering the intrinsic polymer dissolution rate P_A (wt/ $A \cdot t$ where A is area of dissolving surface). The dissolution rate (P_T) may also be expressed in terms of the volume of polymer dissolved in unit time from a disk of diameter $2R$

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

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

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

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

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

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

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

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

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

Consequently from Eqs. (10) and (11)

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

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

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

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

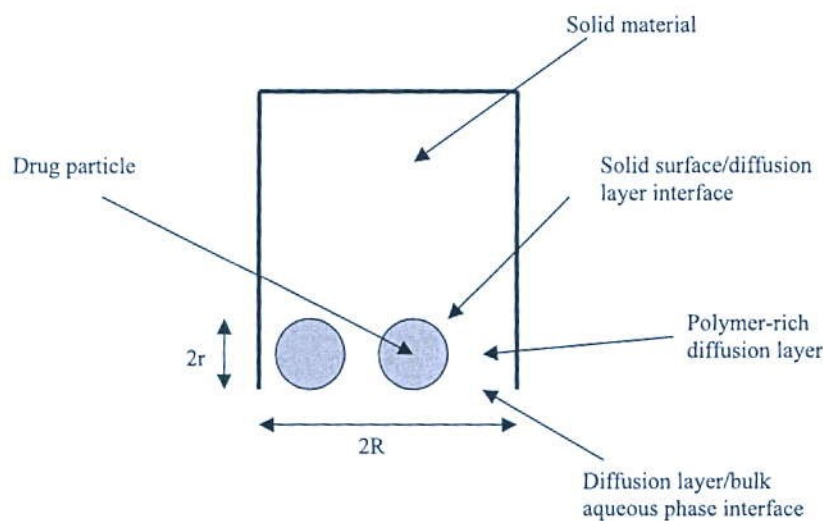


Fig. 5. Schematic representation of the structure of solid dispersions with reference to the model derived for drug-controlled dissolution.

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

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

$$G_T = \frac{3D(C_s - C)R^2xt}{r^4\rho} \int_{t=0}^{t=t} P_A dt \quad (15)$$

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

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

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

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

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

7. Conclusions

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

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