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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ C. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-089792- -00008-0000

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Re: PI.-**ABBOTT LABORATORIES**.-Solicitud de Patente de Invención en
Fase Nacional PCT para "UNA FORMULACIÓN SÓLIDA DE
DOSIFICACIÓN FARMACÉUTICA".-Clase **A61K 31/513**.-
Expediente número **07-089.792**.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 17 de Junio de 2011.

2. Con el fin de responder las objeciones expuestas por el Señor Examinador en su Concepto Técnico No. **1659**, en relación a la Claridad del Capítulo Reivindicatorio actualmente en estudio y al Nivel Inventivo de la presente solicitud, me permito dirigir su atención a las siguientes modificaciones y argumentos técnicos por medio de los cuales se superan completamente dichas objeciones.

3. **CLARIDAD DEL CAPÍTULO REIVINDICATORIO.**

En su referenciado Concepto Técnico No. **1659**, el Señor Examinador objeta la claridad del capítulo reivindicatorio actualmente presentado, por considerar que este define la forma sólida de dosificación de la invención por resultados a alcanzar, y no por sus características técnicas esenciales.

Tomando en consideración esta objeción me permito manifestar que es deseo del solicitante presentar un **nuevo capítulo reivindicatorio**, que reemplaza al anterior, el cual describe de manera clara y concisa la forma de dosificación farmacéutica de la invención, haciendo referencia a sus características técnicas esenciales.

Con respecto al mencionado nuevo capítulo reivindicatorio me permito resaltar que este no constituye de ninguna manera una ampliación al alcance de la invención, tal como fue originalmente presentada, toda vez que se está definiendo la forma de dosificación farmacéutica de acuerdo con las revelaciones de la descripción de la solicitud, como se muestra a continuación:

- **Reivindicación 1.** Esta reivindicación se refiere a la forma de dosificación farmacéutica de la invención, la cual comprende una solución o dispersión sólida de lopinavir en uno o más polímeros farmacéuticamente aceptables y un tensoactivo farmacéuticamente aceptable, donde dicho polímero tiene un valor de Tg de al menos 50°C, tal como se enseña en las páginas 7, 10 y 12 de la descripción de la presente solicitud y dicho tensoactivo tiene un valor de HLB entre 4 y 10, en concordancia a lo revelado en las páginas 12 y 13 de dicha descripción.
- **Reivindicación 2.** La nueva reivindicación 2 indica que el tensoactivo presente en la forma de dosificación farmacéutica de la invención comprende un éster de sorbitán y ácido graso, tal como se señala en la página 13 de la descripción.
- **Reivindicación 3.** La nueva reivindicación 3 considera las cantidades particulares de lopinavir y del tensoactivo que están incluidas en la forma de dosificación de la invención, en concordancia con lo enseñado en las páginas 8 y 14 de la descripción de la solicitud.
- **Reivindicación 4.** Esta reivindicación señala que la forma de dosificación farmacéutica de la invención comprende en una de sus realizaciones preferidas una solución sólida.
- **Reivindicación 5.** La nueva reivindicación 5 se refiere a las formas de dosificación preferidas de la invención en las que el polímero soluble en agua comprende un homopolímero o copolímero de N-vinil pirrolidona, tal como se resalta en la página 12 de la descripción.
- **Reivindicación 6.** Esta reivindicación considera las formas de dosificación en las cuales el polímero soluble en agua comprende un copolímero de N-vinil pirrolidona y acetato de vinilo, según lo revelado en la mencionada página 12 de la descripción.
- **Reivindicación 7.** La nueva reivindicación 7 se refiere a las formas de dosificación de la invención que comprenden como polímero soluble en agua copovidona y como tensoactivo monolaurato de sorbitán, como se enseña en la página 32 de la descripción.

- **Reivindicación 8.** Esta reivindicación señala que la forma de dosificación farmacéutica de la reivindicación 7 comprende en una de sus realizaciones preferidas una solución sólida.

De esta forma, el nuevo capítulo reivindicatorio está constituido por **8 reivindicaciones**, la cuales describen de manera clara y concisa la forma de dosificación farmacéutica objeto de la presente invención, haciendo referencia a las características técnicas esenciales de acuerdo con las enseñanzas de la descripción.

Consecuentemente, el nuevo capítulo reivindicatorio aquí presentado se enmarca completamente dentro de lo estipulado por el Artículo 30 de la Decisión Andina 486 de 2000.

4. **NIVEL INVENTIVO.**

Finalmente, el Señor Examinador asegura que la solicitud en estudio carecería de altura inventiva con respecto a las enseñanzas de los documentos **WO0134119 (D1)** y **WO02096395 (D2)**.

Con respecto a estos documentos, el Señor Examinador señala que las diferencias entre las formulaciones allí reveladas y la forma sólida de dosificación farmacéutica que es parte de la presente invención no serían suficientes para reconocer el nivel inventivo de la solicitud en estudio, toda vez que no existiría un efecto inesperado asociado a dicha forma de dosificación de la invención.

Sobre este particular, me permito resaltar que las enseñanzas de los documentos citados no podrían conducir de ninguna manera a que la persona versada en la materia obtuviera una forma de dosificación farmacéutica que posea específicamente los componentes presentes en aquella que es objeto de la solicitud en estudio, ni mucho menos a predecir que dicha forma de dosificación poseería una biodisponibilidad mejorada del principio activo.

4.1. **Documento WO0134119 (D1).**

El Documento D1 se refiere a una composición farmacéutica de ritonavir, la cual comprende una dispersión sólida del principio activo en un portador soluble en agua, el cual en general es polietilen glicol (PEG), y un inhibidor de cristalización como polivinilpirrolidona o hidroxipropilmetil celulosa.

Si bien el documento D1 podría considerarse el estado de arte más cercano a la invención porque busca mejorar la biodisponibilidad de un inhibidor de proteasa en una composición farmacéutica sólida, dicho documento no podría de ninguna manera sugerir que una forma de dosificación farmacéutica que comprenda una **solución o dispersión sólida** de lopinavir, en un polímero soluble en agua **con una Tg de 50°C o mayor, y un tensoactivo**, como la reclamada por la presente solicitud, tendría efectivamente una mayor biodisponibilidad del principio activo.

Es más, el documento **D1** emplea en general como dispersante una matriz de polímero, PEG, el cual posee **una temperatura de transición vítrea (Tg) extremadamente baja**. Para ilustrar este hecho me permito referirme al documento *Forster, et al International Journal of Pharmaceutics*, 226 (2001) 147-161, el cual revela las formas de seleccionar excipientes para el proceso de extrusión en fundido de dos medicamentos muy poco solubles en agua.

En dicho documento, dentro de la Tabla 2 de la página 153, se reseña que el **PEG 8000**, el cual es usado dentro de las formulaciones de D1 (ver páginas 19 a 22, ejemplo 1; páginas 26 y 27, ejemplo 2, D1), posee una temperatura de transición vítrea de **-50°C**.

En vista de lo anterior, la persona versada en la materia no encontraría en las enseñanzas de D1 ninguna motivación para emplear un polímero soluble en agua con una Tg mucho más alta (mayor a 50°C) para que sirva de soporte en una forma de dosificación farmacéutica que comprende una solución sólida de lopinavir, como la que es objeto de la presente solicitud, tal como se reclama en virtud del nuevo capítulo reivindicatorio presentado adjunto a este memorial.

Así mismo, me permito resaltar que si bien en D1 se emplea un polímero amorfo soluble en agua como aquellos que hacen parte de la forma de dosificación de la presente invención (polivinil pirrolidona, PVP), dicho polímero tiene una función completamente distinta en la formulación de D1; **mientras que en la presente invención dicho polímero es la matriz de la solución o dispersión sólida, en D1 sirve como inhibidor de la cristalización.**

De esta forma, **D1 emplea una matriz cristalina, el PEG**, y la PVP se adiciona a dicha matriz, tal como lo señala la página 11, líneas 7 a 8 de D1: *"Los beneficios de **incorporar PVP dentro de la matriz de PEG** son dobles."* (Resaltado fuera de texto).

Así mismo, D1 indica que *"el beneficio de adicionar PVP es un incremento en el volumen amorfo de la matriz polimérica donde el medicamento reside", y "dado que los polietilenglicoles tienden a ser altamente cristalinos, este incremento en el volumen amorfo puede ser importante para una disolución rápida"* (página 11, líneas 11 a 16, D1).

Sumado a esto, todos los ejemplos específicos revelados en D1 (páginas 19 a 27), la relación de PVP/PEG no es más de 20:80, indicando que es el PEG cristalino y no el PVP amorfo el responsable de la formación de la matriz (página 17, línea 21, PEG:PVP 95:5; página 20, líneas 13 y 14, PEG8000:PVP 85:15; página 20, líneas 15 y 16, *"dispersiones de 10 a 20% PVP 17PF en PEG 8000 sin medicamento"*; página 9, líneas 8 y 9, *"al control de dispersión 90:10 PEG 8000:PVP"*; página 22, líneas 8 y 9, *"usando el control de dispersión 80:20 PEG8000:PVP"*; página 23, líneas 21, PEG:PVP 95:5). Consecuentemente, **la formulación revelada en D1 es una composición basada en una matriz cristalina.**

Contrario a lo anterior, y tal como es evidente en el ya mencionado nuevo capítulo reivindicatorio presentado junto con este memorial, la forma de dosificación farmacéutica de la presente invención emplea como componente mayoritario un polímero soluble en agua **amorfo**, (50 a 85% de la forma de dosificación), el cual sirve de matriz polimérica para la dispersión o solución del compuesto activo.

En conexión con este hecho me permito resaltar que el documento D1 de ninguna manera sugiere la posible utilidad de emplear una matriz amorfa para dispersar o disolver lopinavir, **y más aún D1 muestra desventajas del uso de PVP como único componente de la matriz:** *"Primero, procesar PVP puede ser difícil debido a su higroscopicidad. Segundo, cuando PVP se disuelve se forma una capa viscosa en la interfase sólido líquido. Esta región viscosa puede impedir la disolución del medicamento"* (Página 11, líneas 8-11, D1).

De esta forma, **las enseñanzas de D1 al contrario alejarían a la persona versada en la materia de considerar usar polímeros como PVP para construir la matriz en la cual se disperse o disuelva el principio**

activo, y por lo tanto, el documento D1 no conduce de forma evidente a la forma de dosificación de la presente invención, y mucho menos de la manera que es definida en el nuevo capítulo reivindicatorio presentado junto con este memorial.

Sumado a todos estos hechos, a lo largo del documento D1 no se mencionan los tensoactivos como posibles componentes de una forma de dosificación que comprenda inhibidores de proteasa como principio activo, por lo que de ninguna manera la persona versada en la materia podría suponer la importancia de dicho tensoactivo o de su valor de balance hidrófilo-lipófilo (HLB) en la biodisponibilidad de lopinavir.

En este sentido me permito resaltar que **el solicitante ha comprobado que, de manera sorprendente, el valor de HLB del tensoactivo es de fundamental importancia en la biodisponibilidad de lopinavir**, tal como se observa de los ejemplos 4 y 5 de las páginas 33 a 35 de la descripción de la solicitud.

Es así como el ejemplo 4 revela una forma de dosificación que comprende Cremophor RH 40 como tensoactivo, cuyo valor de HLB es de 14 a 16 (como es claro de su ficha técnica, que se anexa al presente memorial), obteniendo un valor de AUC de **7.43** µg.h/ml/100g para lopinavir. Por su parte, el ejemplo 5 emplea como tensoactivo Span 20, cuyo valor de HLB es de **8.6**, (como lo comprueba su ficha técnica de la casa comercial Sigma-Aldrich, ver anexo), y se obtiene un valor muy superior de AUC para el lopinavir, siendo este de **51.2** µg.h/ml/100g.

Es así como de forma inesperada, **el solicitante ha comprobado que el adicionar un tensoactivo a la forma sólida de dosificación mejora la biodisponibilidad del lopinavir, pero si dicho tensoactivo posee un valor entre 4 a 10, el aumento de biodisponibilidad será significativamente mayor, lo cual de ninguna manera podría ser predicho a partir de las revelaciones de D1.**

Como consecuencia de todo lo anterior, es claro que las enseñanzas de D1 no pueden conducir de forma alguna a la persona versada en la materia a una forma de dosificación farmacéutica que comprenda una dispersión o solución sólida de lopinavir en un polímero soluble en agua que tenga una Tg de 50°C o más y un tensoactivo que posea un valor de HLB entre 4 y 10, como la que es objeto de la presente invención.

Por lo tanto, el documento D1 no puede afectar el nivel inventivo de la solicitud en estudio.

4.2. **Documento WO02096395 (D2).**

Por su parte, el documento **D2** enseña cápsulas blandas las cuales están rellenas de una composición farmacéutica **líquida** que comprende uno o más principios activos, un alcohol y un ácido graso. En general, la composición de relleno comprende una cantidad incrementada de alcohol la cual no sólo permite solubilizar el ingrediente activo, sino que además ayuda a la plastificación de la cubierta de la cápsula. Así mismo, la composición líquida de relleno puede incluir un tensoactivo.

En relación con este documento me permito señalar que si bien D2 busca solucionar un problema similar al enfrentado por la solicitud en estudio, la manera de abordar dicho problema es totalmente distinta y por lo tanto sus enseñanzas no podrían conducir a la forma sólida de dosificación de la presente invención.

De esta forma, el documento D2 revela el principio activo **en solución líquida**, mientras que la forma de dosificación de la invención comprende una **solución o dispersión sólida** de lopinavir.

Sumado a lo anterior, **aún cuando D2 incluye un tensoactivo dentro de su formulación, este documento de ninguna manera señala la importancia del valor de HLB de dicho tensoactivo en la biodisponibilidad de inhibidores de proteasa, por lo que la persona versada en la materia no tendría ninguna motivación para fijar este valor entre 4 y 10 como se hace en la forma de dosificación de la invención, y mucho menos predecir que dicho valor tendría un efecto mejorado en la mencionada biodisponibilidad de lopinavir.**

Así mismo, el documento D2 no indica ni sugiere la posible utilización de un polímero soluble en agua como medio de **dispersión o solución sólida** del lopinavir, y mucho menos permite suponer que dicho polímero debe tener un valor de Tg de 50°C o más.

Consecuentemente, las enseñanzas de D2 no conducen de ninguna manera a obtener la forma de dosificación sólida que es objeto de la presente solicitud, toda vez que dicho documento no se refiere a composiciones en las cuales el

principio activo se encuentre en una solución o dispersión sólida, ni sugiere el tipo de componentes que podrían emplearse para este fin, ni la manera de obtener una alta biodisponibilidad de lopinavir con este tipo de forma de dosificación farmacéutica sólida.

Por lo tanto, el documento D2 claramente no puede afectar el Nivel Inventivo de la solicitud en estudio.

5. **CONCLUSIÓN.**

Para finalizar me permito resaltar que el nuevo capítulo reivindicatorio presentado junto con este memorial es totalmente claro y conciso al reclamar la forma de dosificación farmacéutica de la invención, refiriéndose a sus características técnicas esenciales.

Por otro lado, a la luz de este nuevo capítulo reivindicatorio, y en virtud de los argumentos discutidos con respecto a los documentos D1 y D2, se estableció de manera incontrovertible que ninguno de los documentos citados puede conducir de manera inequívoca a la forma de dosificación farmacéutica de la invención, toda vez que ninguno de ellos sugiere las características técnicas de los componentes de dicha forma de dosificación y mucho menos permite predecir la biodisponibilidad mejorada que brinda dicha forma de dosificación. Por lo tanto se demostró sin lugar a dudas el Nivel Inventivo que conlleva la solicitud en estudio frente al estado del arte más próximo.

6. Anexo me permito presentar:

(i) Copia de las páginas **61 y 62** que corresponde al **nuevo capítulo reivindicatorio**, discutido en el presente memorial, constituido por **8** reivindicaciones;

(ii) Copia de las páginas 147 y 153 del documento *Forster, et al International Journal of Pharmaceutics*, 226 (2001) 147-161, referenciado en el texto;

(iii) Copia de la ficha técnica del tensoactivo Cremophor RH 40;

(iv) Copia de la ficha técnica de la casa Sigma-Aldrich del tensoactivo Span 20.

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En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las modificaciones y los argumentos presentados y conceder el privilegio de patente solicitado.

Señor Superintendente,

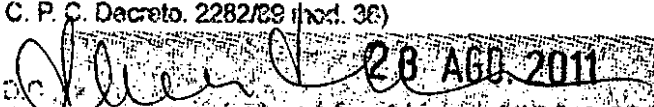

ALICIA LLOREDA RICAURTE

T.P. 53.215

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que comparció personalmente: Alicia Lloreda Ricaurte
identificada (o) con C.C. 39 690 713 y tarjeta
profesional de abogado No. 53215 del Consejo
Superior de la Judicatura, quien autentica la firma puesta por ella
(el) mismo en este escrito.

(Art. 84 C. P. C. Decreto. 2282/89 (mod. 36))

 28 AGO 2011
Bogotá D.C.
ALICIA LLOREDA RICAURTE
C.C. No. 39.690.713 de Usaquén
FIRMA DE LA (EO) COMPARECIENTE

Jeimy Nativy
Morales Beltrán
C.C. 1.015.399.013
V.B. 



REIVINDICACIONES

1. Una forma sólida de dosificación farmacéutica que comprende una solución sólida o una dispersión sólida, donde dicha solución sólida o dispersión sólida comprende:

(2S,3S,5S)-2-(2,6-dimetilfenoxiacetil)amino-3-hidroxi-5-[2S-(1-tetrahidropirimid-2-onil)-3- metilbutanoil]-amino-1,6-difenilhexano (lopinavir),

uno o más polímeros solubles en agua farmacéuticamente aceptables, y
un tensoactivo farmacéuticamente aceptable,

donde dicho polímero soluble en agua tiene una Tg de al menos 50°C, y dicha forma de dosificación comprende de 50 a 85% en peso de la forma de dosificación de dicho uno o más polímeros solubles en agua farmacéuticamente aceptables, y dicho tensoactivo farmacéuticamente aceptable tiene un valor de balance hidrofílico-lipofílico (HLB) entre 4 y 10.

2. La forma de dosificación de la reivindicación 1, donde dicho tensoactivo farmacéuticamente aceptable comprende un éster de sorbitán y ácido graso.

3. La forma de dosificación de la reivindicación 1 la cual comprende, relativo al peso de la forma de dosificación, de 5 a 30% en peso de lopinavir, y de 2 a 20% en peso de dicho tensoactivo farmacéuticamente aceptable.

4. La forma de dosificación de la reivindicación 1, donde dicha solución sólida o dispersión sólida es una solución sólida.

5. La forma de dosificación de la reivindicación 1, donde dichos polímeros solubles en agua comprenden un homopolímero o copolímero de N-vinil pirrolidona.

6. La forma de dosificación de la reivindicación 1, donde dicho polímero soluble en agua comprende un copolímero de N-vinil pirrolidona y acetato de vinilo.

7. La forma de dosificación de la reivindicación 1, donde dicho polímero soluble en agua comprende copovidona, y dicho tensoactivo comprende monolaurato de sorbitán.

8. La forma de dosificación de la reivindicación 7, donde dicha solución sólida o dispersión sólida es una solución sólida.



Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis

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Abstract

The aim of this study was to determine the miscibility of drug and excipient to predict if glass solutions are likely to form when drug and excipient are melt extruded. Two poorly water-soluble drugs, indomethacin and lacidipine, were selected along with 11 excipients (polymeric and non-polymeric). Estimation of drug/excipient miscibility was performed using a combination of the Hoy and Hoftzyer/Van Krevelen methods for Hansen solubility parameter calculation. Miscibility was experimentally investigated with differential scanning calorimetry (DSC) and hot stage microscopy (HSM). Studies were performed at drug/excipient ratios, 1:4, 1:1 and 4:1. Analysis of the glass transition temperature (T_g) was performed by quench cooling drug/excipient melts in the DSC. Differences in the drug/excipient solubility parameters of $< 7.0 \text{ MPa}^{1/2}$ were predicted to indicate significant miscibility and, therefore, glass solution formation on melt extrusion. In comparison, differences of $> 10 \text{ MPa}^{1/2}$ were expected to indicate a lack of miscibility and not form glass solutions when melt extruded. Experimentally, miscibility was shown by changes in drug/excipient melting endotherms and confirmed by HSM investigations. Experimental results were in agreement with solubility parameter predictions. In addition, drug/excipient combinations predicted to be largely immiscible often exhibited more than one T_g upon reheating in the DSC. Melt extrusion of miscible components resulted in amorphous solid solution formation, whereas extrusion of an 'immiscible' component led to amorphous drug dispersed in crystalline excipient. In conclusion, combining calculation of Hansen solubility parameters with thermal analysis of drug/excipient miscibility can be successfully applied to predict formation of glass solutions with melt extrusion. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Melt extrusion; Drug/excipient interactions; Indomethacin; Lacidipine; Solubility parameters; Thermal analysis

1. Introduction

Increasing the dissolution rate of poorly water-soluble drugs is one of the major challenges in dosage form development. One approach is the

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formation of a solid dispersion of drug with a hydrophilic excipient. The ideal type of solid dispersion for increasing dissolution is a glass solution, in which the amorphous drug has a lower thermodynamic barrier to dissolution together with a maximally reduced particle size (Hancock and Zografi, 1997). In addition, the intimate presence of a hydrophilic excipient can increase wetting and lead to super-saturation in the diffusion layer (Chiou and Riegelman, 1971; Shefter, 1981; Ford, 1986). A glass solution is formed when two or more components are entirely miscible in the molten state and cool to form an amorphous one-phase system. However, to form a glass solution that is physically stable over prolonged periods of time the glass transition temperature (T_g) should be higher than the storage temperature. Hancock and Zografi (1997) suggest that the T_g should be at least 50 °C above the storage temperature to ensure that the product remains stable over its shelf-life.

A number of studies have recently shown the potential of melt extrusion to form glass solutions of drug and excipient (Gruenhagen, 1996; Breitenbach, 2000; Breitenbach et al., 1998; Forster et al., 2001). Melt extrusion has advantages over solvent based methods of forming glass solutions, including ease of use, decreased environmental implications, absence of residual solvents, decreased costs and the possibility of continuous processing (Gruenhagen, 1996). To date most pharmaceutical research with melt extrusion has focused on the use of thermoplastic polymers as carriers, such as polyvinylpyrrolidone (PVP) and polymethacrylates (Gruenhagen, 1996; Repka et al., 1999; Breitenbach, 2000). However, an extensive number of excipients including cellulose derivatives, sugars and sugar alcohols have been investigated as potential carriers using solid dispersion preparation methods other than melt extrusion (Chiou and Riegelman, 1971; Ford, 1986; Hatley, 1997; Suzuki and Sunada, 1998; Serajuddin, 1999).

Laboratory-scale melt extruders require considerable quantities of drug substance, which are not often available at the early developmental stage when pilot formulation studies are undertaken. Therefore, the aim of the current investigation was to evaluate ways to predict if a glass solution

was likely to be formed when a particular drug and excipient mixture was melt extruded at a specific drug/excipient ratio using minimal quantities of drug. In this study, prediction was based on comparison of the solubility parameters of drug and excipient, experimental determination of miscibility by differential scanning calorimetry (DSC) and hot stage microscopy (HSM), and analysis of the glass transition temperature (T_g) of rapidly cooled drug/excipient melts. Analysis of the T_g is useful for two reasons; comparison of the T_g to the normal storage temperature (20–30 °C) allows prediction as to whether the melt extrudate will be in the glassy or rubbery state. Secondly, a single T_g at an intermediate temperature between the T_g of both amorphous components, is further evidence of a miscible system (Lu and Zografi, 1998). The Gordon–Taylor equation states that the T_g of an ideally mixed solid solution will be a sum of the weight fraction, thermal expansion and T_g of the individual components (Schneider, 1989).

Indomethacin and lacidipine were used in this study as model drugs. Both compounds are poorly water-soluble and have shown increased dissolution when melt extruded with PVP (Forster et al., 2001).

2. Experimental

2.1. Materials

Indomethacin, polyethylene glycol 8000 (PEG 8, average MW 7000–9000), polyethylene glycol 10 000 (PEG 10, average MW 8500–11 500), polyvinyl alcohol (PVA) and polyvinylpyrrolidone k12 (PVP 12, average MW 2500) were obtained from Sigma Chemicals (Dorset, UK). Lacidipine, citric acid, glucose, lactose anhydrous, mannitol, polyvinylpyrrolidone k30 (PVP 30, average MW 50000) and sucrose anhydrous, were provided by GlaxoSmithKline (Ware, UK). Polyvinylpyrrolidone-co-vinyl-acetate (PVP/VA, MW 45 000–70 000) was obtained from ISP (Manchester, UK). All chemicals were of laboratory reagent grade. Experiments with lacidipine were performed under subdued light.

2.2. Solubility parameter calculation

The Hansen solubility parameters of the compounds were calculated from the chemical structures using the approaches of Hoftyzer/Van Krevelen, and Hoy (Van Krevelen, 1990). As an example, the calculations carried out for lacidipine are given in Fig. 1. For polymeric excipients determination of the solubility parameter was based on the average molecular weight. The units of solubility parameters are $\text{MPa}^{1/2}$, $(\text{J m}^{-3})^{1/2}$ or $(\text{cal cm}^{-3})^{1/2}$, where $1 (\text{cal cm}^{-3})^{1/2}$ is equivalent to $2.0421 \text{ MPa}^{1/2}$ (Hancock et al., 1997).

2.3. Preparation of physical mixtures

A series of physical mixtures of drug and excipient were prepared at three mass ratios, 1:4, 1:1 and 4:1, by gently grinding accurately weighed quantities using a mortar and pestle for 2 min. Homogeneity of mixing was considered uniform when three separate DSC thermograms were similar when superimposed. The enthalpy of fusion for all mixtures at all mass ratios had an average coefficient of variation of 4.7%.

2.4. Differential scanning calorimetry

A TA Instruments DSC 2920 (Surrey, UK) was used at 10 K min^{-1} with a nitrogen purge at 20 ml min^{-1} . Preparation of melts and determination of miscibility were performed using crimped aluminium sample pans with a pierced lid and a sample size of 5–10 mg. An empty pan was used for reference and calibrations for temperature and enthalpy were performed routinely with indium (Laboratory of the Government Chemist, Middlesex, UK).

The T_g of individual components and drug/excipient blends was determined by melting the sample in the DSC and rapidly cooling the melt by placing a stainless steel holder filled with liquid nitrogen over the DSC cell ('quench cooling'). This method has been used successfully to prepare glasses of both indomethacin and lacidipine (Forster et al., 1999). The cooled melt was then reheated in the DSC and the T_g noted. With this method, the effect of moisture is removed, as all

blends were heated in pierced pans to at least 150°C using dry nitrogen purge gas.

For melt extrudates water absorbed after manufacture made accurate analysis of the T_g difficult. Therefore, modulated temperature DSC (MTDSC) was used as this approach separates thermodynamically reversing events (e.g. T_g), from non-reversing events (e.g. dehydration) (Craig and Royall, 1998). MTDSC was performed using the TA Instruments DSC 2920 with a liquid nitrogen cooling accessory. Samples (5–10 mg) were sealed in aluminium pans without a pinhole in the lid. A linear heating rate of 2 K min^{-1} with an oscillation of $\pm 0.25 \text{ K}$ every 40 s was applied, ensuring at least six modulations per thermal event. Calibration of the MTDSC was performed for temperature and enthalpy at 2 K min^{-1} using indium.

2.5. Hot stage microscopy

A Linkam TMS 92 hot stage (Surrey, UK) and Olympus light microscope with a JVC video-link and Image Pro Plus software (Media Cybernetics, Silver Spring, USA) were used to investigate drug/excipient miscibility. The heating rate was 10 K min^{-1} . Cross-polarisation was used to investigate crystallinity.

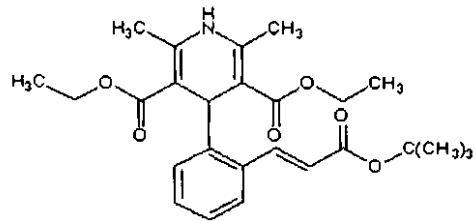
2.6. Thermogravimetric analysis

Thermal decomposition of some drug/excipient mixtures was investigated using a TA Instruments 2950 Hi-res TGA at a heating rate of 10 K min^{-1} and a nitrogen flow of 100 ml min^{-1} . Samples (20–30 mg) were heated until weight loss was detected. Temperature was calibrated by measuring the Curie point of nickel and alumel (TA Instruments) at 10 K min^{-1} .

TGA was also used to determine the moisture content of the melt extrudates. Weight loss up to 150°C was taken as dehydration and the weight change equivalent to moisture content.

2.7. X-ray powder diffraction

X-ray powder diffraction (XRPD) was performed on a Philips X'pert MPD with a count



$$\delta_d = \frac{\sum F_{di}}{V} = \frac{6960}{378.4} = 18.4$$

Group _z	F _{di}	F ² _{pi}	E _{hi}	Σ ² V/cm ³ mol ⁻¹
(7) CH ₃	2940	0	0	234.5
(2) CH ₂	540	0	0	32.2
(1) NH	160	210	3100	4.5
(1) C	-70	0	0	-19.2
(1) CH	80	0	0	-1.0
(4) C=	280	0	0	-22
(1) Phenylene	1270	110	0	52.4
(2) HC=	400	0	0	27
(3) COO	1170	1470	21000	54
(1) ring (6)	190	-	-	16
Σ	6960	1790	24100	378.4

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} = \frac{\sqrt{1790}}{378.4} = 0.11$$

$$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}} = \sqrt{\frac{24100}{378.4}} = 7.98$$

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} = 20.1$$

(a) Hoftyzer and Van Krevelen

z is the functional group, F_{di} is the group dispersion component giving δ_d, F²_{pi} the group polar component, E_{hi} the hydrogen bonding component and V the molar volume from Hildebrand analysis (Fedors, 1974). δ_t is the total solubility parameter calculated from the various components (dispersion forces δ_d, hydrogen bonding δ_h and polar interactions δ_p).

Group _z	F _t	F _p	Δ _T	V
(7) CH ₃	2124.5	0	0.161	150.85
(2) CH ₂	538	0	0.04	31.1
1) NH	368	368	0.031	11.0
(1) C	65.5	0	0	3.56
(1) CH	176.0	0	0.012	9.56
(4) C=	692	252	0	28.72
(1) Phenylene	20.2	-13.3	0	-
(2) HC=	498	119	0.036	26.36
(3) COO	1920	1584	0.141	71.1
(1) ring (6)	-48	61	0	-
(5) CH _{ar}	1205	312.5	0.055	67.1
(1) C _{ar}	201	65	0.011	7.42
Σ	7760.2	2748.2	0.487	406.8

$$\delta_t = \frac{F_t + B}{V} = \frac{7760.2 + 277}{406.8} = 19.8$$

Base = 277

(b) Hoy

F_t is the molar attraction constant, F_p the polar component, Δ_T the Lyderson correction for non-ideality, V the molar volume and Base is a constant. Note, only the calculation for δ_{t(total)} is given in figure.

Fig. 1. Solubility parameter calculations for lacidipine.

time of 1 s and step size of $0.02^\circ 2\theta$ using Ni filtered Cu-K α radiation (50 kV and 40 mA). Back filled samples were prepared using approximately 300 mg of powder.

2.8. Scanning electron microscopy

Samples were coated with a thin gold-palladium layer by sputter coating (Bio-rad E5100, Watford, UK) and investigated with a Cambridge S360 Scanning Electron Microscope (SEM, Cambridge, UK), which was operated with an acceleration voltage of 10 kV.

2.9. Melt extrusion

Drug and excipient blends were prepared by mixing accurately weighed quantities of drug and excipient in a plastic bag for 5 min. Extrusion was performed in a low humidity (<25% RH) and controlled temperature (20 °C) environment using a Brabender Plasti-corder PL2000 (Duisburg, Germany) with counter-rotating intermeshing twin screws (diameter 3 and 1/4 in., L/D ratio 18). The heating barrel is divided into four temperature zones. For each drug/excipient blend, the first zone ('throat') was initially heated by conduction and then cooled to 20 °C using a water cooler to avoid plasticised material blocking flow through the machine. Zones 2–4 were kept at a constant temperature for each drug/excipient blend. The following extrusion temperatures were used; indomethacin/PVP 30 (1:1) 155 °C, (4:1) 150 °C, indomethacin/PVP/VA (1:1) 150 °C, lacidipine/PVP 30 (1:1) 180 °C, (1:4) 175–200 °C, lacidipine/PVP/VA (1:1) 170 °C, lacidipine/mannitol (1:1) 185 °C. The screw speed was adjusted to 20–30 rpm, and the extrudate was cooled on a conveyer belt.

The extrudate was reduced in particle size by milling in a hammer mill through a 0.5-mm screen. A particle size range of 25–250 μm was selected for analysis.

3. Results and discussion

3.1. Solubility parameter calculation

Estimates of the solubility parameter (δ) have

been used with some success to predict the miscibility of drugs and excipients (Suzuki and Sunada, 1997; Greenhalgh et al., 1999; Hancock et al., 1997). Greenhalgh et al. (1999) used Hildebrand solubility parameters, which account for the dispersive forces (E_d). The same authors suggested that interactions between polar (E_p) and hydrogen bonding groups (E_h), which also may affect solubility, should be incorporated in the estimation of the solubility parameter. These values are combined in the Hansen solubility parameter (Greenhalgh et al., 1999), which can be estimated based on the methods of Hoftyzer/Van Krevelen and Hoy (Van Krevelen, 1990). In this study the average of the Hoftyzer/Van Krevelen and Hoy values have been used to calculate δ (Table 1).

Compounds with similar values for δ are likely to be miscible. This is because the energy of mixing released by interactions within the components is balanced by the energy released by interaction between the components (Greenhalgh et al., 1999). Greenhalgh et al. (1999) classified excipients based on the difference between the solubility parameters of excipients and drugs ($\Delta\delta$). The authors demonstrated that compounds with a $\Delta\delta < 7.0 \text{ MPa}^{1/2}$ were likely to be miscible. When the $\Delta\delta > 10 \text{ MPa}^{1/2}$ the compounds were likely to be immiscible. Since the values for δ are fairly similar for indomethacin and lacidipine (22.1 $\text{MPa}^{1/2}$ and 20.0 $\text{MPa}^{1/2}$, respectively), it can be predicted that an excipient with a δ less than 27–29 $\text{MPa}^{1/2}$ should show some miscibility with both drugs, whereas an excipient with a δ over 30–32 $\text{MPa}^{1/2}$ is likely to be immiscible.

From the results summarised in Table 1 the excipients in this study can be grouped into three categories based on the $\Delta\delta$. Excipients with a $\Delta\delta < 2.0 \text{ MPa}^{1/2}$ are termed 'group 1' and are likely to be miscible and form glass solutions when melt extruded with both drugs. Those excipients with $\Delta\delta > 10 \text{ MPa}^{1/2}$ are termed 'group 3' and are likely to be significantly immiscible and are not expected to form glass solutions. Citric acid is classified as 'group 2' and may show some miscibility with indomethacin since the $\Delta\delta$ is 5.6. Lacidipine is less likely to be miscible with citric acid since the $\Delta\delta$ is 7.7 $\text{MPa}^{1/2}$. PVA is also classified as 'group 2' with

respect to indomethacin as the $\Delta\delta$ is 8.9 MPa^{1/2}, but as ‘group 3’ with respect to lacidipine as the $\Delta\delta$ is 11.0 MPa^{1/2}.

3.2. Thermal analysis of miscibility

Miscibility is detected in the DSC by changes in the melting endotherm of the drug (Ford and Timmins, 1987; Mura et al., 1998). Analysis of the melt endotherm onset temperature (T_{mo}) and heat of fusion were used in this study to investigate miscibility. DSC was complemented by HSM, which allows visualisation of both melting events and dissolution of one component in the melt of the other. It must be noted that melt endotherms may be a mixture of the heat of fusion and heat of solution, but that these two events cannot be resolved with DSC (Ford and Timmins, 1987). Table 2 gives the T_{mo} and heats of fusion for drugs and excipients. In the case of PVP 12, PVP 30 and PVP/VA the T_{mo} and heats of fusion are not reported, as the polymers are completely amorphous. PVA is a partially amor-

phous polymer and, therefore, has a low value for heat of fusion (Van Krevelen, 1990). The heat of fusion for lactose anhydrous could not be experimentally determined due to degradation on melting.

Thermal investigation indicated strong evidence for miscibility of both drugs with PEG 8 and PEG 10. Fig. 2a shows the DSC thermograms for lacidipine/PEG 10 and clearly shows that the T_{mo} and heat of fusion of the drug are decreased with increasing PEG 10. Fig. 3a shows that lacidipine begins to dissolve in molten PEG 10 well before the melting point of drug alone.

Decreases in T_{mo} indicated that PVP 12 and PVP/VA were miscible with both drugs and that indomethacin was also miscible with PVP 30. These findings were supported with HSM (Fig. 3b). For lacidipine/PVP 30 at all mass ratios the T_{mo} remained unchanged, indicating a lack of miscibility (Table 3). However, HSM of lacidipine/PVP 30 (1:1) demonstrated that PVP 30 begins to dissolve in the molten lacidipine at around 180 °C (Fig. 3c).

Table 1
Solubility parameters of drugs and excipients

Compound	Solubility parameters (δ)			Group ^a
	Hofsteyer/Van Krevelen (MPa) ^{1/2}	Hoy (MPa) ^{1/2}	Average ^b	
Indomethacin	22.3	21.9	22.1	–
Lacidipine	20.1	19.8	20.0	–
PEG 8	21.6	21.6	21.6	1
PEG 10	21.5	21.6	21.6	1
PVP 12	22.4	20.7	21.3	1
PVP 30	22.4	20.7	21.6	1
PVP/VA ^c	21.5	20.6	21.1	1
PVA	31.7	30.3	31.0	2/3
Citric acid	29.4	25.9	27.7	2
Glucose	38.9	37.8	38.4	3
Mannitol	39.1	38.7	38.9	3
Lactose	35.7	33.0	34.4	3
Sucrose	36.0	33.5	34.8	3

Group 1 compounds likely to be miscible with indomethacin and lacidipine. Group 2 compounds likely to be immiscible with indomethacin and lacidipine. Group 3 borderline miscibility.

^a Where the difference in solubility parameter (average) between drug and excipient is, group 1 <2.0 MPa^{1/2}, group 2 = 5–8.9 MPa^{1/2} and group 3 >10.0 MPa^{1/2}.

^b Is the average of the Hofsteyer/Van Krevelen and Hoy solubility parameters.

^c PVP/VA 60/40 (S-630).

Table 2
DSC data of drugs and excipients (heating rate 10 K min⁻¹)

Compound	Melting endotherm onset (°C)	Heat of fusion (ΔH , J g ⁻¹)	T_g (°C)
Indomethacin	159.4	110.3	43.7
Lacidipine	182.1	100.9	48.0
PEG 8	57.8	189.6	-55
PEG 10	56.4	183.8	-50
PVP 12	—	—	114.0
PVP 30	—	—	164.2
PVP/VA	—	—	106.2
PVA	173.0	11.3	85
Citric acid	155.6	210.0	21.3
Lactose	229.6	Degrades	14.6
Mannitol ^a	166.1	328.7	12.6
Glucose	152.0	200.6	30.2
Sucrose	189.3	132.8	70.7

($n = 3$ For drug and $n = 2$ for excipient). Note, PVP, PVP/VA are amorphous polymers.

^a Mannitol recrystallises on cooling of the melt, therefore, the T_g value estimated by Yu et al. (1998) is used.

For 'group 3' excipients minimal evidence for miscibility of drugs with excipients was found with thermal analysis. In the DSC thermograms two distinct melting endotherms, for drug and excipient at the expected T_{mo} , were detected (Fig. 2b and Table 3). Fig. 2b shows that a minimal increase in the heats of fusion for indomethacin and 'group 3' excipients was found, which may be evidence of some miscibility. However, in the case of indomethacin/mannitol and indomethacin/sucrose the resolution of the respective melt endotherms was not complete.

For indomethacin/citric acid and indomethacin/glucose only one melt endotherm was visible at a DSC heating rate of 10 K min⁻¹ due to overlapping melting events. Changing the DSC heating rate to 2 K min⁻¹ separated the indomethacin/glucose melt endotherms, but did not resolve the melts of indomethacin and citric acid. HSM of indomethacin and lacidipine/citric acid did not show any sign of miscibility (data not shown). For lacidipine/citric acid the T_{mo} could not be determined due to citric acid decomposition, which begins around 165 °C (Ford, 1986). TGA demonstrated a weight loss starting at 160 °C related to decomposition (data not shown).

For indomethacin/PVA, there was a significant decrease (Δ 8.4 °C) in the T_{mo} and a slight decrease in the heat of fusion at a (1:4) mass ratio (Δ

6.8 J g⁻¹). HSM analysis of indomethacin/PVA showed miscibility of indomethacin with amorphous regions of PVA. Crystalline PVA did not melt until around 200 °C and was not soluble in the molten indomethacin.

In general, thermal analysis supported the predictions from δ calculations. 'Group 1' excipients with a $\Delta\delta < 2$ MPa^{1/2} exhibited miscibility with both drugs indicated by changes in the drug T_{mo} and visual evidence of miscibility with HSM. The excipients in 'group 3', with $\Delta\delta > 10$ MPa^{1/2}, showed small changes in the drug melt heat of fusion, but the drug T_{mo} remained virtually unchanged and HSM did not show evidence for miscibility. For indomethacin/PVA the $\Delta\delta$ is 8.9 suggesting limited miscibility based on the classification of Greenhalgh et al. (1999). DSC and HSM investigations indicated some miscibility between the compounds. For indomethacin/citric acid the $\Delta\delta$ is 5.6, suggesting miscibility, but this was not evident in experimental investigations. A miscible glass solution, however, has been reported for indomethacin/citric acid up to weight fraction of 0.25 citric acid (Lu and Zografi, 1998).

3.3. Thermal analysis of the glass transition

An amorphous solution will only be in the glassy state at a storage temperature below the T_g .

At storage temperatures above the T_g a less viscous, rubbery state will form, with an increased tendency to recrystallise (Lu and Zografi, 1998). The T_g of an amorphous solution will depend on both the drug and excipient T_g values and, therefore, a single T_g at a temperature between the T_g

values of both components is evidence for formation of a miscible system. Partial miscibility is evident when the T_g of the drug is shifted towards the T_g of the excipient, or vice-versa.

The T_g values of the individual drugs and excipients are shown in Table 2. The T_g values of drug/excipient quench cooled melts were determined for all 'group 1' excipients, mannitol and sucrose ('group 3') and both PVA and citric acid ('groups 2 and 3'). Table 4 shows the T_g values determined experimentally for both indomethacin and lacidipine/excipient blends.

In general, for 'group 1' excipients a single T_g at an intermediate temperature between the drug and the excipient T_g values was found. This supports the prediction from δ calculation and thermal analysis that these excipients are miscible with both drugs and, therefore, are likely to form an amorphous solid solution when melt extruded.

The T_g values of the drug/PEG melts were well below 25 °C and, therefore, an amorphous solution formed with these excipients will be in the rubbery state, prone to recrystallise and difficult to process. In the case of lacidipine/PEG 1:4 the T_g could not be detected as it may have been below the lowest temperature reached during the experiments (–35 °C).

Drug/PVP 12 and drug/PVP/VA melts had a single T_g value well above normal storage temperature (25 °C) and consequently glass solution formation is likely when the components are melt extruded. However, not all the T_g values are 50 °C above the storage temperature, and as detailed by Hancock and Zografi (1997) this suggests that there may be issues with the physical stability of these drug/excipient blends on long-term storage. Thermograms of both indomethacin/PVP 12 (1:1) and indomethacin/PVP/VA (1:1) melts are shown in Fig. 4A and B. Drug/PVP 30 (1:1 and 4:1) melts also exhibited a single T_g , at an appropriate temperature for storage. However, at a (1:4) mass ratio two T_g values were visible for indomethacin and lacidipine, one at an intermediate temperature and the other close to the T_g of PVP 30 (Fig. 4C shows lacidipine/PVP 30 melt as an example). As PVP 30 is a high molecular weight polymer this is probably due to the increased viscosity of the plasticised

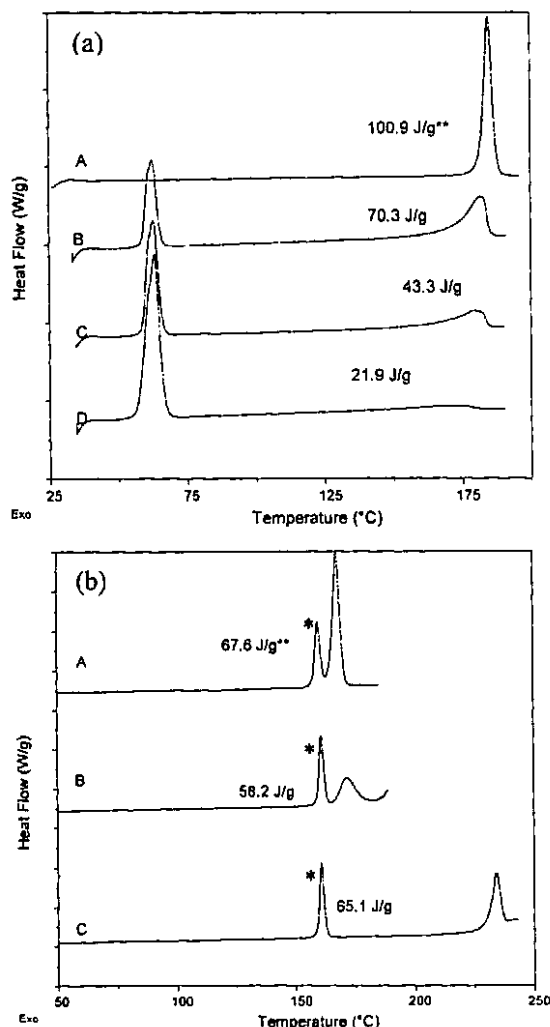


Fig. 2. DSC thermograms of drug and drug excipient mixtures. **, Heat of fusion for drug melts (ΔH). Expected ΔH ($J g^{-1}$) of drug based on dilution with excipient: lacidipine (4:1) 80.7, (1:1) 50.5, (1:4) 20.2. Indomethacin (1:1) 55.2. (a) Lacidipine/PEG 10, (A) lacidipine drug substance; (B) lacidipine/PEG (4:1); (C) lacidipine/PEG (1:1); (D) lacidipine/PEG (1:4). (b) Indomethacin, *, indomethacin melt; (A) indomethacin/mannitol (1:1); (B) indomethacin/sucrose (1:1); (C) indomethacin/lactose (1:1).

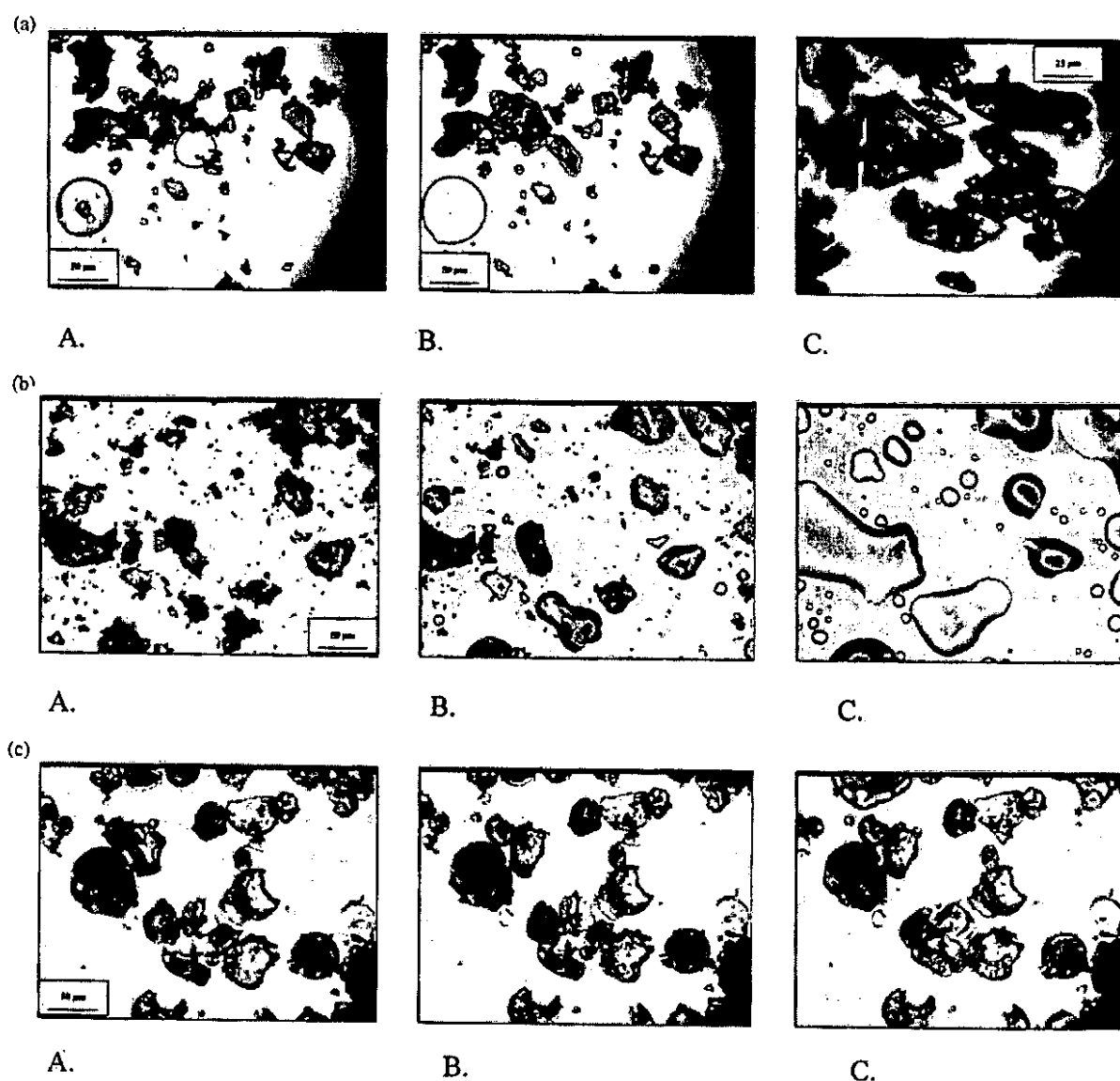


Fig. 3. (a) HSM of lacidipine and lacidipine/PEG 10 (1:1), (A) lacidipine/PEG 145 °C; (B) lacidipine/PEG 169 °C; (C) lacidipine 180 °C. (b) HSM of indomethacin/PVP/VA (1:1), (A) indomethacin/PVP/VA ambient; (B) indomethacin/PVP/VA 148 °C; (C) indomethacin/PVP/VA 164 °C. (c) HSM of lacidipine/PVP 30 (1:1), (A) lacidipine/PVP 30 ambient; (B) lacidipine/PVP 30 125 °C; (C) lacidipine/PVP 30 180 °C; *, regions of PVP dissolution.

polymer. High polymer viscosity has been previously reported to limit the miscibility of nifedipine and HPMC in DSC studies (Suzuki and Sunada, 1998).

Drug/mannitol melts (1:1) had an experimental T_g close to the temperature of drug alone. This is due to the recrystallisation of mannitol. In Fig.

5A it can be seen that mannitol forms a crystalline inclusion within the lacidipine glass following melting and quench cooling in the DSC. Lacidipine/sucrose melts exhibited two distinct T_g values at all mass ratios. Fig. 4D shows the T_g values of a lacidipine/sucrose (1:1) melt. As the temperature of both the T_g values remains practically un-

changed at all mass ratios this is strong evidence of an immiscible amorphous mixture (Yu et al., 1998) and confirms the lack of miscibility predicted by δ calculation and thermal analysis. Indomethacin/sucrose melts exhibited a single T_g , which was below the T_g of either component at a similar temperature for all mass ratios. From δ calculation ($\Delta\delta$ 12.7 MPa^{1/2}) and thermal analysis an immiscible system was predicted. Further in-

vestigation is required to explain the finding, but a similar result has been previously reported by Raudonus et al. (2000) for isomalt/sucrose melts. Indomethacin/PVA melts exhibited a single experimental T_g , but also an endotherm at ~ 187 °C, due to melting of PVA (data not shown). These results support the HSM finding that indomethacin is only miscible with the amorphous PVA phase. Lacidipine/PVA melts exhibited two

Table 3
Melt onset temperature (°C) for indomethacin/excipient and lacidipine/excipient mixes at various mass ratios

	Indomethacin			Lacidipine		
	1:4 ^a	1:1	4:1	1:4	1:1	4:1
PEG 8	— ^a	101.5, 159.0 ^b	144.6	— ^a	157.2	176.9
PEG 10	— ^a	106.1, 158.5 ^b	146.9	124.2	166.8	171.7
PVP 12	122.5	126.5	151.8	169.3	166.3	174.8
PVP 30	— ^c	140.4	155.3	179.6	179.5	181.0
PVP/VA	— ^c	134.0	156.4	176.3	178.7	179.8
PVA	151.0	154.5	157.9	181.2	182.4	181.3
Citric Acid	— ^d	— ^d	— ^d	— ^e	— ^e	— ^e
Glucose ^f	156.2	155.7	155.8	179.9	179.8	180.0
Lactose	159.2	159.1	159.0	181.1	181.4	181.6
Mannitol	157.2	157.4	157.8	181.4	181.2	181.2
Sucrose	159.0	159.1	159.1	183.6	183.3	183.6

(n = 3). ^a, 1:4 Corresponds to a drug:excipient mass ratio.
^a Not detectable.
^b Two distinct fusion events.
^c Not detected due to dehydration of polymer.
^d Not determined as melting endotherms overlap.
^e Decomposition of citric acid interferes with lacidipine melt endotherm.
^f DSC heating rate was 2 K min^{−1}.

Table 4
Glass transition temperatures (°C) of drug/excipient blends prepared by quench cooling the melt in a DSC

	Indomethacin			Lacidipine		
	1:4 ^a	1:1	4:1	1:4	1:1	4:1
PEG 8	−12.1	−35.1	6.8	4.4	4.2	22.5
PEG 10	−10.0	−31.7	8.6	—	−9.8	9.1
PVP 12	84.2	68.8	49.8	92.2	76.2	54.8
PVP 30	84.9/163.0	71.7	72.9	86.4/161.1	64.8	54.3
PVP/VA	87.1	67.0	50.1	100.4	73.3	59.3
PVA	66.5	52.7	46.6	70.1/49.8	70.5/49.1	69.8/47.6
Citric acid	19.7/12.3	31.7/16.9	35.3/15.2	Degrades		
Mannitol		45.6			50.5	
Sucrose	38.0	38.0	39.4	68.9/50.5	70.7/49.5	71.4/49.9

^a 1:4 Corresponds to a drug:excipient mass ratio.

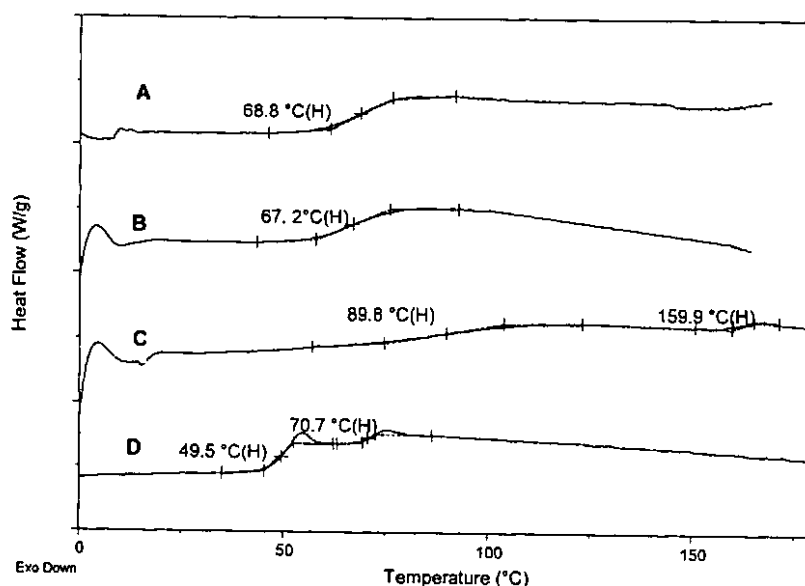


Fig. 4. T_g determination of quench cooled drug/excipient melts by DSC. (A) Indomethacin/PVP 12 (1:1); (B) indomethacin/PVP/VA (1:1); (C) lacidipine/PVP 30 (1:4); (D) lacidipine/sucrose (1:1).

T_g values similar to the respective T_g of each component confirming the lack of miscibility of the two compounds. Indomethacin/citric acid melts showed two T_g values and changing the mass ratio of drug to excipient led to significant changes in the T_g values. This indicates a degree of plasticisation by citric acid and that the components are partially miscible.

3.4. Melt extrusion

Due to the large quantities of drug substance required for melt extrusion not all drug/excipient blends were melt extruded.

Melt extrusion of indomethacin/PVP 30 (1:1 and 4:1), indomethacin/PVP/VA (1:1), lacidipine/PVP 30 (1:1) and lacidipine/PVP/VA (1:1) produced transparent and brittle solids typical of a glass solution (Fig. 5B shows lacidipine/PVP 30 (1:1) as an example). XRPD of the milled drug/PVP 30 (1:1 and 4:1) and drug/PVP/VA (1:1) extrudates showed an amorphous pattern, and SEM demonstrated a uniform morphology consistent with glass solution formation (Fig. 5D). Single T_g values well above the storage temperature were seen for both drugs when extruded with PVP

30 and PVP/VA (Table 5). These results for 'group 1' excipients support the prediction of a miscible glass solution from comparison of the calculated δ , thermal analysis of miscibility using DSC/HSM and T_g analysis. A summary of these findings is shown in Table 6. Lacidipine/PVP 30 (1:4) was not successfully melt extruded at 175 °C as the shear pins of the extruder broke, indicating high strain on the extruder. Increasing the temperature of the extruder up to 200 °C led to degradation. This anomaly was predictable from DSC/HSM and T_g analysis, but not from δ comparison, which does not account for the viscosity of the components (Table 6).

In comparison, melt extrusion of lacidipine with a 'group 3' excipient, mannitol (1:1), produced an opaque solid with peaks apparent in the X-ray powder diffractograms due to recrystallised mannitol. SEM of the extrudate provided evidence of crystalline particles in the lacidipine/mannitol system (Fig. 5C). Lacidipine/mannitol extrudate exhibited a T_g similar to that of the drug, due to the recrystallisation of mannitol (Table 5). Therefore, extrusion of lacidipine and mannitol resulted in a two-phase dispersion, one phase of amorphous drug and the other phase of

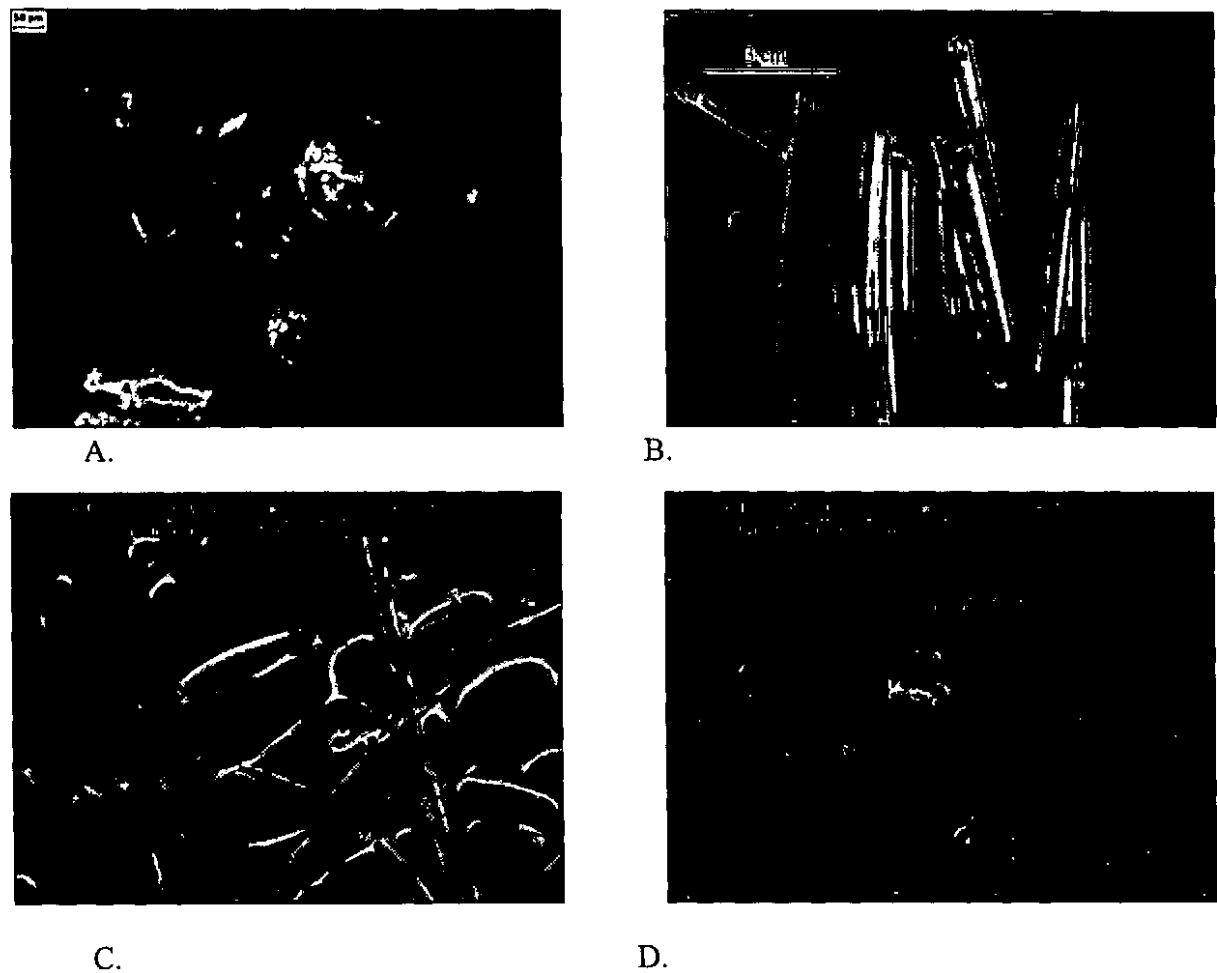


Fig. 5. Photograph and micrographs of lacidipine extrudates, (A) Polarised light microscopy of lacidipine/mannitol 1:1 quench cooled melt; (B) lacidipine/PVP 1:1 extrudate; (C) lacidipine/mannitol 1:1, intact; (D) lacidipine/PVP 1:1, intact.

Table 5
Glass transition (°C) of indomethacin and lacidipine melt extrudates

Drug	Excipient	Mass ratio	Water (% w/w)	T _g ^a extrudate (°C)
Indomethacin	PVP 30	1:1	1.7	76.1
		4:1	0.8	56.1
	PVP/VA	1:1	0.7	64.5
Lacidipine	PVP 30	1:1	2.5	78.4
	PVP/VA	1:1	0.5	75.6
	Mannitol	1:1	0.8	53.7

^a Determined with MTDSC.

Table 6
Summary table of drug/excipient miscibility

Excipients	Group	Indomethacin					Lacidipine				
		$\delta_{\text{Hoflyzer/Hoy}}$	DSC melting	HSM	DSC T_g	Melt extrusion	$\delta_{\text{Hoflyzer/Hoy}}$	DSC melting	HSM	DSC T_g	Melt extrusion
PEG 8	1	+	+	+	+		+	+		+	
PEG 10	1	+	+		+		+	+	+	+	
PVP 12	1	+	+	+	+		+	+		+	
PVP 30	1	+	+		+/- ^a	+ ^b	+	-	+	+/- ^a	+/- ^b
PVP/VA	1	+	+	+	+	+	+	+	+	+	+
PVA	2/3	^c	+	+/- ^d	+		-	-	-	-	
Citric acid	2	^e	^e	-	-		^e	Degrades			
Glucose	3	-	-				-	-	-		
Lactose	3	-	-				-	-			
Mannitol	3	-	-		-		-	-		-	-
Sucrose	3	-	-	-	-		-	-		-	

+, Miscible, as indicated by a change in the onset of drug melting (DSC melting), observed with HSM, a single T_g for quench cooled drug/excipient blends or melt extrudates (DSC T_g). -, Immiscible.

^a Miscible at a drug/PVP 30 ratio of 1:1 and 4:1, immiscible at 1:4.

^b A miscible glass solution was formed at a drug/PVP 30 ratio of 1:1 and 4:1 (indomethacin only), but not at 1:4 (lacidipine only).

^c Cannot be predicted from δ calculation.

^d Only miscible with amorphous PVA.

^e Melting endotherms could not be resolved by DSC.

crystalline excipient, supporting the prediction from comparison of δ and thermal analysis of miscibility using DSC and HSM (Table 6).

Overlapping melts complicated predictions of the miscibility of indomethacin and citric acid. The fact that two T_g values were present at all mass ratios for quenched cooled indomethacin/citric acid blends indicated, at best, limited miscibility and not formation of an amorphous solid solution. Additionally, the low T_g values of the quenched cooled melts would indicate potential problems with stability and handling. In the case of lacidipine, citric acid was not a suitable candidate due to degradation.

The difficulty in determining the solubility behaviour of PVA could be related to its partially crystalline nature. Crystalline polymers are well known to be relatively insoluble and often only dissolve other components at their melting point (Van Krevelen, 1990). Indomethacin was found to be miscible with the amorphous component of PVA, but not with the crystalline component. The presence of crystalline material in the dispersion prevents solid solution formation and may affect physical stability of the amorphous component and, therefore, PVA is not a suitable melt extrusion candidate for indomethacin.

4. Conclusion

The selection of excipients for melt extrusion with a specific drug can be based on the difference between the calculated solubility parameters of drug and excipient. When the difference between drug and excipient solubility parameters is $< 2.0 \text{ MPa}^{1/2}$, ('group 1') a glass solution is likely to result when the components are melt extruded. However, it must be borne in mind that the viscosity of the excipient may limit the drug/excipient ratio that can be extruded and, therefore, even for 'group 1' excipients further analysis using thermal methods should be undertaken before the drug and excipient are melt extruded. When the difference between drug and excipient solubility parameters is $> 10 \text{ MPa}^{1/2}$ ('group 3') it is unlikely that a glass solution will be formed with melt extrusion. When the difference in solubility

parameters is between $5\text{--}10 \text{ MPa}^{1/2}$ ('group 2'), prediction of glass solution formation is not possible, unless further investigation is performed with thermal analysis. However, DSC analysis of onset of drug melting was found to have limitations in assessing miscibility when both the drug and the excipient melt at similar temperatures. T_g analysis from DSC prepared quench cooled melts of drug and excipient provided an alternative means of predicting miscibility. Additionally, DSC T_g analysis indicated whether a glass solution formed with a specific drug and excipient for a given mass ratio would have a T_g above the storage temperature, which is important for physical stability.

Further studies are required to assess if this approach of combining the calculation of solubility parameter with thermal analysis to select suitable combinations of drug and excipient for glass solution formation by melt extrusion is applicable to a wider range of drugs and excipients.

Acknowledgements

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References

- Breitenbach, J., 2000. Feste lösungen durch schmelzextrusion—ein integriertes herstellkonzept. *Pharmazie* 29, 46–49.
- Breitenbach, J., Berndt, G., Neumann, J., Rosenberg, J., Simon, D., Zeidler, J.D., 1998. Solid dispersions by an integrated melt extrusion system. *Proc. Int. Symp. Control. Rel. Bioact. Mater.* 25, 6330.
- Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersions. *J. Pharm. Sci.* 60, 1281–1302.
- Craig, D.Q.M., Royall, P.G., 1998. The use of modulated temperature DSC for the study of pharmaceutical systems: potential uses and limitations. *Pharm. Res.* 15, 1152–1153.
- Ford, J.L., 1986. The current status of solid dispersions. *Pharm. Acta Helv.* 61, 69–88.
- Ford, J.L., Timmins, P., 1987. *Pharmaceutical Thermal Analysis*. Ellis Horwood, New York.
- Forster, A.H., Hempenstall, J., Tucker, I., Rades, T., 1999. Selection of drug candidates for melt extrusion by thermal methods. *Proc. Aust. Pharm. Sci. Assoc.* 64.

- Forster, A.H., Hempenstall, J., Rades, T., 2001. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. *Journal of Pharmacy and Pharmacology* 53, 303–315.
- Greenhalgh, D., Williams, A., Timmins, P., York, P., 1999. Solubility parameters as predictors of miscibility in solid dispersions. *J. Pharm. Sci.* 88, 1182–1190.
- Gruenhagen, H.H., 1996. Polymer/drug-melt extrusion: therapeutic and technological appeal. *Pharm. Technol. Eur.* 11, 22–27.
- Hancock, B.C., Zografi, G., 1997. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* 86, 1–12.
- Hancock, B.C., York, P., Rowe, R.C., 1997. The use of solubility parameters in pharmaceutical solid dosage form design. *Int. J. Pharm.* 148, 1–21.
- Hatley, R., 1997. Glass fragility and stability of pharmaceutical preparations—excipient selection. *Pharm. Dev. Technol.* 2, 257–264.
- Lu, Q., Zografi, G., 1998. Phase behaviour of binary and ternary amorphous mixtures containing indomethacin, citric acid and PVP. *Pharm. Res.* 15, 1202–1206.
- Mura, P., Faucci, M.T., Manderioli, A., Furlanetto, S., Pinzauti, S., 1998. Thermal analysis as a screening technique in preformulation studies on picotnamide solid dosage forms. *Drug Dev. Ind. Pharm.* 24, 747–756.
- Raudonus, J., Bernard, J., JanBen, H., Kowaczyk, I., Carle, R., 2000. Effect of polymeric additives on glass transition, viscosity, and crystallisation of amorphous isomalt. *Food Res. Int.* 33, 41–51.
- Repka, M.A., Gerding, T.G., Repka, S.L., McGinity, J., 1999. Influence of plasticisers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. *Drug Dev. Ind. Pharm.* 25, 625–633.
- Schneider, H.A., 1989. Glass transition behaviour of compatible polymer blends. *Polymer* 30, 771–779.
- Serajuddin, A.T.M., 1999. Solid dispersion of poorly soluble drugs: early promises, subsequent problems and recent breakthroughs. *J. Pharm. Sci.* 88, 1058–1066.
- Shefter, E., 1981. Solubilization by solid-state manipulation. In: Yalkowsky, S.H. (Ed.), *Techniques of Solubilisation of Drugs*. Marcel Dekker, New York, pp. 159–182.
- Suzuki, H., Sunada, H., 1997. Influence of water-soluble polymers on the dissolution of nifedipine solid dispersions with combined carriers. *Chem. Pharm. Bull.* 45, 1688–1693.
- Suzuki, H., Sunada, H., 1998. Comparison of nicotinamide, ethylurea and polyethylene glycol as carriers for nifedipine solid dispersions systems. *Chem. Pharm. Bull.* 46, 482–487.
- Van Krevelen, D.W., 1990. *Properties of Polymers*. Elsevier, Amsterdam.
- Yu, L., Mishra, D.S., Rigsbee, D.R., 1998. Determination of the glass properties of D-mannitol using sorbitol as an impurity. *J. Pharm. Sci.* 87, 774–777.

Abbott Laboratories
Exp. 07-009.792
(11)

Technical Information
ME 069 e (262) August 1987 (MPM)
Register 5

Cremophor® RH 40

® - Registered trademark of
BASF Aktiengesellschaft

For the pharmaceuticals industry

Cremophor RH 40 is a solubilizer for fat-soluble vitamins, essential oils and other hydrophobic pharmaceuticals. Particular features are that it has very little odour and in aqueous solutions is almost tasteless.

The use of Cremophor RH 40 grades in cosmetic preparations is the subject of a separate leaflet.

Fine Chemicals

BASF

Generic name	Polyoxyl 40 Hydrogenated Castor Oil (USP/NF). Macrogol-Glycerolhydroxystearat (DAB). Polyoxyethylenglyceroltrihydroxystearat (DAC).																						
Chemical nature	Cremophor RH 40 is a nonionic solubilizer and emulsifying agent obtained by reacting 45 moles of ethylene oxide with 1 mole of hydrogenated castor oil. The main constituent of Cremophor RH 40 is glycerol polyethylene glycol oxystearate, which, together with fatty acid glycerol polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethoxylate.																						
Properties	Cremophor RH 40 is a white to yellowish thin paste at 20 °C. The HLB value lies between 14 and 16. Particular features are that it has very little odour and in aqueous solutions is almost tasteless.																						
Specification	<table border="1"> <tr> <td>Solidification point</td><td>20 – 28 °C</td></tr> <tr> <td>Saponification value</td><td>50 – 60</td></tr> <tr> <td>Hydroxyl value</td><td>60 – 75</td></tr> <tr> <td>Acid value</td><td>≤ 1</td></tr> <tr> <td>Iodine value</td><td>≤ 1</td></tr> <tr> <td>Water content, K. Fischer</td><td>≤ 2 %</td></tr> <tr> <td>pH value of 10 % aqueous solution</td><td>6 – 7</td></tr> <tr> <td>Colour strength of 10 % aqueous solution (Ph. Eur.)</td><td>Yellow 6 max.</td></tr> <tr> <td>Viscosity, Hoeppler, at 25 °C, 30 % aqueous solution</td><td>20 – 40 mPa · s</td></tr> <tr> <td>Ash</td><td>≤ 0.25 %</td></tr> <tr> <td>Heavy metals</td><td>≤ 10 ppm</td></tr> </table> Unless stated otherwise, the analytical methods have been taken from the monograph "Macrogol-Glycerolhydroxystearat" in DAB. The product fulfills the requirements of this monograph and those of USP/NF monograph "Polyoxyl 40 Hydrogenated Castor Oil".	Solidification point	20 – 28 °C	Saponification value	50 – 60	Hydroxyl value	60 – 75	Acid value	≤ 1	Iodine value	≤ 1	Water content, K. Fischer	≤ 2 %	pH value of 10 % aqueous solution	6 – 7	Colour strength of 10 % aqueous solution (Ph. Eur.)	Yellow 6 max.	Viscosity, Hoeppler, at 25 °C, 30 % aqueous solution	20 – 40 mPa · s	Ash	≤ 0.25 %	Heavy metals	≤ 10 ppm
Solidification point	20 – 28 °C																						
Saponification value	50 – 60																						
Hydroxyl value	60 – 75																						
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pH value of 10 % aqueous solution	6 – 7																						
Colour strength of 10 % aqueous solution (Ph. Eur.)	Yellow 6 max.																						
Viscosity, Hoeppler, at 25 °C, 30 % aqueous solution	20 – 40 mPa · s																						
Ash	≤ 0.25 %																						
Heavy metals	≤ 10 ppm																						
Solubility	Cremophor RH 40 forms clear solutions in water, ethanol, 2-propanol, n-propanol, ethyl acetate, chloroform, carbon tetrachloride, toluene and xylene. Solutions become cloudy as the temperature increases. Cremophor RH 40 can be mixed with all other Cremophors. At elevated temperatures it forms clear mixtures with fatty acids and fatty alcohols.																						
Stability	Pure Cremophor RH 40 is chemically very stable. Prolonged exposure to heat can cause physical separation into a liquid and a solid phase on cooling but the product can be restored to its original form by homogenization. Cremophor RH 40 is stable in aqueous alcohol and purely aqueous solutions. However, it must be noted that strong bases or acids should not be added, as otherwise the ester components may be saponified. Aqueous Cremophor RH 40 solutions can be sterilized by heating to 120 °C. Allowance must be made for the fact that this can cause a slight decrease in the pH value. The phases may also separate during sterilization, but this can be remedied by agitating the solution while it is still hot. The preservatives normally used in the pharmaceuticals industry may be added to the aqueous solutions. The requisite concentrations should be determined in tests. Cremophor RH 40 is largely insensitive to water hardness.																						

Application

Solubilization

Aqueous solutions of vitamins A, D, E and K for oral and topical administration can be prepared with the aid of Cremophor RH 40. The fact that the solubilizer has very little taste and odour is an asset for such applications.

In order to ensure that clear, aqueous solutions are obtained, the fat-soluble vitamins must first be intimately mixed with the solubilizer. Best results with vitamin A are obtained if it is in the form of vitamin A palmitate 1.7 million I.U./g, or vitamin A propionate 2.5 million I.U./g; or, in the case of vitamin K, if it is in the form of vitamin K 1 (phytomenadione).

As the method of preparing the solubilize is very important, the production of a 150 000 I.U./ml aqueous vitamin A palmitate solution is described in detail as a typical example:

Vitamin A palmitate 1.7 million I.U./g	8.8 g
Cremophor RH 40	25.0 g
Water	ad 100 ml

The vitamin is mixed with Cremophor RH 40 and heated to 60 – 65 °C. The water, also heated to 60 – 65 °C, is added very slowly with thorough stirring into this mixture. As a result of hydration, the solution thickens, with the viscosity attaining a maximum after about half of the water has been added. Further addition of water then decreases the viscosity again. If the first half of the water is added too quickly, the solution can become opalescent. Alternatively, the warm mixture of the vitamin and Cremophor RH 40 can be slowly stirred into the water, which results in a lower increase in intermediate viscosity.

The following three diagrams demonstrate the use of Cremophor RH 40 for producing clear, highly concentrated, aqueous solutions of vitamin A palmitate, vitamin A propionate and vitamin E acetate.

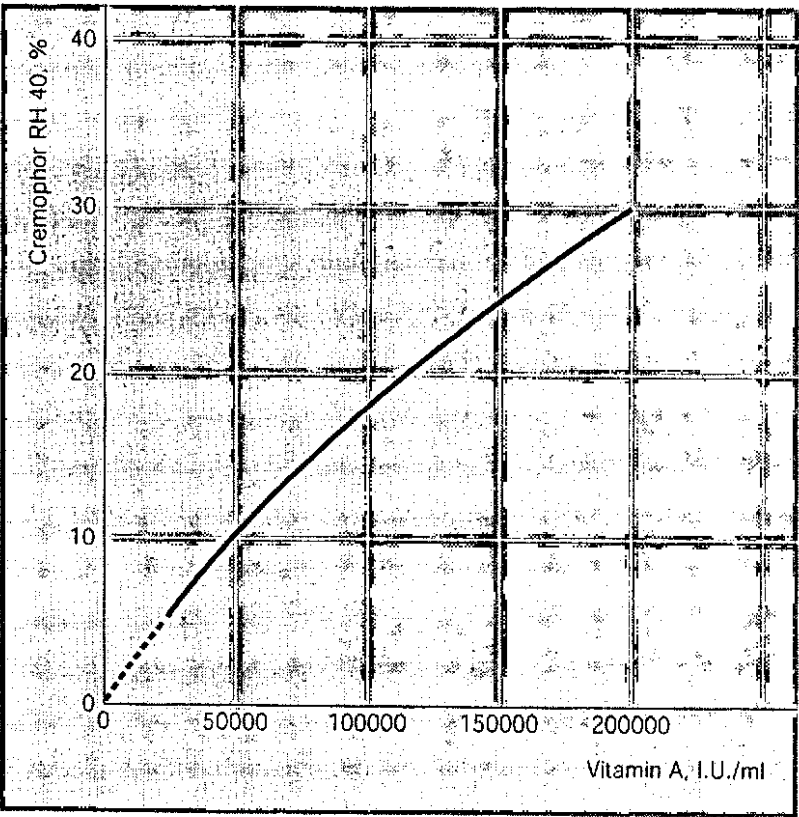


Fig. 1 Solubilization of vitamin A palmitate 1.7 million I.U./g

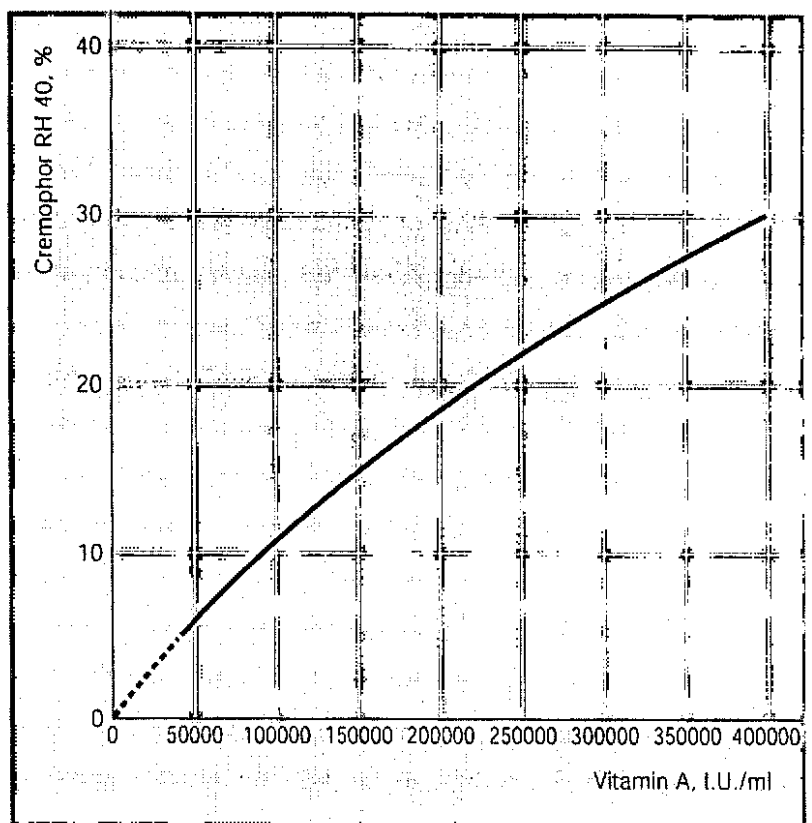


Fig. 2 Solubilization of vitamin A propionate 2.5 million I. U./g

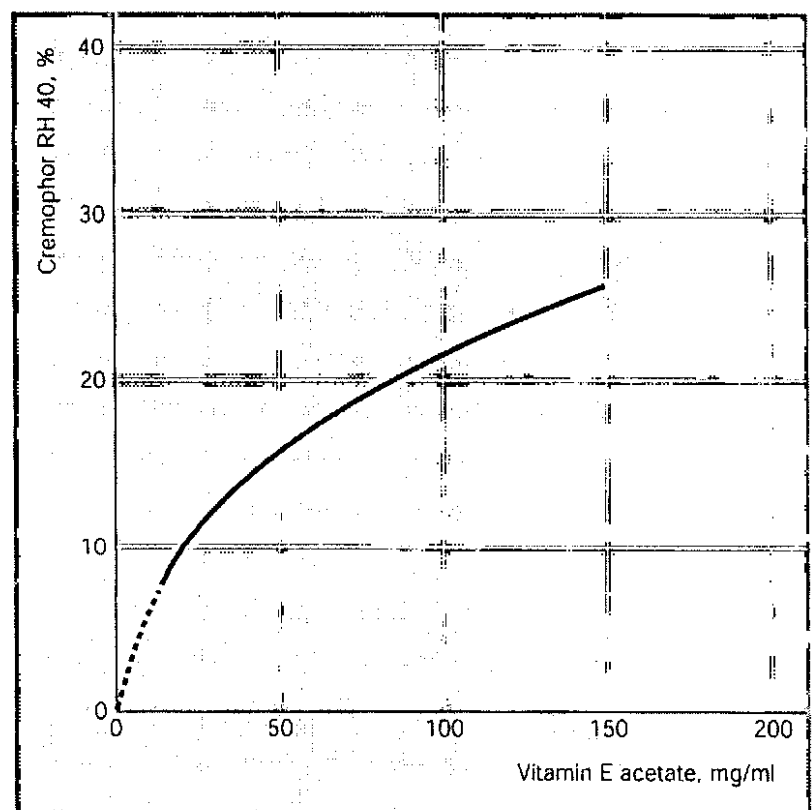


Fig. 3 Solubilization of vitamin E acetate

Likewise, the following vitamin quantities can be solubilized by a 6 % Cremophor RH 40 solution.

8 - 9 mg/ml Vitamin D ₂ (400 000 I. U.), or
5 mg/ml Vitamin D ₃ (125 000 I. U.), or
10 mg/ml Vitamin K ₁

Less Cremophor RH 40 is usually required for mixtures of vitamins.

A small addition of polyethylene glycol (Lutrol® E 400), 1,2-propylene glycol or glycerol allows the preparation temperature and sometimes also the concentration of Cremophor RH 40 to be reduced. Typical formulations are contained in the brochure "Vitamin formulations - Solutions and tablets". The stability of most solubilized vitamins is affected by light.

Miscellaneous
solubilizer applications

Clear, aqueous solutions of hydrophobic substances other than vitamins can be obtained with Cremophor RH 40. Examples are essential oils and certain drugs for oral and topical application. A feature of the solutions thus obtained is their good stability. The following substances serve as examples:

Hexachlorocyclohexane	Miconazole
Hexeditine	Gramicidin
Levomepromazine	Eucalyptol
Thiopental	Azulene
Benzocaine	Oil of anise
Clotrimazole	Oil of sage
Diazepam	

Cremophor RH 40 shows little tendency to foaming, which is particularly important for solutions in aqueous ethanol. Further foam suppression can be obtained by the addition of a small quantity of Polypropylene Glycol 2000.

Use as emulsifier

Cremophor RH 40 is also very suitable as an emulsifying agent. It will emulsify a wide range of hydrophobic substances, e.g. fatty acids, fatty alcohols and drugs.

Toxicity

Acute toxicity

The following values for the average lethal dose (LD 50) with a seven-day follow-up period were determined for Cremophor RH 40:

Species	Route	LD 50
		g/kg body weight
Rat	oral	> 16.0
Mouse	intraperitoneal	> 6.4
Mouse	intravenous	> 12.0

Subacute toxicity

For four weeks, rats were given feed containing Cremophor RH 40 in proportions of 3.2 % and 6.4 %. None of the animals displayed any symptoms whatever of poisoning.

Similarly, beagles tolerated Cremophor RH 40 in concentrations of 1%, 3 % and 9 % in their feed for four weeks without any clinically detectable symptoms.

The tolerance of Cremophor RH 40 was checked by intravenous administration in rats over a period of four weeks. It was found that, of the three dosages tested, the lowest, 300 mg/kg body weight/day was tolerated locally, while the next, 900 mg/kg body weight/day was tolerated generally.

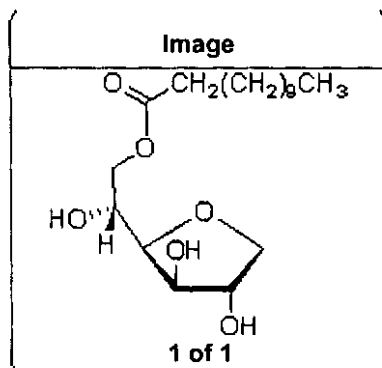
Chronic toxicity

In feeding tests that lasted for six months, Cremophor RH 40 was tolerated in concentrations of up to 5 % by dogs and in concentrations of up to 10 % by rats.

Inhalation toxicity	Air saturated at 20 °C with any volatile components that may have been given off by the product was inhaled by rats for eight hours without any injury. It should also be noted that the use of Cremophor RH 40 in surface active inhalants for aerosol application to the mucous membranes of the human respiratory tract does not cause any irritation.
Compatibility with the skin and mucous membranes	Swab tests have demonstrated that Cremophor RH 40 is compatible with human skin. The compatibility with the mucous membranes was investigated by applying a 30% aqueous solution of Cremophor RH 40 to the eyes of rabbits. This solution did not cause any inflammation.
Sensitization	Cremophor RH 40 solutions of 20% and 50% concentration in acetone were brushed ten times onto the skin of guinea pigs. They did not cause any sensitization of the skin. Likewise, no indications of a sensitizing effect on the skin of guinea pigs were observed in the Magnusson and Kligman maximization test (J. invest. Derm., 52, 268 – 276 [1969]).
Teratogenicity	This was investigated by the FDA guidelines for reproduction studies for safety evaluation of drugs for human use (Food and Drug Administration, Washington, January 1966). Cremophor RH 40 was administered orally ten times in doses of 5 000 and 10 000 mg/kg of body weight to pregnant NMRI mice from the sixth to the fifteenth day post coitum. No teratogenic or embryotoxic effects were detected. Likewise, 5% and 10% of Cremophor RH 40 added on days zero to twenty post coitum to the feed of pregnant Sprague-Dawley rats did not exert any embryotoxic or teratogenic effects.
General	In common with other surfactants, Cremophor RH 40 may alter the rate of absorption of active substances. For this reason, it is advisable to subject preparations containing Cremophor RH 40 to pharmacological and clinical tests before they are released for general use. Attention is also drawn to local legislation concerning the handling of foodstuffs, food wrappings, cosmetics etc. As there have been isolated reports of an anaphylactic reaction in animals and humans to the parenteral use of pharmaceutical products containing Cremophor EL (see technical leaflet Cremophor EL, BASF), similar reactions cannot be precluded for products containing Cremophor RH 40. No such reactions have been observed after oral administration.
Storage	The drums in which Cremophor RH 40 is stored should be kept tightly closed. The method of production employed for Cremophor RH 40 ensures that it is practically sterile. If the containers are repeatedly opened, microorganisms may grow in the product, particularly if the equipment used is not sterile.
Packaging	Drums of 40 kg capacity.
Product No.	67 363/1/36
Safety Data Sheet	A Safety Data Sheet is available.
Note	The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

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Synonym:	Sorbitan monolaurate, Span® 20
CAS Number:	1338-39-2
Linear Formula:	C ₁₈ H ₃₄ O ₆
Molecular Weight:	346.46
Bellstein Registry Number:	8355657
EC Number:	215-663-3
MDL number:	MFCD00005365
PubChem Substance ID:	24888379

[Details](#)[Related Products](#)[References](#)**Description**

Legal Information Span is a registered trademark of Croda International PLC

Propertiesrefractive index $n_{20/D}$ 1.474(lit.)

HLB value 8.6±1.0

density 1.032 g/mL at 25 °C(lit.)

Safety

Personal Protective Equipment Eyeshields, Gloves, Type N95 respirator (US)

WGK Germany 1

RTECS WG2920000

Flash Point(F) >235.4 °F

Flash Point(C) >113 °C

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