

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
office@olarteraisbeck.com

ASUNTO	Radicación	09 139 945	
	Trámite	11	
	Evento	379	
	Actuación	519	15145
	Oficio		
	Folios	19	

Patente de Invención



Patente de Modelo de Utilidad

Vía Nacional

Vía PCT (Fase Nacional)



Capítulo I

Capítulo II



No. Solicitud Internacional

PCT/US2008/065838

Fecha de Presentación Internacional

05/Junio/2008

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

1. Documentos estudiados

Descripción:	Folios 29 a 51	07/Diciembre/2009
Reivindicaciones:	Folios 52 a 54	07/Diciembre/2009
Oposiciones:	Folios 98 a 155	Synthesis 14/Abril/2011
	Folios 156 a 183	Lafranco 15/Abril/2011
	Folios 184 a 221 y 225 - 271	Tecnoquímicas 15/Abril/2011 y 15/Julio/2011
Prioridad:	EP 07109816.4	07/Junio/2007
	US 60 974 197	21/Septiembre/2007

2. Análisis de la Prioridad

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

Expediente 09-139945 1er Art 45

3. Objeto de la invención

Título de la solicitud: "Formas amorfas estabilizadas de mesilato de imatinib".

El problema planteado en esta solicitud consiste en la necesidad de suministrar formas amorfas estables de mesilato de imatinib con mayor velocidad de disolución que las formas cristalinas.

Para resolver este problema técnico la solicitud en estudio proporciona una forma amorfa estabilizada de mesilato de imatinib.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/506//9/16, A61P35/02.

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

El objeto de la reivindicación 16 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 15 y 17 no es patentable, de acuerdo con el Art 14.

6. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es clara cuando emplea el término "estabilizada"

La reivindicación 2 no es clara cuando emplea la expresión "un principio de formulación que estabiliza la forma amorfa..." sin definir el principio de formulación al que se refiere, porque se definen los componentes de la composición por su función pero no por un compuesto como tal, lo que hace que se obtengan un número indefinido de composiciones, de las cuales no se encuentra soporte en la descripción. Se sugiere al solicitante definir claramente los componentes de la composición farmacéutica de acuerdo a lo que esté debidamente soportado en la descripción.

La reivindicación 11 no es clara cuando emplea el término "aproximadamente", el cual es impreciso, por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.

7. Análisis de las Oposiciones

Argumentaciones de Laboratorios Synthesis S.A.S

Dice el oponente que esta solicitud no cumple con dos de los tres requisitos de patentabilidad:

1. Carece de novedad: a la fecha de prioridad, 07 de junio de 2007, ya era conocido, de acuerdo al documento D1 (US 2006/275372, publicado el 07 de agosto de 2003) nanopartículas de mesilato de imatinib en un estado amorfo estable para el tratamiento de leucemia, obtenidos mediante el proceso de molido conjunto con estabilizadores de superficie, sobre lo cual busca protección el capítulo reivindicatorio.

2. Carece de altura inventiva: a la fecha de prioridad, 07 de junio de 2007, ya era conocido, de acuerdo al documento D1 (US 2006/275372, publicado el 07 de agosto de 2003), en combinación con D2 (WO 2004/106326, publicado el 09 de diciembre de 2004), era obvio para un experto en la materia concebir una forma amorfa estabilizada de mesilato de imatinib, composiciones farmacéuticas como cápsulas o tabletas que las contienen y el uso del principio de formulación estabilizando la forma amorfa de mesilato de imatinib como intermediario en la preparación de composiciones farmacéuticas.

Argumentaciones de LafrancoI

Afirma el oponente que esta solicitud incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, de acuerdo a los siguientes argumentos:

En primer lugar, "cualquier persona medianamente versada en la materia reconoce que los sólidos pueden existir, de acuerdo con su estructura u ordenamiento interno, en formas cristalinas o amorfas". Agrega que: "las formas amorfas o las alteraciones en el hábito cristalino o que no suponen variaciones en la red cristalina interna de la molécula no reportan avance técnico alguno, en la medida en que simplemente muestran una estructura u organización diferente". Además, afirma que "la caracterización de las formas amorfas o cristalinas de las sustancias son una manifestación del comportamiento natural de una molécula, en función de las condiciones ambientales y demás variables a que esta sea sometida, y el reporte de dichos resultados no constituyen de manera alguna un aporte inventivo de quien realiza dicho procedimiento de obtención y caracterización".

En segundo lugar, "ante la reivindicación textual de concentraciones (dosis) de mesilato de imatinib, específicamente reivindicaciones 7 y 14[...], [...] no tiene naturaleza inventiva, ya que no cumplen con el estándar de aplicabilidad industrial, dado que dichas modificaciones solo tiene efectos en el organismo (verificables en el organismo) y no efectos técnicos".

En tercer lugar, "la utilización de complejos de ciclodextrinas o la formación de

dispersiones sólidas de cualquier principio activo no puede sustentar nivel inventivo alguno". "Algunos documentos revelan la anterioridad de la utilización de formas sólidas de imatinib estabilizadas para formulaciones farmacéuticas, la formación de complejos de imatinib con ciclodextrinas y la versatilidad de formulaciones tipo dispersiones sólidas". Los documentos corresponden a: publicación internacional WO2004/106326, publicada el 09 de diciembre de 2004; publicación científica "Cyclodextrin/Imatinib complexation: binding mode and charge dependent stabilities", publicada en noviembre de 2006; y publicación científica "Improving drug solubility for oral delivery using solid dispersions", publicada en julio de 2000.

Argumentaciones de Tecnoquímicas S.A.

Afirma el oponente que esta solicitud incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, de acuerdo a los siguientes argumentos:

En primer lugar, "cualquier persona medianamente versada en la materia reconoce que los sólidos pueden existir, de acuerdo con su estructura u ordenamiento interno, en formas cristalinas o amorfas". Agrega que: "las formas amorfas o las alteraciones en el hábito cristalino o que no suponen variaciones en la red cristalina interna de la molécula no reportan avance técnico alguno, en la medida en que simplemente muestran una estructura u organización diferente". Además, afirma que "la caracterización de las formas amorfas o cristalinas de las sustancias son una manifestación del comportamiento natural de una molécula, en función de las condiciones ambientales y demás variables a que esta sea sometida, y el reporte de dichos resultados no constituyen de manera alguna un aporte inventivo de quien realiza dicho procedimiento de obtención y caracterización".

En segundo lugar, "ante la reivindicación textual de concentraciones (dosis) de mesilato de imatinib, específicamente reivindicaciones 7 y 14[...], [...] no tiene naturaleza inventiva, ya que no cumplen con el estándar de aplicabilidad industrial, dado que dichas modificaciones solo tiene efectos en el organismo (verificables en el organismo) y no efectos técnicos".

En tercer lugar, "la utilización de complejos de ciclodextrinas o la formación de dispersiones sólidas de cualquier principio activo no puede sustentar nivel inventivo alguno". "Algunos documentos revelan la anterioridad de la utilización de formas sólidas de imatinib estabilizadas para formulaciones farmacéuticas, la formación de complejos de imatinib con ciclodextrinas y la versatilidad de formulaciones tipo dispersiones sólidas". Los documentos corresponden a: publicación internacional WO2004/106326, publicada el 09 de diciembre de 2004; publicación científica "Cyclodextrin/Imatinib complexation: binding mode and charge dependent stabilities", publicada en noviembre de 2006; y publicación científica "Improving drug solubility for oral delivery using solid dispersions", publicada en julio de 2000.

Finalmente, para complementar los argumentos de falta de novedad y nivel inventivo, la patente americana US 2006/275372, publicada el 07 de diciembre de 2006, revela la obtención de una dispersión acuosa de nanopartículas de mesilato de imatinib, que anticipa específicamente las reivindicaciones 1 y 2. Además, la publicación internacional WO 2006/121941, publicada el 16 de noviembre de 2006, revela la obtención de extrudidos de mesilato de imatinib con polímero u otros excipientes, lo que anticipa las reivindicaciones 1 y 2.

Respuestas del Solicitante

El solicitante no dio respuesta a las oposiciones.

Respuesta del Examinador Técnico

El documento WO2004/106326, publicado el 09 de diciembre de 2004, divulga la forma amorfa del compuesto mesilato de imatinib, la cual es estable y composiciones farmacéuticas que lo contienen, con lo que desvirtúa la novedad y el nivel inventivo del objeto de esta solicitud; por lo cual se considerará dentro del examen de patentabilidad.

El documento US 2006/275372, publicado el 07 de diciembre de 2006, enseña la forma amorfa del compuesto mesilato de imatinib, la cual es estable y composiciones farmacéuticas que lo contienen, por lo que desvirtúa la novedad y el nivel inventivo del objeto de esta solicitud; por lo cual se considerará dentro del examen de patentabilidad.

El documento WO 2006/121941, da a conocer la forma amorfa del compuesto mesilato de imatinib, la cual es estable y composiciones farmacéuticas que lo contienen. Como desvirtúa la novedad y el nivel inventivo del objeto de esta solicitud; por lo cual se considerará dentro del examen de patentabilidad.

El artículo "Cyclodextrin/Imatinib complexation: binding mode and charge dependent stabilities", publicado en noviembre de 2006, enseña que el mesilato de imatinib puede estabilizarse mediante complexación con ciclodextrinas. Como este documento en combinación con alguno de los tres anteriores desvirtúa el nivel inventivo del objeto de esta solicitud se considerará dentro del examen de patentabilidad.

El artículo "Improving drug solubility for oral delivery using solid dispersions", publicado en julio de 2000, enseña que los principios activos en estado amorfo pueden estabilizarse mediante la formulación con dispersiones sólidas. Como este documento en combinación con alguno de los tres primeros documentos desvirtúa el nivel inventivo del objeto de esta solicitud se considerará dentro del examen de patentabilidad.

8. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 07 de junio de 2007 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO2004/106326	Novel polymorphs of imatinib mesylate	09/Diciembre/2004
D2	US2006/275372	Nanoparticulate imatinib mesylate formulations	07/Diciembre/2006
D3	WO2006/121941	Pharmaceutical compositions comprising imatinib and a release retardant	16/Noviembre/2006
D4	Artículo ¹	Cyclodextrin/imatinib complexation: binding mode and charge dependent stabilities	07/Noviembre/2006
D5	Artículo ²	Improving drug solubility for oral delivery using solid dispersions	Enero/2000

D1 (folios 135 – 145) divulga (fl 145, figura 2; fls 140 – 141, ejemplos 6 y 8, reivindicaciones) la forma amorfa del compuesto mesilato de imatinib, la cual es estable y composiciones farmacéuticas que lo contienen.

D2 (folios 117 - 133) divulga (fl 121, pár. 0029 – 0030 y 0034) la forma amorfa del compuesto mesilato de imatinib, la cual es estable y composiciones farmacéuticas que lo contienen.

D3 (folios 249 - 271) divulga (fls 261 – 263 y fls 263-268, ejemplos 1 – 7) la forma amorfa del compuesto mesilato de imatinib, la cual es estable y composiciones farmacéuticas que lo contienen.

D4 (folios 274 – 277) divulga (todo el documento) estabilización de mesilato de imatinib mediante complexación con ciclodextrinas.

D5 (folios 278 – 283) divulga (fl 279 -283, pg. 50 - 57) principios activos en estado amorfo que pueden estabilizarse mediante la formulación con dispersiones sólidas

9. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una forma amorfa estabilizada de mesilato de imatinib.

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

Características esenciales	D1	D2	D3
Forma amorfa estabilizada de mesilato de imatinib	Forma amorfa estable de (fl 145, fig. 2; fls 140 – 141, ejemplos 6, 8) mesilato de imatinib	Forma amorfa estable de (fl 121, pár. 0034) mesilato de imatinib	Forma amorfa estable de (fls 263-268, ejemplos 1-7) mesilato de imatinib

¹ Beni S, et al: Cyclodextrin/imatinib complexation: binding mode and charge dependent stabilities; European Journal of Pharmaceutical Sciences; Vol. 30, pg. 167-174; fls 274-277.

² Leuner C; Improving drug solubility for oral delivery using solid dispersions; European Journal of Pharmaceutics and Biopharmaceutics; Vol. 50; 2000; pg. 47-60; fls 278-283

Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D1 y D2, los cuales dan a conocer la forma amorfa del compuesto mesilato de imatinib, la cual es estable (D1: fl 145, figura 2; fls 140 – 141, ejemplos 6 y 8; D2: fl 121, pár. 0034; D3: fls 263-268, ejemplos 1 - 7).

En consecuencia, la reivindicación 1 no es nueva, según lo divulgado en el documento D1, D2 y D3.

Además, D2 y D3 enseñan composiciones farmacéuticas que comprenden un principio de formulación que estabiliza la forma amorfa de mesilato de imatinib y mesilato de imatinib amorfo, opcionalmente junto con por lo menos un vehículo farmacéuticamente aceptable (D2: fl 121, pár. 0034; fl 128, ejemplo 1; D3: fls 263-268, ejemplos 1 - 7).

Por lo tanto, las reivindicaciones dependientes 6 - 14 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

Nivel Inventivo (Art18 D486)

La reivindicación 3 consiste en una composición farmacéutica de acuerdo con la reivindicación 2, en donde el principio de formulación se selecciona de dispersiones sólidas, complejos de ciclodextrina y co-molienda con excipientes seleccionados.

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

Características esenciales	D1	D2	D3	D4	D5
Composición farmacéutica que comprende:	Composición farmacéutica (reivindicación 22) que comprende:	Composición farmacéutica (fl 236, pár. 0029-0030), comprende:	Composición farmacéutica (fls 263-268, ejemplos 1-7) comprende:	Composición farmacéutica (fl 277, conclusión) comprende:	Estabilización de (fl 279 - 283, pg. 50 - 57):
mesilato de imatinib amorfo	mesilato de imatinib amorfo	mesilato de imatinib amorfo	mesilato de imatinib amorfo	Imatinib amorfo	Principios activos insolubles
un principio de formulación que estabiliza la forma amorfa de mesilato de imatinib seleccionado de dispersiones sólidas, complejos de ciclodextrina y co-molienda	No se menciona	No se menciona	No se menciona	Ciclodextrinas	Dispersiones sólidas

Opcionalmente un vehículo farmacéuticamente aceptable.	Opcionalmente un vehículo farmacéuticamente aceptable.	Opcionalmente un vehículo farmacéuticamente aceptable.	Opcionalmente un vehículo farmacéuticamente aceptable.	No se menciona	No se menciona
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Los documentos D1, D2 y D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 3 porque composiciones farmacéuticas que comprenden mesilato de imatinib amorfo estable y un vehículo farmacéuticamente aceptable (D1: reivindicación 22; D2: fl 121, pár. 0029 - 0030; D3: fls 263-268, ejemplos 1 - 7).

La diferencia entre la invención, definida en la reivindicación 3 y las composiciones farmacéuticas de D1, D2 y D3 consiste en que divulga de manera específica que el principio de formulación que estabiliza la forma amorfa de mesilato de imatinib es seleccionado de dispersiones sólidas, complejos de ciclodextrina o co-molienda,

El efecto que logra el incluir esta característica es que las composiciones farmacéuticas contienen el activo con mayor velocidad de disolución (mesilato de imatinib amorfo).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de composiciones farmacéuticas que comprendan mesilato de imatinib amorfo estable, para obtener formas farmacéuticas con mayor velocidad de disolución.

Sin embargo, la utilización de ciclodextrinas y dispersiones sólidas como método para estabilizar principios activos en estado amorfo y mejorar sus propiedades fisicoquímicas como la solubilidad, ya está divulgada en los documentos D4 y D5, que señalan que principios activos en estado amorfo pueden estabilizarse mediante complexación con ciclodextrinas o por la formulación con dispersiones sólidas respectivamente (D4: fls 274 - 277, todo el documento; D5: fl 279 -283, pg. 50 - 57).

En consecuencia, la persona del oficio normalmente versada en la materia, realizaría la complexación con ciclodextrinas de D4 o la formulación con dispersiones sólidas de D5 al mesilato imatinib de las composiciones farmacéuticas de D1, D2 o D3, para llegar así al objeto de la reivindicación 3 de la solicitud. Por lo cual se considera obvia.

Conclusión: La reivindicación 3 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18), de acuerdo a los documentos D4 con D1, D4 con D2, D4 con D3, D5 con D1, D5 con D2 o D5 con D3.

Puesto que las reivindicaciones dependientes 4 - 14 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

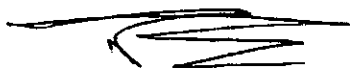
10. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2004/106326	1, 2, 6 -14	Novedad
D2	US2006/275372	1, 2, 6 -14	Novedad
D3	WO2006/121941	1, 2, 6 -14	Novedad
D1	WO2004/106326	3 -14	Nivel inventivo
D2	US2006/275372	3 -14	Nivel inventivo
D3	WO2006/121941	3 -14	Nivel inventivo
D4	Artículo	3 -14	Nivel inventivo
D5	Artículo	3 -14	Nivel inventivo

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

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



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
12 8 AGO. 2012

Elaborado por: Rubiela Pacanchique Vargas
Revisado por: Jacqueline Alfonso Roza



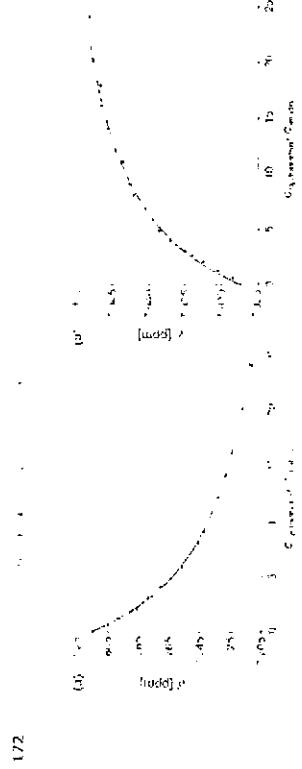


Fig. 5 - ^1H NMR titration curves of (a) H-19 and (b) H-25,29 imatinib protons as functions of host-guest concentration ratio, together with curves fitted by the OPUS program.

the resonances of cyclodextrin (Bernini et al., 2004). Rubino et al., 2005), but substituted by pronounced changes in our study.

During the NMR titration at pH 5.1, 96% of imatinib reacted as monoanionic H^+ species with the 3D host. Only downward titration shifts were observed on an alkaline hydrogen, the most significant being H 16 (4.4 to 0.92 ppm), H 9 (25.23 to 0.65 ppm), H 26.78 (0.95 ppm), H 27 (1.17 ppm), H 9 (0.15 ppm) and H 32.36 (0.06 ppm). The simultaneous decrease of titration curves of these nuclei yielded $\log K_{\text{eq}}$ as -2.20 ± 0.06 . Both this value and the trend of reactivity are in accord with those by potentiometry (see Table 1). The enhanced effects shown by H 25, 29, 31, 26.78 and 16 suggest that the benzamide fragment of imatinib may play a major role in the inclusion process. To verify this hypothesis, 2D NMR spectra were also recorded at the same pH. The expansion of this 2D spectrum in Fig. 6 contains an intermediate cross peak between H 30 (3.77 ppm) and H 26.78 (1.47 ppm) nuclei at virtually 100% of the viewpoint of concentration. Inter-molecular cross-peaks of H 26.78 with the aromatic protons H 9 (at 3.80 ppm) and H 13 (at 3.91 ppm), imipal

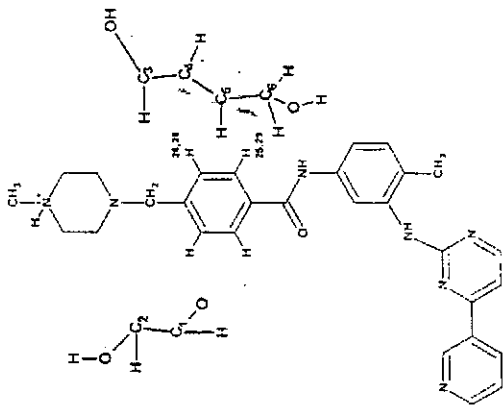


Fig. 7 - Proposed geometric arrangement of InsulinB in the cavity of β -CD, based on the ROESY experiment.

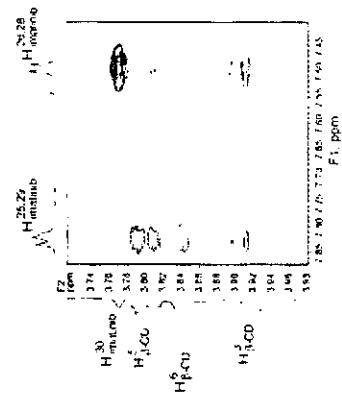


Fig. 6 Expansion of the ROESY spectrum of a pH 5.4 aqueous sample containing imatinib and β -CD at 2:1 molar ratio

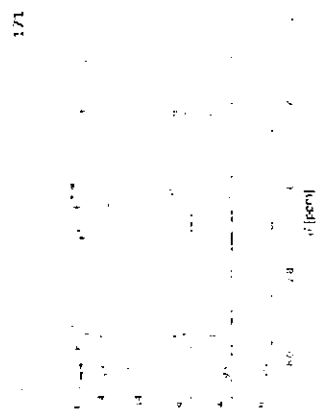


Fig. 4. Representative ^1H NMR spectra from the titration of 0.5 mM imatinib with increasing amounts of β -CD at pH 7.5.

stability to constants ranging from 10^{-6} to 10^4 foldings, β and γ are 1. In the majority of investigations, the chemical shift titration method is used, followed by non-linear curve fitting (Schneider et al. 1998; Feilding, 2000). The incorporation of datasets of several nuclei into the simultaneous evaluation results in more robust, unbiased estimates of affinity (K) and stoichiometry (n), with smaller error bounds. At the same time, the observed titration shifts ($\Delta\delta$) provide insight into the structure of the complexes (Schneider et al. 1993; Fernandes et al. 2003; Ribeiro et al. 2005), which is hardly possible to extract from UV titrations and principally impossible from proton magnetic data. Difficulties in NMR titrations may arise when the chemical shift changes during the titration are small or they are not primary consequences of the association process. For instance, interference by the simultaneous acid-base equilibrium of guest can lead to misinterpretation of the observed chemical shift changes. To prevent this problem, we carried out the titrations with a CD using two buffer solutions of carefully selected pH.

In course of the ^1H NMR titration conducted at $\text{pH} \approx 7$, the predominant imatinib species H_2P^+ (53%), and also, H_2P^+ (23%) and H_3P^{2+} (22%) the minor, but significant species interact with $\beta\text{-CD}$. The spectral series in Fig. 4 shows that an unusual upfield shift is observed on H 19. This nucleus exhibits a similar exceptional shift during the NMR titration of imatinib (Szankiewicz et al., 2004), while active aromatic imatinib proteins undergo downfield shifts. Significant changes in the chemical shifts were registered also on the aromatic, hydroxygens H5, H8, H12, H16, H17, H18, H19, as well as on the NH 21 amide proton, the mentioned datasets were included into the simultaneous evaluation according to Eq. (7). The titration curves of two selected imatinib nuclei are shown in Fig. 5. The agreement of the resulting K_{app} with stability constant in Table 1 is satisfactory with that from pH -metry, considering the other protonation forms present in the NMR samples. The greatest complexation induced chemical shifts were observed for H 19 ($\Delta\delta = 0.124 \text{ ppm}$) and NH ($\Delta\delta = 0.076 \text{ ppm}$). However, it is known from previous literature that interpretation based exclusively on the $\Delta\delta$ values of guest can be misleading in identifying the molecular fragment penetrated into the cavity. The progress of complexation may be reflected more directly by

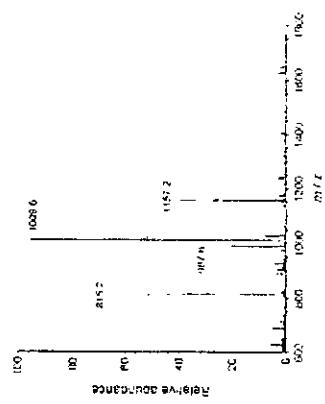


Fig. 3 - Positive ion mode mass spectrum of an imatinib: K-CID sample of 1:2 molar ratio.

In 1990, the ZAVNO bearing up to foreign obligations on behalf of the state, the stability was below the trend, while the budget was steadily exceeding the stability, where means of monetary financing increased by 10.5%.

3.3 7SI-MS experiments

The study of host-guest interactions in the gas phase follows the detection of specific interactions not usually present in solution. It is giving complementary pictures of the chemical job chemical is possible for molecules to perform (P. M. H. 1993). All these are interpretative, independent, in addition, spectra of supramolecular assemblies, it is difficult to identify the species present in the mass spectra, compared to those present in solution, or rather they result from processes occurring under high vacuum conditions. Moreover, it is not clear whether the molecular ions observed are real or present even previous to any real diatomic external addition, so-called "false positives" (Gund and Houten, 1993). In our particular case, however, a comparison is easily made with solutions obtained from independent solution-phase techniques.

to identification of the major peaks in the $100-400\text{ meV}$ spectral range (data not shown) is based on the literature assignment by Marai and Kurland¹ (2009), Fig. 3 shows the normalized upper part of the mass spectrum of a typical sample containing trimethyl and $n\text{-C}_{12}$ at a 2:1 molar ratio. The most intense peak of the desorption range at $m/z\ 1020.6$ is assumed to be the sodium ion adduct of monomeric dimers, formed only in the gas phase, while the peak at $m/z\ 987.6$ refers to the proton adduct of the dimer. The third intense peak at $m/z\ 1157.2$ corresponds to the sodium ion adduct of uncomplexed $n\text{-C}_{12}$. Finally, the signal at $m/z\ 815.2$ supports the formation of the doubly charged 1:1 complex. Thus, ESI-MS/MS spectra show that 3 complex with stoichiometry other than 1:1 does not form even in the gas phase.

3.4. ¹³C NMR experiments

¹³C NMR spectroscopy is the most suitable method for quantification of non-covalent molecular interactions in terms of

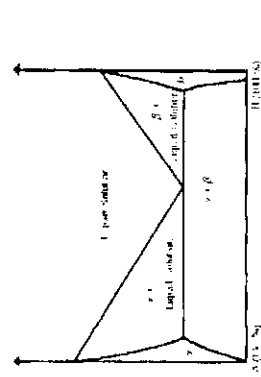


Fig. 1 Phase diagram for a two-component solid solution (reproduced with modification from Ref. [13]).

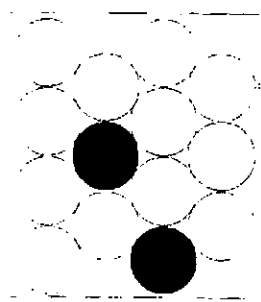


Fig. 3 Substitutional crystalline solid solution (reproduced with modification from Ref. [13]).

Phase diagrams shown in Fig. 2, 3 and 4 show the regions of two solid solutions. In these regions, one of the solid components is completely dissolved in the other solid solution. Note that below a certain temperature, the mutual solubilities of the two components start to decrease, due to practical considerations it has been suggested by Goldberg et al. [11] that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

2.2.2 Substitutional crystalline, interstitial crystalline and amorphous solid solutions

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

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

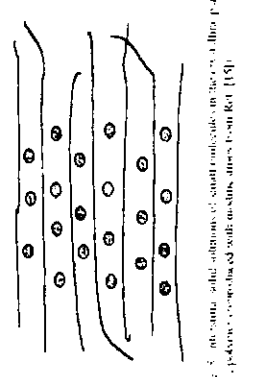


Fig. 5 Amorphous solid solution (reproduced with modification from Ref. [13]).

In the early 1980s, Sekiguchi et al. reported that formulation of eutectic mixtures could lead to an improvement in the release rate and thereby the bioavailability of poorly soluble drugs. Eutectic combinations such as salicylic acid/urea [9] and chlorpheniramine/urea [17] served as examples for the preparation of a poorly soluble drug in a highly water-soluble carrier. Both preparations exhibited faster release and better bioavailability than conventional formulations. The explanation offered for this behaviour was that, after dissolution of the urea, a fine suspension of drug particles was exposed to the dissolution medium (or GI fluids) and that both the smaller particle size and better wettability of the drug particles in this suspension contributed to a faster dissolution rate.

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

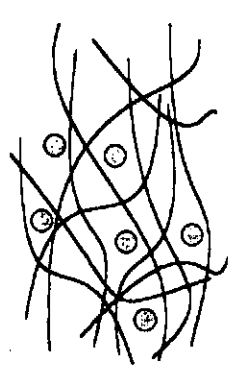


Fig. 6 Amorphous solid solution (reproduced with modification from Ref. [13]).

if it is molecularly dispersed in the dissolution medium, i.e. present in solution form. A further reason for the improvement in the dissolution rate is that the eutectic has no crystalline structure in the solid solution [21]. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolve is not a hindrance to the release of the drug from a solid solution. After the solid solution has dissolved, the drug is present as a supersaturated solution. In some cases, the carrier may serve to inhibit precipitation of the drug from the supersaturated solution [23-25]. It has also been speculated that if the drug does precipitate, it will precipitate out as a metastable polymorph with a high solubility compared to that of the most stable form [21,26]. A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug [13]. Even carriers that are not surface active, e.g. urea and citric acid, can improve wetting characteristics. Of course, if carriers with surface activity such as cholic acid, bile salts [27], cholesterol esters, 281 and lecithin [29] are used, the improvements in wetting can be much greater. Another way in which the carrier can influence the drug's dissolution properties is via direct solubilization or a cosolvent effect. The relationship between the release characteristics of the solid solution and a physical mixture of the two components varies with the drug/carrier combination. For example, the release rate from a solid solution of prednisolone in Cremonophore[®] is almost identical with the release rate from a simple mixture of the two components [30]. A physical mixture of glycerol and PEG 6000 exhibited better solubility and faster dissolution than that of the pure drug [31]. The solubility of paracetamol is greater in urea than alone [10]. However, the solubility of salicylic acid is adversely affected by mixing with urea [9]. In general, dissolution rates are compared among the pure drug, a physical mixture and the solid solution to assess the benefits of preparing a solid solution.

3.1 Methods for preparing solid solutions

3.1.1 Hot melt method

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

approach is to prepare the solid dispersion by hot-spin melting, as demonstrated by Wacker et al. [31].

An alternative prerequisite to the hot-spin method is solid solutions by the hot melt method. In this method, the drug and the carrier in the molten form are mixed together in a hot melt mixer. This usually leads to a product that is not molecularly dispersed. Another major limitation to the hot melt method is the thermodynamic stability of the drug and the carrier. If too high a temperature is required, the drug may decompose or evaporate. Of course, oxidative reactions can be avoided by processing in an inert atmosphere or under vacuum, while evaporation can be avoided by processing in a closed system.

Because of these limitations, the solvent method became more popular in the 1970s and 1980s. In recent years, however, the hot melt method has enjoyed a renaissance in the form of hot melt extrusion. Extrusion of molten powders has been well known in the pharmaceutical sciences for many years [32]. Hot melt extrusion is a very common way of processing plastics in the polymer industry, but Spitzer [33,34] and Hattenschalk [35] were the first to adapt the process for pharmaceutical purposes. In recent years, this method has been applied to the manufacture of solid solutions. A scheme of a hot melt extruder is shown in Fig. 7. The drug/carrier mix is typically processed with a twin-screw extruder of the same type used in the polymer industry. The drug/carrier mix is simultaneously melted, homogenized, and then extruded as tablets, granules, pellets, sheets, sticks, or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed.

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

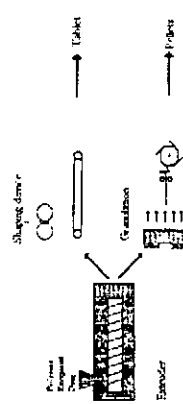


Fig. 7. Scheme of a hot melt extruder (reproduced with modifications from Ref. [37]).

date on black carbon (see [38]). Processed with [39] and [40].

3.1.3. Solvent method

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

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

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

3.2. Carriers

3.2.1. General characteristics of PEGs

Poly(ethylene glycol) (PEG) is a linear polymer of ethylene oxide with a molecular weight (MW) usually falling in the range 200–300,000 for the manufacture of solid dispersions and solid solutions. PEGs with molecular weights of 1,000–30,000 are usually employed. As the MW increases, so does the viscosity of the PEG. At MW of up to 100,000, PEGs are described as aqueous solutions, 200,000 to 600,000 as waxes, and those with MW of 20,000 and above as solid. PEGs are generally good, but decrease with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g., the m.p. of PEG 1000 is 30–31°C, the m.p. of PEG 4000 is 50–58°C, and the m.p. of PEG 20,000 is 60–65°C) [48]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds [31] and also to improve compound wetability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000 [49].

3.2.2. Influence of the PEG chain length (MW) on the manufacture of solid dispersions

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

The importance of the carrier to performance of the solid dispersion was illustrated in a study of 14 different drugs formulated as solid dispersions in PEG 6000 [53]. In this study, Dubois and Ford showed that, when the drug is present in a low drug/carrier ratio (<2%, in the case of phenylbutazone, up to 15% in the case of paracetamol), the release rate is dependent only on the carrier and not on the drug properties. Results with indomethacin showed similar behavior. Further studies indicated that the release rate is inversely proportional to the chain length of the PEG [54]. Similar results were obtained with cefepime [55] and griseofulvin [16]. However, other studies revealed contradictory behavior. For example, glyceride release from a solid dispersion in PEG 4000 was faster than from a similar dispersion in PEG 4000 [51]. Possible

reasons for the faster release from PEG 6000 are that the PEG 6000 was able to dissolve more of the drug than the PEG 4000 carrier in a carrier:excipient, due to the molecular weight of the carrier and that the higher viscosity of the PEG 6000 hindered precipitation of the drug in low drug concentrations.

A comprehensive study of phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW [5]. When the percentage of drug used was low (0.5–2%), the release followed the rank order: PEG 1000 > PEG 1000 + 1000 > 20,000 at percentages of 1 and 1%, the rank order was PEG 1000 > 4000 > 20,000 and at 5% loading the order was 20,000 > 4000 > 1000 > 6000. Since the rank order could be clearly correlated with the crystallinity of the solid dispersion, the authors concluded that the release is dependent on the extent to which a molecular dispersion can be formed. On the other hand, contradictory results were obtained with cefepime/PEG solid dispersions, in which the rank order of release was PEG 6000 > 4000 > 12,000 > 20,000 [55]. In yet other cases, the MW of the PEG had no influence at all on the release rate. For example, Mori et al. [56] showed that 10% dispersions of naproxen in PEG 1000, 6000 and 20,000 all exhibited similar release.

3.2.3. Influence of the drug/PEG ratio

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

3.2.4. Drug/PEG systems

Griseofulvin is probably the most studied drug with respect to dispersion in PEGs. Chien and Riegelman [16] were able to achieve a noticeable increase in the release rate of griseofulvin from solid dispersions in PEG 4000, 6000 and 20,000. The fruit of research with PEG-griseofulvin combinations is the marketed product, Griseofulvin. More recent studies with griseofulvin and PEGs have focused on mixtures with various emulsifying agents. Shikvet et al. [58] investigated small quantities of polyacrylate 80, polyethyleneoxide (polyethylene glycol 75), sodium dodecyl sulphate (SDS) and dodecylammonium bromide into 10% w/w dispersions

of gelation in 10-15 min and by using 5% were able to achieve substantial increases in both the rate and extent of dissolution. Best results were achieved with NCS. Other conventional systems, such as a gel of 5% PEG 4000 in water, could only achieve a slow rate of dissolution (10-15 min) and by using 5% were able to achieve only a small increase in both the rate and extent of dissolution. However, the gel system had the advantages of being easier to process, no long-term toxicity, and an increase in the release rate by 10-15 min.

An increase in the release rate by 10-15 min as a solid dispersion in PEG 4000 has been observed for many drugs including oxycodone [50], propofol [51], and propofol [52]. In some cases, in vivo data have verified the importance of the increase in release rate to the bioavailability of the drug in question. Aron et al. [62] were able to show that a doubling of the release rate in vivo could be translated into an increase in the duration of action of a drug in rats. A good correlation between release data from solid dispersions of nifedipine in PEG 4000 and the effect of the drug in rats was documented in human studies [63]. Similarly, a two-fold increase in the release rate of carbamazepine achieved by formulation as a solid dispersion in PEG 4000 and 6000 was translated into an increase in the bioavailability relative to a suspension of the drug and the marketed product, Tegretol[®] [64].

However, even better results could be achieved with a hydroxypropyl- β -cyclodextrin complex, Nifedipine/PEG 6000 solid dispersion also produce a moderate increase in bioavailability [64]. Further drugs which exhibit elevated release rates when formulated as PEG solid dispersions include 3,3'-diethyl-5,5'-dimethyl-4,4'-biphenyl, a new calcium antagonist [65], ketoprofen [66], oxycodone [67], nifedipine [68], phenylpropanolamine [69], dextroamphetamine [70], fenofibrate [71] and prednisolone [72].

There have also been several studies with PEGs of higher MW. Feng et al. [51] achieved a ten-fold increase in the release rate of an experimental 5-hydroxytryptamine inhibitor with PEG 8000 using a hot melt method. Studies of co-solvents of isopropyl alcohol with PEG 10 000 with the same system and with mixtures of the two indicated that the mixture of the PEG with water produced the best results [52].

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

MW is used so that the drug has a plasticizing effect on the PEG [54].

3.2.2. Polyvinylpyrrolidone (PVP)

3.2.2.1. General characteristics of PVP. Polyvinylpyrrolidone (PVP) is a synthetic polymer with a wide range of molecular weights ranging from 1500 to 1 000 000. These can be classified according to their K value, which is calculated using the following equation [73]. Table 2 provides an overview of the relationship between the K value and the approximate molecular weight of PVP.

The glass transition temperature of a given PVP is dependent on its MW and also on the amount of water content. In general, the glass transition temperature (T_g) is high, for example, PVP K25 has a T_g of 155°C [73]. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for fentanyl acid [74].

3.2.2.2. Influence of the PVP chain length. The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration [72]. Studies with co-solvents of chloramphenicol and PVP revealed that the dissolution of chloramphenicol was slower when PVPs of higher MW were used as the carrier [55]. Similarly, the slower dissolution of indomethacin from PVP K30 compared to PVP K12 was attributed to the higher viscosity generated by PVP K30 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion [54]. Other drugs for which release is known to be slower when incorporated in PVPs of higher MW include sulphathiazole [44] and phenytoin [69]. In the case of probucol, however, a somewhat different relationship was seen, here the rank order of release rate was PVP K30 > K25 > K30 [75]. In

Table 2
K values of PVP and the corresponding molecular weights [73].

K value	Approximate molecular weight
12	2500
15	3000
17	10000
23	30000
30	50000
40	100000
60	200000
90	400000
170	1000000

general, though, the dependence of the release rate on MW is clear for the PVPs, that is, the case of solid dispersions prepared with PEGs.

3.2.2.3. Drug/PVP ratio. Similarly to PEG solid dispersions, preparations with high proportions of PVP tend to exhibit a higher drug solubility and release rate than those with high proportions of drug. For example, for PVP on the release rate, an increase in the drug/PVP ratio from 1:1 to 1:10 leads to an increase in the release rate [76]. Doskovic and York [77] studied the release behaviour of furosemide/PVP dispersions as a function of the degree of crosslinking of the preparation. When solid dispersions comprising 50% furosemide were prepared, crystalline regions could be detected by X-ray diffraction. In contrast, when the drug/copolymer ratio was 2:3, the dispersion was amorphous. Dispersions containing crystalline areas exhibited biphasic release profiles, with the amorphous areas dissolving quickly and the crystalline areas more slowly. Similar behaviour was reported by Kearney et al. [43] for the experimental anti-infective compound C1-987. When the carrier comprised 50% of the dispersion, no crystalline areas could be detected and the release rate of the compound was rapid. Interestingly, when the carrier was further increased, the release rate became slower in the case of procainamide/PVP solid dispersions [78]. The release rate increased with the PVP up to a ratio of drug/copolymer of 1:1, after which it fell again at ratios of 1:5 and 1:10. These results were clarified with X-ray diffraction studies. Only the dispersion containing a 1:1 ratio was amorphous; at all other ratios semi-crystalline areas could be detected. In this case, the 1:1 ratio proved to be optimal for the formulation of procainamide in PVP K30.

3.2.2.4. Drug/PVP systems. Most studies of PVP solid dispersions reported in the literature have used PVPs of MW 2500-50 000 (K12 to K30). As in the case of PEGs, gelatin has been one of the most widely studied compounds. The first solid dispersions of griseofulvin in PVP were reported in 1966 by Mayersohn and Gibaldi [42]. Improved dissolution of the test compound from solid dispersions prepared with PVP K17 have been reported variously for sulphathiazole [44], hydrochlorothiazide [79], and procainamide [80]. For a series of non-steroidal anti-inflammatory drugs (NSAIDs) including mefenamic acid, azapropazone, glaucin and flufenamic acid, it was shown that co-solvents prepared with PVP K25 improved the release and bioavailability of the drug more than those prepared with PEG 6000 [81]. Furthermore, it was shown in the same studies that the NSAIDs were less likely to cause ulceration in the GI tract when administered as a solid dispersion. In another study, the release rates from solid dispersions of cephalexin in PEGs and PVPs were compared [50]. PVP K25 produced faster release than PEG 3000, 6000 or 8000. On the other hand, the release rate from PEG 3000 and 6000 was higher than from PVP K17. Using PVP K30 as the carrier, the release

rate of the 5-hydroxytryptamine inhibitor 5-HT₂ (100-5) a weakly basic experimental compound, K5 8350 [82], and 5-hydroxytryptamine (5-HT) could all be improved. In the case of amphetamine, improvement in release rate using PVP K30 was observed after 30 min, but the release rate from other carriers was not [83].

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

3.2.3. Polyvinylalcohol (PVA) copolymers (PVP-CLA, polyvinylalcohol-polyvinylpyrrolidone copolymer (PVP))

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

