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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación: 444

Referencia : Expediente No. 04.016.766
Asunto : Solicitud de patente para: " POLIMORFO
DE FLIBANSERINA, Y PROCEDIMIENTO
INDUSTRIAL PARA SU PREPARACION".

Solicitante : BIDACHEM S.P.A.
Fecha de Solicitud: 25 de febrero de 2004

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 9358 Notificado por fijación en lista del 3 de Agosto de 2007.

2. Mediante el Oficio No. 9358 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Con memorial del 12 de Octubre de 2007 solicité prórroga para dar respuesta al Oficio No.9358. Atiendo a las observaciones de la manera siguiente:

3. Claridad de la solicitud:

3.1 Con relación a las reivindicaciones 1, 7 y 10, su Despacho enuncia lo siguiente:

La reivindicación 1 no es clara, ya que una sustancia no puede caracterizarse por un análisis térmico.

La reivindicación 7 se refiere a un "compuesto" el cual debe caracterizarse por los componentes que lo constituyen y no por su uso.

En la reivindicación 10 la expresión "opcionalmente" no es clara ni concisa y por lo tanto no permite detallar la materia a proteger.

Por otro lado, las reivindicaciones 8 y 9 reclaman el uso y de acuerdo con la legislación Colombiana el uso reclamado no se considera para protección por patente.

4 Análisis de la novedad:

Con relación al requisito de novedad su Despacho enuncia que el documento D1 (EP 0526434) afecta la novedad de las reivindicaciones 1 a 7 y 10 de la presente invención debido principalmente a lo siguiente:

"Se cita que D1 enseña el compuesto específicamente Flibanserina y que según su Despacho es la característica técnica esencial concreta y reivindicada que define a la invención. Aunque no se nombran literalmente los polimorfos de la misma en el D1 para su caracterización, se entienden

comprendidos en el estado de la técnica; ya que las formas cristalinas son intrínsecas a cada sustancia específica. Y por consiguiente se afirma, que el hecho de divulgar previamente esta característica esencial del compuesto reivindicado, destruye la novedad".

"Por otro lado, se menciona que el procedimiento de la reivindicación 3 ya era conocido en D1".

Por último cita que las composiciones farmacéuticas de la reivindicación 10 que comprenden un compuesto polimorfo A de Flibanserina...ya son conocidos por D1".

5. MODIFICACION A UNA SOLICITUD EN TRAMITE:

Con el fin de atender a las anteriores observaciones y de acuerdo al artículo 34 de la Decisión 486, se presenta un nuevo capítulo reivindicatorio conformado por 7 reivindicaciones como sustituto del anteriormente presentado, donde se efectuaron las siguientes modificaciones:

Se cancelaron las reivindicaciones de uso, es decir las anteriores reivindicaciones 7,8 y 9. Así mismo se canceló la expresión "opcionalmente" de la reivindicación 10 que ahora corresponde a la nueva reivindicación 7.

El título de la invención se modificó de la siguiente forma:

"POLIMORFO DE FLIBANSERINA, Y PROCEDIMIENTO INDUSTRIAL PARA SU PREPARACION".

Así mismo se modificó la reivindicación 1 de tal forma que el polimorfo de flibanserina ahora se caracteriza por los picos de difracción, los cuales son características del polimorfo.

Los picos de difracción que ahora caracterizan al polimorfo de la reivindicación 1 se determinan mediante difracción de rayos X de polvo(PXRD).

La nueva reivindicación 1 está totalmente sustentada en la memoria descriptiva inicialmente presentada, específicamente en la tabla 1, en la cual se identifica los ángulos [$^{\circ}2\theta$] (columna 1) y las intensidades relativas de cada pico en la columna 7 de dicha tabla.

Con respecto a la modificación de la nueva reivindicación 1, mi representada desea dar la siguiente explicación:

La tabla 1 representa un altísimo nivel de precisión de la caracterización del polimorfo A de la flibanserina. Esta altísima precisión se ve más a menudo en el procedimiento de caracterizar un nuevo compuesto o una nueva forma de un compuesto. Debido a que cada análisis por separado de PXRD del mismo compuesto, varia probablemente para ambas mediciones de los valores obtenidos, una persona experta en PXRD entenderá que el polimorfo revelado en la presente solicitud, y en los análisis posteriores, no necesariamente presentará valores de medición idénticos a los registrados en la tabla 1.

Para mediciones rutinarias contrario a una caracterización inicial, típicamente se utiliza una medición menos precisa. Por lo tanto, en tal situación, es convencional informar de

patrones de difracción de un compuesto mediante la identificación de sus picos más destacados. (Para mayor explicación por favor ver: Solid state Chemistry of Drugs, 2nd Ed.1999, page 63 4th par., (Anexo 7) y para redondear todos los valores de medición del ángulo 2θ hasta una décima de un grado, por favor ver: The United States Pharmacopoeia, page 388, columna derecha, última tercera frase (Anexo 8).

Por las razones dadas anteriormente, una persona experta en el arte PXRD, de la lectura de la tabla 1, entiende que el polimorfo puede caracterizarse a lo largo de un rango de valores derivados de la tabla 1, los puntos diferentes en el rango representan la variación en los niveles de precisión que se podrá razonablemente esperar en las mediciones PXRD de un compuesto a ser analizado para la posible identidad del polimorfo A de flibanserina.

6. ARGUMENTOS EN FAVOR DE LA NOVEDAD:

Mi representada argumenta que la presente invención es patentable ya que no se está reivindicando la flibanserina como tal, sino una forma muy específica de la flibanserina, es decir, el polimorfo A de la flibanserina. Y este polimorfo específico no se reveló en la referencia EP 0 526 434. Por lo tanto, la presente reivindicación 1 es nueva con relación al documento citado por su Despacho.

Por otro lado, el examinador argumenta que los elementos característicos de este compuesto (es decir, el polimorfo A de flibanserina, llamado Flibanserina^{BasePA}) fueron previamente revelados en el estado de la técnica, refiriéndose a la página 16, ejemplo 1, compuesto 3 de la citada referencia). Sin embargo, en tal referencia se describió la sal clorhidrato de flibanserina, llamada Flibanserina*HCl. Por el contrario, la presente invención relaciona la base libre de Flibanserina en su forma polimórfica A.

Por lo anteriormente expuesto, los elementos característicos de flibanserina revelados en la referencia pertenecen a la Flibanserina*HCl y no a la Flibanserina^{BasePA}.

Adicionalmente, la Flibanserina^{BasePA} muestra propiedades superiores sobre la Flibanserina*HCl, dichas propiedades superiores no se enseñan ni se deducen del arte previo.

Las anteriores afirmaciones se sustentan por los siguientes resultados experimentales:

a) La Flibanserina*HCl (de acuerdo con la EP 0526 434) absorbe humedad (higroscopicidad). Contrario a esto, el clorhidrato de Flibanserina^{BasePA} no muestra higroscopicidad a diferentes rangos de temperatura para diferentes valores de humedad relativa.

156
156

El anexo 1 presenta dicho comportamiento de los compuestos contra la humedad. Mientras que la Flibanserina^{BasePA} a temperatura ambiente para 53%, 75% y 94% R.H no absorbe ninguna humedad (Anexo 1, figura de la izquierda), la Flibanserina*HCl almacenada a 93% R.H. recoge humedad sin ninguna limitación al menos hasta donde va el periodo de observación. (Anexo 1 figura de la derecha).

En otros términos, la Flibanserina^{BasePA} puede fácilmente ser utilizada en la preparación de un producto fármaco, mientras que la Flibanserina*HCl es definitivamente problemática para el desarrollo farmacéutico como una capsula o una tableta. Lo más importante por la presente es la falta de control de peso o el cambio en las propiedades fisicoquímicas. Esta ventaja y para un producto médico propiedad importante de la Flibanserina^{BasePA} no se enseña ni se sugiere de manera obvia por la EP 0 526 434 y, por lo tanto, se prueba su superioridad inesperada sobre el arte previo.

b) De acuerdo a su comportamiento térmico la Flibanserina*HCl del arte anterior puede dar lugar a muchos polimorfos. Este polimorfismo puede ser problemático en términos de estabilidad.

El anexo 2 muestra el comportamiento térmico de la Flibanserina*HCL en un análisis de DSC. La gráfica muestra muchos eventos que tienen lugar a temperaturas diferentes.

Mientras los eventos a 107 y 135°C son relativos al agua y al disolvente de desorción, los eventos a 153 y 190-194°C son sugeridos de las transiciones en un estado físico diferente, 226°C es el punto de fundición.

Por su parte, los anexos 3 a 5 muestran un DSC obtenido para la Flibanserina*HCl del arte anterior después del almacenamiento a 40°C y 75% de humedad relativa, y 70°C/75% R.H., respectivamente, o RT/90%R.H. Los puntos DSC muestran el comportamiento térmico diferente de la sal como una función de las condiciones de almacenamiento, sugiriendo cambios relevantes en las propiedades fisicoquímicas.

El anexo 6 se muestra el comportamiento térmico de la Flibanserina ^{BasePA}, donde solamente un simple evento, la fundición a 161°C puede encontrarse. El mismo comportamiento no se cambia cuando el compuesto es almacenado a 40°C y 75% de humedad relativa, respectivamente 70°C/75% R.H. o RT/90% R.H.

Esta ventaja y esta propiedad importante para un producto médico de Flibanserina ^{BasePA} no se enseñó ni se deriva de manera obvia por D1 y, por lo tanto, esto prueba su superioridad inesperada sobre el arte previo.

c) Una evaluación cualitativa de la solubilidad de acuerdo a la *European Pharmacopeia* conduce a los hallazgos que tanto la Flibanserina ^{BASEPA} y la Flibanserina*HCl son

igualmente insolubles en agua. El inesperado hallazgo de que el polimorfo A de base libre de acuerdo a la invención muestra una solubilidad igual si se compara con el clorhidrato del arte previo debe ser sorpresivo para una persona experta en el arte quien normalmente esperaría que la sal de adición ácida es superior es este aspecto.

De nuevo esto fue totalmente inesperado por una persona experta en el arte.

d) Finalmente, a pesar de un comportamiento de solubilidad igual de la Flibanserina ^{BasePA} y del clorhidrato del arte previo en agua, se recalca que la Flibanserina*HCl probó ser absolutamente inadecuada para formar suspensiones homogéneas, mientras que la Flibanserina BasePA es adecuada. La consecuencia práctica es que aunque es imposible preparar suspensiones del clorhidrato para uso oral, la Flibanserina ^{BasePA} es aplicable también en esta clase de formulaciones.

En vista de lo anterior, se puede concluir que la Flibanserina ^{BasePA} de acuerdo a la invención muestra superioridad sobre el clorhidrato del arte anterior que no se enseña ni se sugiere de manera obvia para una persona medianamente experta en el arte por el documento citado. En consecuencia la presente invención cumple con los requerimientos de novedad y de nivel inventivo.

159
150

Teniendo en cuenta que la materia objeto de la reivindicación 1 es nueva, las composiciones de la reivindicación 10 también son novedosas ya que estas comprenden la Flibanserina de la reivindicación 1.

Con respecto a la observación de la reivindicación 3, mi representada argumenta que en ninguna parte del documento EP 0526434 se revela la piperazina 3 como se describe en la solicitud en estudio. Por lo tanto, dicha reivindicación también es novedosa.

Se concluye entonces que el nuevo capítulo reivindicatorio cumple con el requisito de claridad y con los requisitos de patentabilidad establecidos en la Decisión 486.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

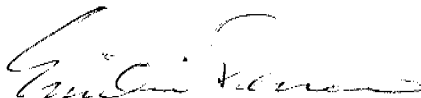
7. Anexos:

- Nuevo pliego reivindicatorio conformado por 7 reivindicaciones.
- Formulario para modificaciones.
- Recibo por valor de \$99.000 por concepto de modificaciones en solicitud pendiente.
- Anexo 1 (Clorhidrato vs Base: Estudios comparativos de Higroscopicidad).

160
160

- Anexo 2 DSC-Termograma de Filbanserina*HCl
- Anexo 3 DSC termograma de Filbanserina*HCl después de almacenamiento a 40°C/75% de humedad relativa.
- Anexo 4 DSC termograma de Filbanserina*HCl después de almacenamiento a 70°C/75% de humedad relativa
- Anexo 5 DSC termograma de Filbanserina*HCl después de almacenamiento a RT/90% de humedad relativa.
- Anexo 6 DSC termograma de Filbanserina ^{BasePA}.
- Anexo 7 Copia de "Solid State Chemistry of Drugs", Second Edition.
- Anexo 8 copia de "The United States Pharmacopeia".

Señora
Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

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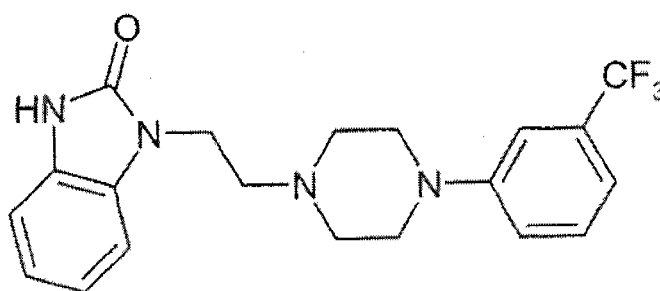
1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BIDACHEM S.P.A. sociedad constituida y existente bajo las leyes de Italia. Dirección: Strada Statale 11, (Padana Sup.) N. 8, I-24040 Fornovo S Giovanni, Bergamo, Italia Domicilio: Fornovo S Giovanni, Bergamo, Italia Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 438.019 TP 31.929
4	Número de expediente: <u>04.016.766</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 7 reivindicaciones así como nuevo título "POLIMORFO DE FLIBANSERINA Y PROCEDIMIENTO INDUSTRIAL PARA SU PREPARACION" con el fin de subsanar las observaciones realizadas por su Despacho en el oficio de fondo.	
6	Comprobante de pago No. <u>7-98.202</u> Fecha: <u>3 de diciembre de 2007</u>	
7	Anexos ☒ Comprobante de pago de la tasa por valor de \$99.000.00 ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929

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162

Reivindicaciones

1) Un polimorfo de flibanserina 1,

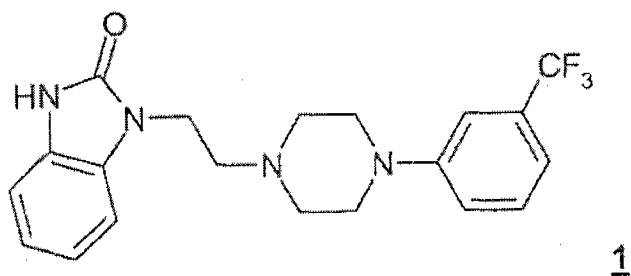


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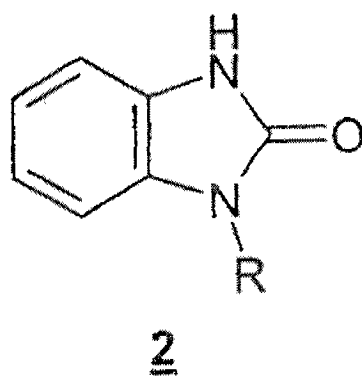
que tiene un máximo endotérmico a 161°C que se produce durante un análisis térmico usando DSC, caracterizado por un pico de difracción ($^{\circ}2\theta$) alrededor de 5.2, 9.0, 9.3, 10.0, 10.6, 11.3, 13.2, 14.6, 15.5, 16.7, 17.1, 17.3, 17.4, 18.1, 18.6, 19.1, 19.8, 20.1, 20.4, 21.2, 21.9, 22.6, 23.2, 24.4, 24.6, 25.0, 25.3, 26.6, 27.2, 27.3, 27.9, 28.2, 28.3, 28.6, 29.5, 30.2, 31.1, 31.9, 32.4, 33.3, 33.6, 34.9, 35.3, 36.1, 36.9, 37.2, 37.7, 39.4, 39.4, 39.7, 40.3, 40.9, 41.4, 42.0, 42.7, 43.2, 44.2, 46.1, 46.5, 48.3, 48.9, 50.3, 51.0, 53.6, 54.5, 55.4, 56.2, 56.8, 57.4 y 58.5 obtenidos por difracción de rayos X sobre polvo.

2) La flibanserina 1 que comprende la forma A de acuerdo con la reivindicación 1.

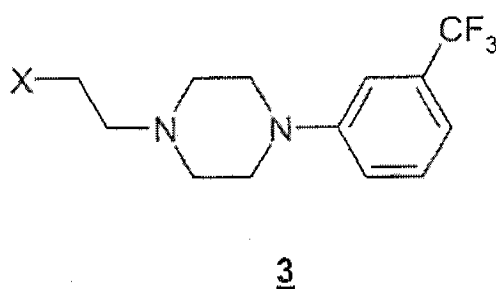
3) Un procedimiento para la preparación industrial de flibanserina 1 de acuerdo con la reivindicación 1 ó 2,



caracterizado porque, en una primera etapa de reacción, una benzoimidazolona 2



en la que R representa un grupo protector adecuado de aminas, se hace reaccionar con una piperazina 3



en la que X es un grupo saliente seleccionado entre cloro, bromo, yodo, metanosulfonato, trifluorometanosulfonato y para-toluenosulfonato, en un disolvente adecuado seleccionado entre agua, alcoholes, mezclas de agua con alcoholes, disolventes apróticos polares y mezclas de los mismos con

164
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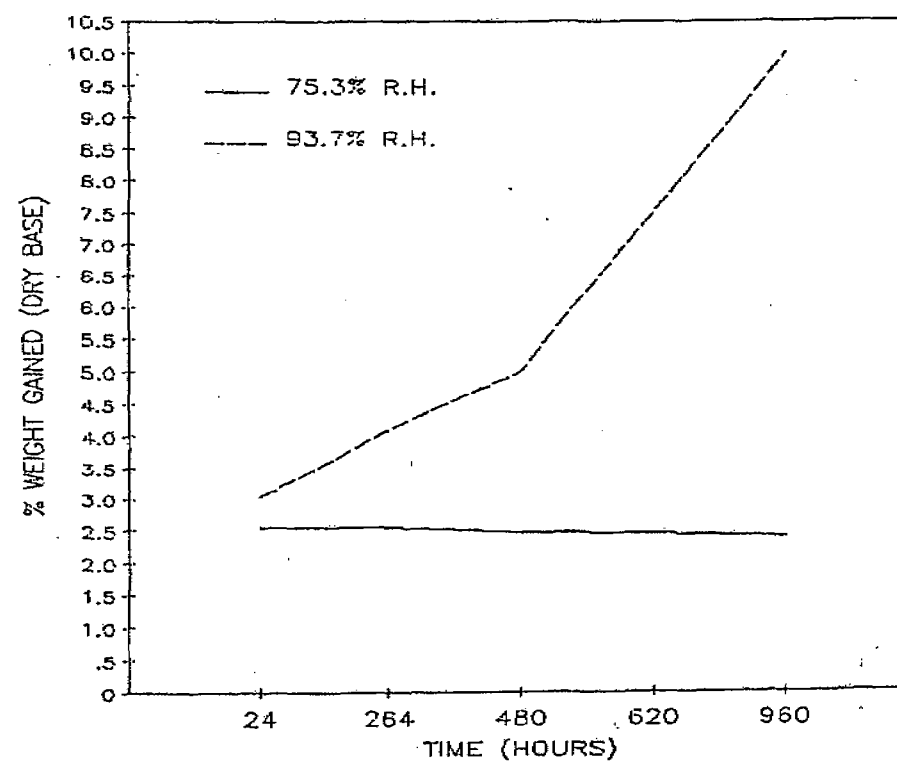
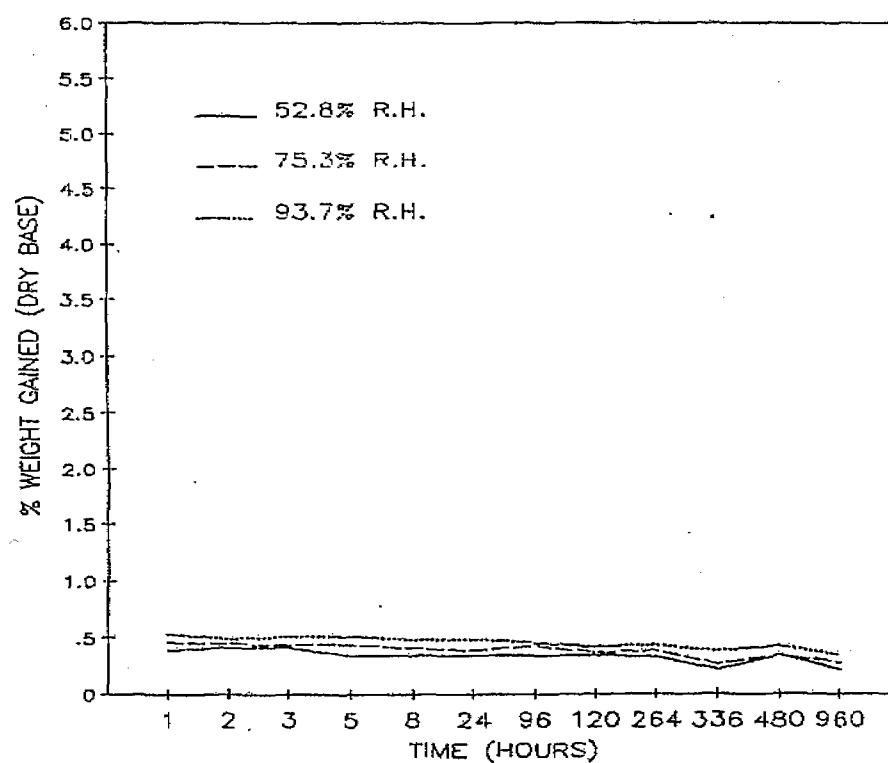
agua, en presencia de una base adecuada, y porque, en una segunda etapa de reacción, el grupo R protector amino es clivado bajo unas condiciones de clivaje adecuadas.

4) Un procedimiento de acuerdo con la reivindicación 3, caracterizado porque la reacción de 2 con 3 es llevada a cabo a una temperatura de al menos 50°C.

5) Un procedimiento de acuerdo con la reivindicación 4, caracterizado porque el calentamiento es llevado a cabo durante un periodo de aproximadamente 10 minutos a aproximadamente 12 horas.

6) El compuesto polimorfo A de flibanserina 1 obtenible de acuerdo con una de las reivindicaciones 3 a 5.

7) Composiciones farmacéuticas que comprenden un compuesto polimorfo A de flibanserina de acuerdo con una de las reivindicaciones 1, 2 y 6, como un ingrediente activo, en mezcla con uno o más vehículos, agentes diluyentes o excipientes farmacéuticos.

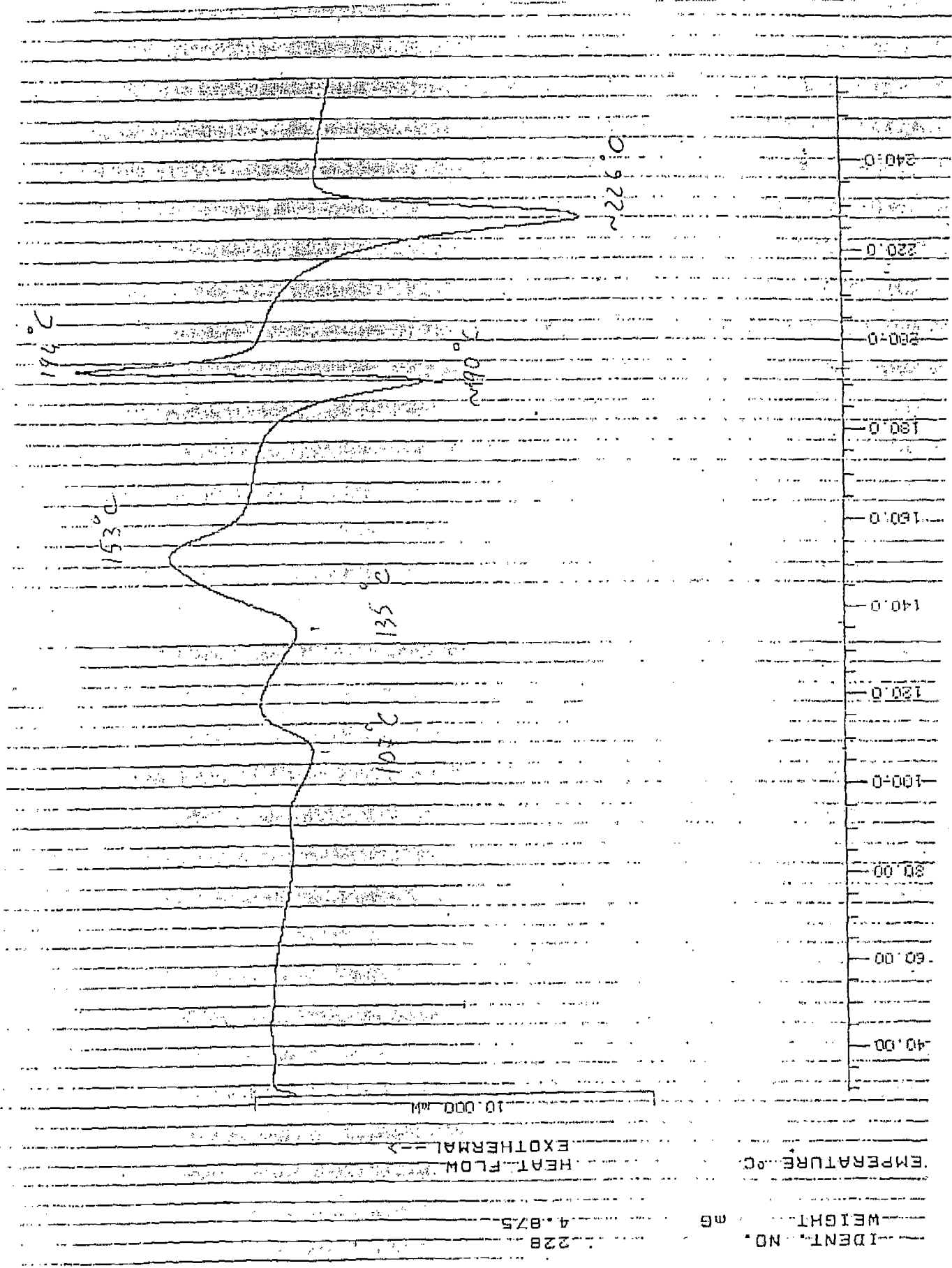
Base vs Hydrochloride: Comparative Hygroscopicity Studies

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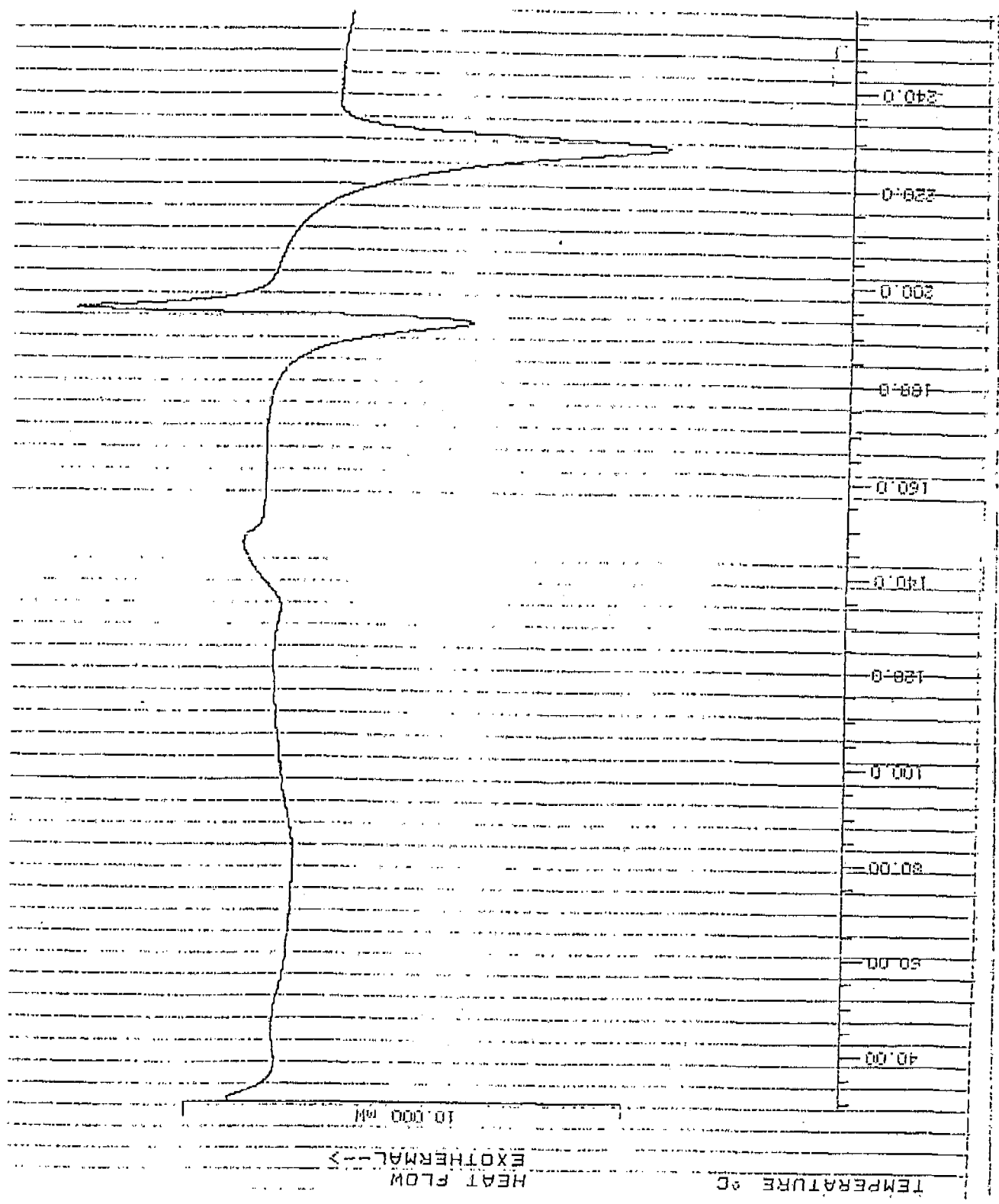
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Annex 2: DSC-Thermogram of Filbanserin*HCl



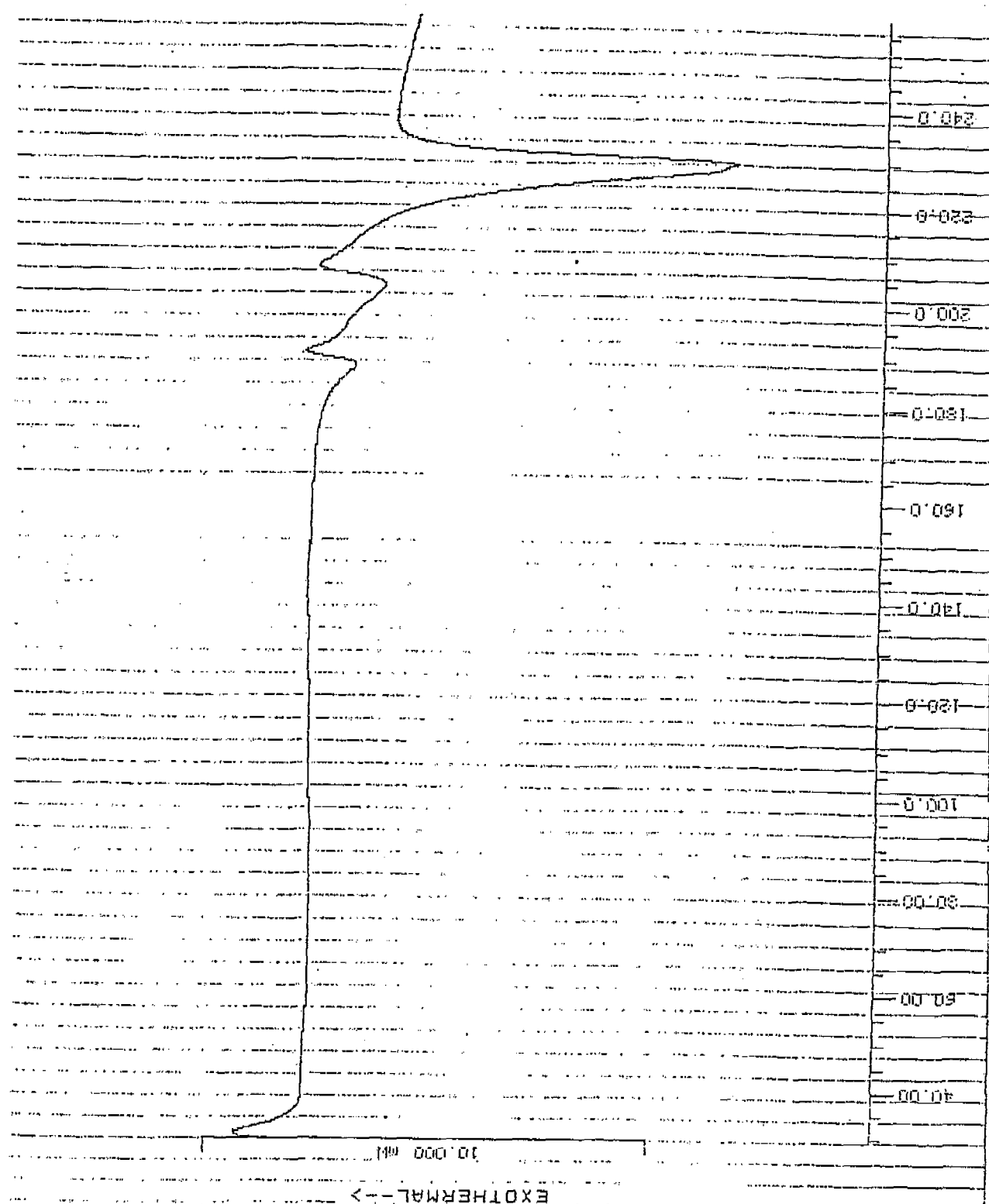
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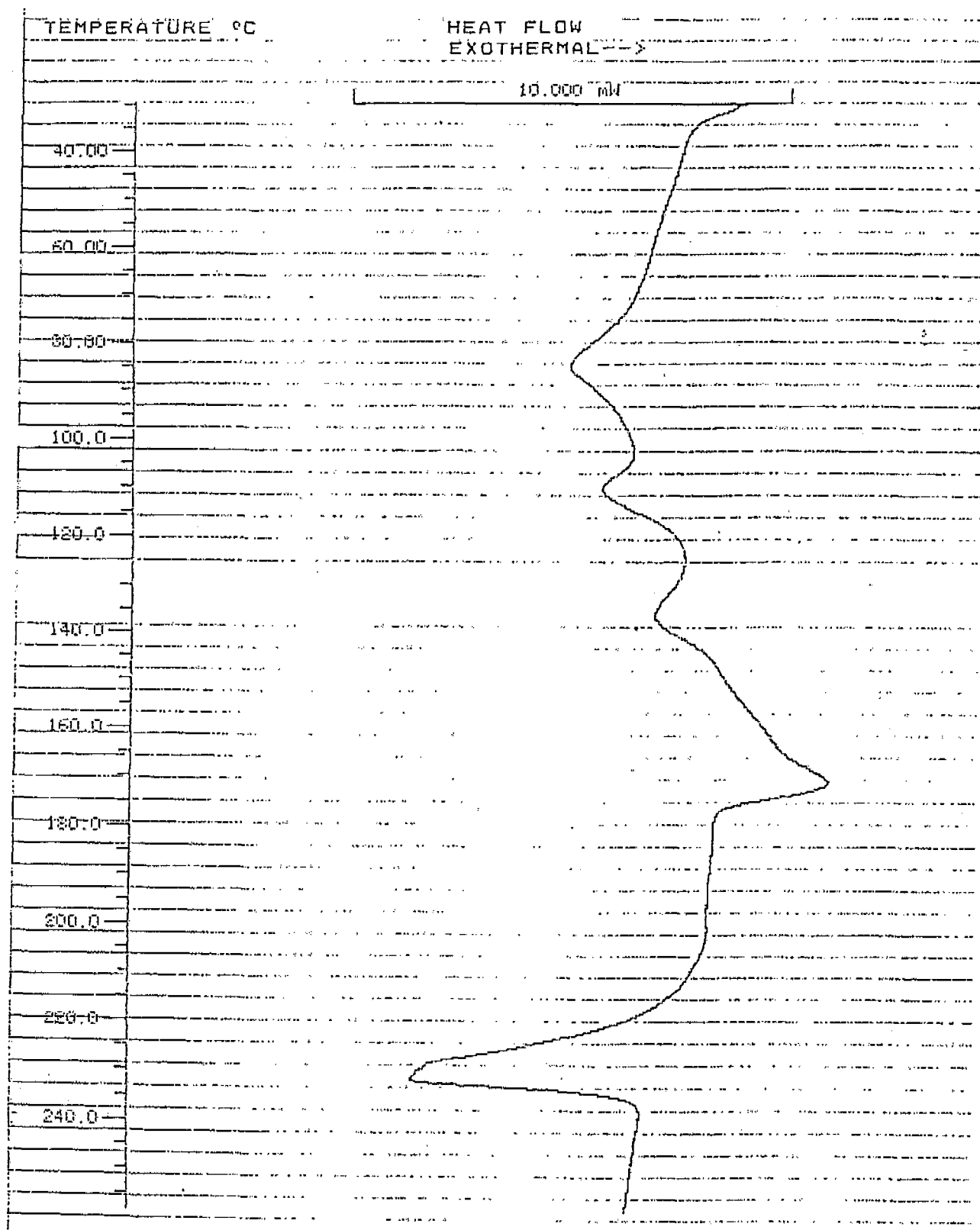
Annex 3: DSC-Thermogram of Filbanserin*HCl after storage at 40°C / 75% relative humidity



168
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Annex 4: DSC-Thermogram of Filbanserin*HCl after storage at 70°C / 75% relative humidity



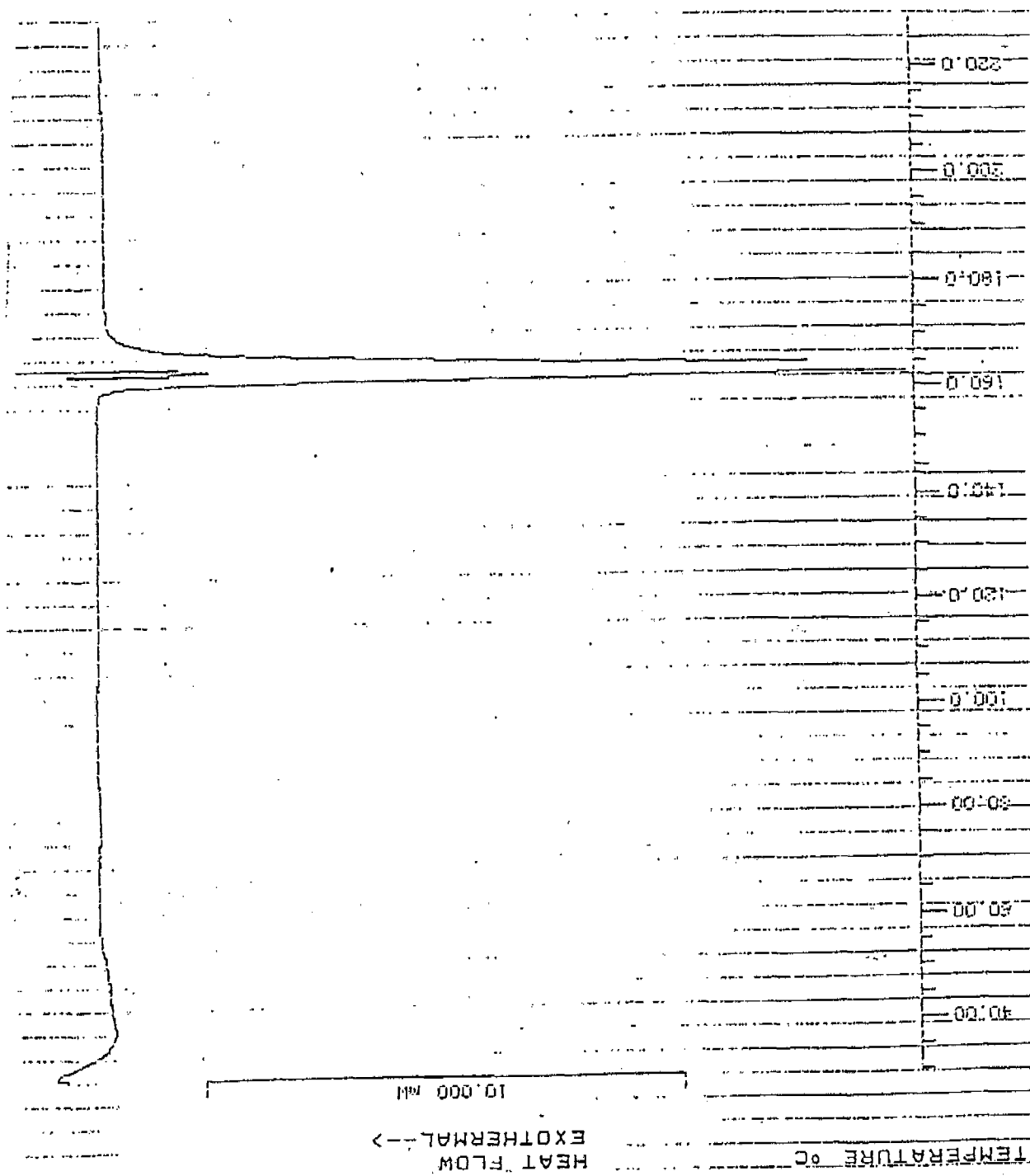


Annex 5: DSC-Thermogram of Filbanserin*HCl after storage at RT / 90% relative humidity

169

170
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Annex 6: DSC-Thermogram of Filbanserin^{BasePA}



Anexo 7 171

Solid-State Chemistry of Drugs

SECOND EDITION

Stephen R. Byrn
Ralph R. Pfeiffer
Joseph G. Stowell

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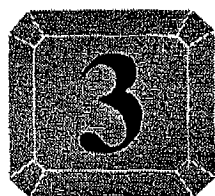
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Cover illustration: The figures are space-filling representations of prednisolone 21-*tert*-butylacetate crystal packing diagrams. On the top is Form IV illustrating the densely packed crystal lattice. On the bottom is Form V showing the oxygen-accessible tunnels produced by desolvation.



The X-Ray Powder Diffraction Method

X-ray powder diffraction, like the single crystal method discussed in the previous section, is an effective method of distinguishing solid phases having different internal structure. The X-ray powder method is experimentally simple and does not require large single crystals, but instead can readily be applied to any powdered sample. While the powder method is much simpler, it gives data about only a relatively few hkl planes of a substance, *i.e.*, only the most strongly diffracting planes. Nevertheless, this information is quite adequate to distinguish among any solid phases present.

3.1 INSTRUMENTS FOR POWDER DIFFRACTION MEASUREMENTS

Instruments used in the X-ray powder diffraction method fall into two categories: diffractometers and cameras. Figure 3.1 shows a schematic drawing of a modern powder diffractometer and Figure 3.2 shows a photograph of a powder X-ray camera. All instrumentation for X-ray powder diffraction yields the same information about the diffraction characteristics of the sample, namely the intensities of the maxima and the angles at which they occur. The raw data are recorded either on film (which takes about

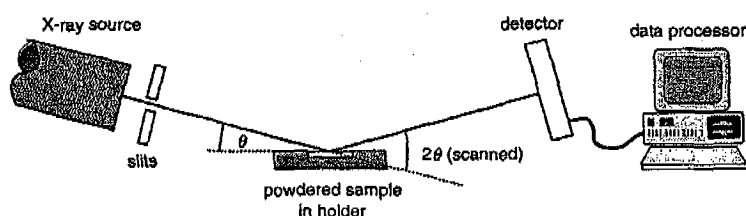


Figure 3.1 Schematic drawing of a modern 2θ powder X-ray diffractometer

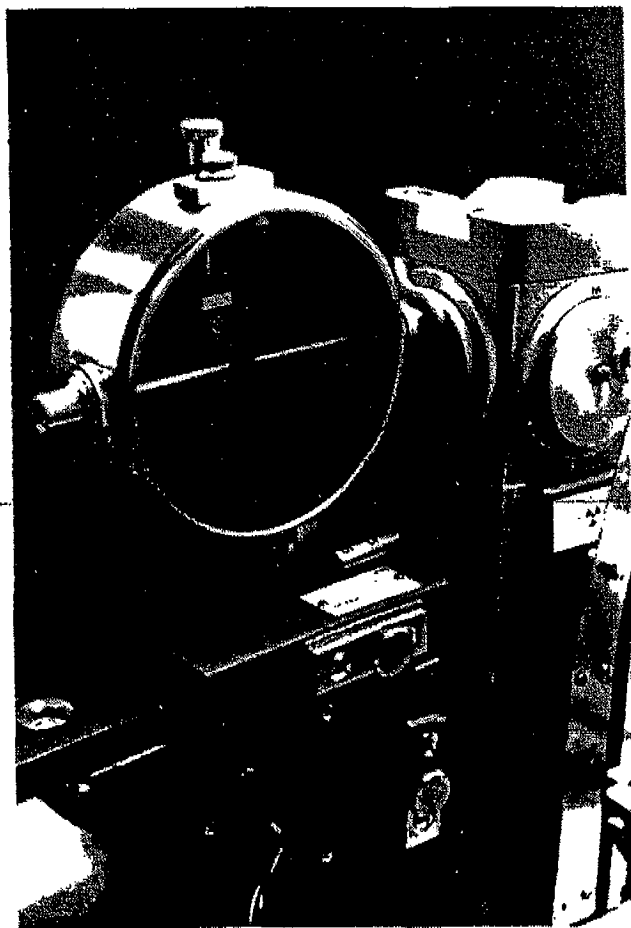


Figure 3.2 A Debye-Scherrer powder camera.

two hours) or on a plotter or strip chart (which takes from a few minutes up to about a half hour). Examples of these data presentations are shown in Figure 3.3 and either is suitable for making direct visual comparisons.

Further treatment of the film data, by visual measurement or with automated densitometer, reduces the data to the universal standard form: d versus $I/I_{\max}$ where d is the "d-spacing" (in Ångströms) obtained from Bragg's law ($n\lambda = 2d\sin\theta$) and $I/I_{\max}$ is the peak intensity relative to the strongest peak in the pattern. Likewise, strip chart data is readily converted, usually by a computer program, to the same universal standard form. Modern instruments with computerized data handling features can express the data in any desired format.

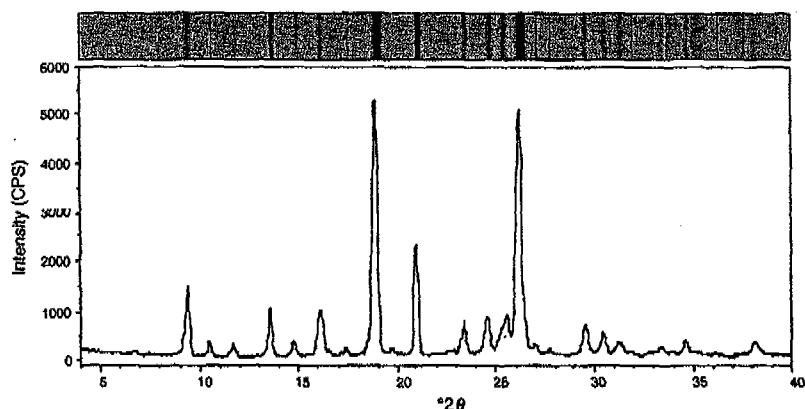


Figure 3.3 Two forms of powder diffractogram data presentation for the same material. The top bar represents the film diffractogram obtained by a powder camera and corresponds to the diffractogram below it obtained by a computer controlled diffractometer.

3.2 POWDER DIFFRACTION USING SYNCHROTRON RADIATION

In recent years, major advances have been made in applying synchrotron X-radiation to powder diffraction problems. The high intensity and nearly monochromatic radiation obtained from a synchrotron allow measurement of high resolution diffraction patterns. In favorable cases, synchrotron radiation has been used to obtain enough diffraction data to solve crystal structures of small organic molecules including cimetidine (Cernik *et al.*, 1991) and 6,13-dichlorotriphenyldioxazine (Fagan *et al.*, 1995). In the future, high speed computers and better computational methods are expected to allow more complicated structures to be determined. Even in cases where the structure cannot be determined, synchrotron powder diffraction allows accurate determination of the unit cell parameters and space group. This information is especially important for detecting extraneous phases.

3.3 THE HANAWALT SYSTEM

Hanawalt *et al.* (1938) devised a system for cataloging the X-ray powder data for any substance. The system requires the data to be in the universal standard form: d versus $I/I_{\max}$. In this form, wavelength and instrument constants are eliminated, and therefore data can be compared between laboratories that may be using different conditions.

A central file is maintained by the ICDD (International Centre for Diffraction Data, 1998) [formerly called the Joint Commission on Powder Diffraction Specifications (JCPDS)] in printed and electronically retrievable forms. Updates are made available periodically and, of course, the system is suited to customized additions by any user.

An example of the file data for a typical entry is given in Figure 3.4. All diffraction peaks for the compound are listed in decreasing order of d value along with the corresponding relative intensity. Other useful crystallographic data, including optical data, are also included when available.

62 Chapter 3 The Powder Diffraction Method

10-310

d	2.49	2.92	1.46	2.92	MnAl ₃ O ₄							*		
I/I ₀	100	60	45	60	MANGANESE ALUMINATE	(GALAXITE)								
Rad. CuK _α	λ 1.5405				Filter Ni	d Å	I/I ₀	hkl	d Å	I/I ₀	hkl			
Cut off	I/I ₀ DIFFRACTOMETER					2.921	60	220						
Ref. NAT. BUR. STANDARDS (U.S.) CIRC. 539 9 (1959)						2.492	100	311						
						2.383	10	222						
						2.065	25	400						
						1.6862	20	422						
Sys. CUBIC	S.G. O ₇ H - F03M (227)					1.5896	40	511						
a ₀ 8.258	b ₀	c ₀	A	C		1.4600	45	440						
α	β	γ	Z 8	D _x 4.077		1.3060	8	620						
Ref. IBID.						1.2596	12	533						
						1.1037	10	642						
ex	naβ	ey	Sign			1.0749	25	731						
ZV	D	mp	Color BROWN			1.0322	14	800						
Ref. IBID.						0.9732	8	822						
						0.9534	20	751						
						0.8656	16	931						
						0.8429	30	844						
						0.8097	12	10.2.0						
						0.7983	18	951						
SAMPLE PREPARED BY NBS BY HEATING MnCO ₃ AND AL(OH) ₃ TO 1300°C. FOR 24 HOURS.														
SPECT. ANAL. SHOWNED: < 1.0% CO, NA; < 0.1% SI; < 0.01% CR, CU, FE, MG.														
SPINEL-TYPE STRUCTURE.														
PATTERN MADE AT 25°C.														

10-310	JCPDS-ICDD Copyright (c) 1989	Quality: 1	DELETED								
				d Å	Int.	h k l					
MnAl ₃ O ₄ 2 4				2.921	60	2 2 0					
Manganese Aluminum Oxide				2.492	100	3 1 1					
Galaxite, syn				2.383	10	2 2 2					
				2.065	25	4 0 0					
				1.6862	20	4 2 2					
Rad: Cu				1.5896	40	5 1 1					
Lamda: 1.54056				1.4600	45	4 4 0					
Filter: Ni				1.3060	8	6 2 0					
Cutoff: Int				1.2596	12	5 3 3					
Ref: See comments box for primary powder pattern reference.				1.1037	10	6 4 2					
Sys: Cubic				1.0749	25	7 3 1					
a ₀ 8.258				1.0322	14	8 0 0					
At: B				0.9732	8	6 6 0					
Ref: Ibid.				0.9534	20	7 5 1					
D _x 4.08				0.8656	16	9 3 1					
D _y 55/PQ4: F18-12(.045,33)				0.8429	30	8 4 4					
ex: nnd				0.8097	12	10 2 0					
Ref: ey: Sign: Zvt				0.7983	18	9 5 1					
PSC: c56. Deleted by 29-840. INVALID reference: For original reference see PDF card set prior to 1980. Mnt: 172.90. Volume(00): 563.15.											

Figure 3.4 Examples of powder diffraction data from the Powder Diffraction File (PDF): (top) a card entry and (bottom) an entry from the CD-ROM (International Centre for Diffraction Data, 1998).

Note that retrieval is based on the d values of the four most intense peaks (boxes at upper left). While this system is generally adequate for retrieving close matches, some flexibility in applying it does need to be exercised in view of the possible unknown effects of **preferred orientation** on the intensities (see Sect. 3.4). A group of, say, three or four close matches can then usually be reduced or eliminated on the basis of other available information.

3.4 COMPARING X-RAY POWDER DATA

The most useful method to compare X-ray powder diffraction data obtained from different samples and on the same instrumentation is to overlay and align the respective films or plots. When plots are available, a tracing of each previously characterized form on transparent film is very helpful. The ensuing comparisons of peak positions and intensities may fall anywhere between complete agreement to complete disagreement of the patterns. In either of these extreme cases, the respective conclusions are, of course, unequivocal: the structures are the same or they are different. An alternative method involves comparing 2θ values versus intensities of the various forms and noting any differences.

Often, however, two patterns may show many differences but also have several peaks that appear to coincide. A judgment must be made as to whether the coincident peaks: 1) are indeed, just a few coincidences and the samples do have different structures; or 2) are due to the presence of a common component implying the sample is a mixture of structures. The patterns of highly unequal mixtures will contain only the stronger peaks of the minor component at greatly reduced intensity, but all of the peaks of the major component. With experience, the pattern recognition capabilities of the human mind will play an important role in these comparisons.

Let us turn to some factors that affect the quality of the X-ray powder diffraction data, (i.e., factors that affect the accuracy of peak locations and intensities). Most errors in peak locations are usually minor and arise from either film shrinkage in the camera method or sample misalignment in the diffractometer method. In both situations, these errors can be detected and corrected by mixing an internal standard with the powder.

The observed intensities of one or more peaks, however, can vary considerably among different samples of the same substance. This variability is most often the result of preferred orientation of the crystals that comprise the powder. For an individual single crystal, a given hkl plane gives a single diffraction spot when the crystal is at a fixed orientation to the X-ray beam and detector. A powder, containing many crystals randomly oriented with respect to the X-ray beam and detector, produces a uniform cone of diffracted radiation for each hkl plane. This uniform cone results in a uniform intensity measurement regardless of the geometry of the diffraction equipment. Preferred orientation is most likely to arise when the powder consists of needle-like or plate-like crystals (i.e., shapes that are prone to align in a non-random or *preferred orientation*). For example, if several handful of soda straws are thrown into a shoe box, the straws will mostly align parallel to each other. Similarly, scatter a deck of cards on a table and all of the cards lay flat on the table. For needle- and plate-like crystals, the preferred orientation effects can be minimized by reducing the size of the crystals (usually by grinding) before the sample is placed onto the sample holder. However, care must be taken to guard against grinding to an extent that phase transitions to other crystal forms or an amorphous form are induced. Where amorphous material is produced, the incoherent scattered radiation from the amorphous fraction of the sample adds to the general background of the powder pattern (a diffuse halo on films, a broad hump of higher background scatter on diffractometer tracings). Therefore, when the pattern of a substance is found to gradually become weaker as the material is milled or ground, it may be taken as strong evidence that the structure is being destroyed by the process. If these changes occur, serious consideration must be given to how particle-size reduction

178
178

64 Chapter 3 The Powder Diffraction Method

is achieved. In addition, observations of this kind are useful indications of what kind of solid-state changes might occur during processing of the drug product.

Another situation in which fixed peaks may vary in intensity arises when a solvated crystal loses solvent but does not lose its crystal structure. (See Chapter 16 on Solvates and Desolvated Crystals.) In this case, the loss of solvent may affect the intensity of certain planes more than others. It is therefore good practice to obtain reference patterns of solvated crystals using powders damp with the appropriate solvent. The effect of solvent loss on peak intensities will then be easier to interpret.

3.5 VARIABLE TEMPERATURE AND ATMOSPHERE STUDIES

Modern diffractometers can be fitted with an environmental chamber that allows control of the atmosphere as well as the temperature. This method has been quite useful in the study of interconversions of crystal forms under different conditions as well as for the study of desolvations and other processes. If changes in the X-ray powder diffraction pattern are observed upon heating, additional studies are needed to determine whether desolvation, degradation, or a polymorphic transformation is occurring. The method is also useful in conjunction with differential scanning calorimetry (DSC) and other thermal methods (see Chapter 5).

3.6 QUANTITATIVE ANALYSIS OF MIXTURES

X-Ray powder diffraction has also been used to quantify the percentages of a crystal form in a mixture of forms. Quantification usually requires extensive calibration using known mixtures of the two components, but the effort can provide a powerful method for pharmaceutical analysis and assurance of a consistent product.

Matsuda *et al.* (1984) have shown that X-ray powder diffraction can be used to analyze mixtures of α - with δ - and β - with δ -phenylbutazone as shown in Figures 3.5 and 3.6. In these cases, Matsuda and co-workers made known mixtures of α - with δ - and β - with δ -phenylbutazone and obtained the powder diffraction patterns shown in Figure 3.5. Figure 3.6 shows the calibration curves obtained by taking the intensity ratios of the peaks indicated by the arrows in Figure 3.5. They were able to use these calibration curves to determine the rate of interconversion of α - to δ - and β - to δ -phenylbutazone. It is important to note that some calibration curves are nearly horizontal, meaning that large errors can result. However, in other cases, the calibration curves have a relatively large slope and can give more accurate results. Because the intensity ratio of the α - δ mixture at 6.6° and 7.1° approached infinity at low concentrations, the reciprocal ratio was also used to establish the calibration curve. Thus for the α - δ mixtures, Figure 3.6 shows two curves (diamonds and filled circles) for the peaks at 6.6° and 7.1° where the lower portions of the curves (bolded) were used for the calibration.

Suryanarayanan (1989) has used powder diffraction extensively to study the different polymorphs and hydrates of carbamazepine determining the relative amounts of α - and β -carbamazepine in mixtures. In this case, the integrated intensities of the 10.1 Å line (unique to α -carbamazepine) in the mixtures were measured. Plots of the integrated intensity of this line versus the weight fraction of the α form gave a good straight-line calibration curve with coefficients of variation of up to 10% and a mini-

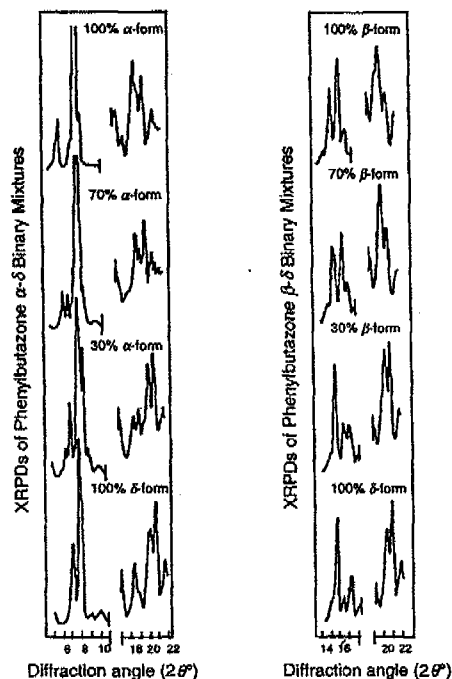


Figure 3.5 X-Ray diffraction patterns of α - mixed with δ -phenylbutazone and β - mixed with δ -phenylbutazone binary mixtures in various ratios (Matsuda *et al.*, 1984).

imum detectable limit of less than 5%. Furthermore, Suryanarayanan stated that preferred orientation can have a major effect on quantification of powder mixtures and that it is thus important to grind the samples in quantitative studies.

Suryanarayanan (1990) also used powder diffraction to determine the ratios of anhydrous carbamazepine and carbamazepine dihydrate in mixtures. In these studies he measured the ratios between the 6.78 and 9.93 Å lines. The 6.78 Å line was used to analyze for anhydrous carbamazepine and the 9.93 Å line to analyze for carbamazepine dihydrate. Interestingly, he found that if he analyzed loosely packed powders, a rather large coefficient of variation resulted. When he compressed the samples, the coefficients of variation were greatly reduced.

Suryanarayanan and Herman (1991) also used powder diffraction to quantify the amount and form of carbamazepine in tablets that also contained microcrystalline cellulose, starch, and stearic acid. In this study, the tablets were ground in a ball mill and the powder was mixed with LiF (as an internal standard) in a 20% w/w mixture. These studies allowed the determination of the carbamazepine content of unknown tablets with a coefficient of variation of between 0.28–2.1%. This study was very successful in part because carbamazepine was the major ingredient in the tablet.

Recently, profile-fitting approaches, rather than single-line measurement, have been used to quantitate X-ray powder diffraction (Tanninen and Yliruusi, 1992). These

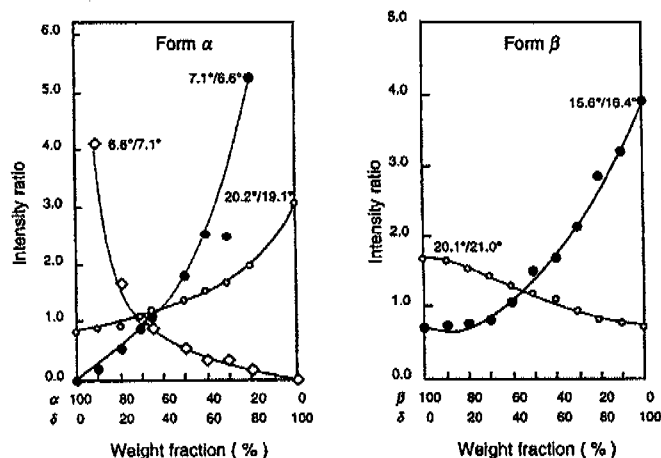


Figure 3.6 Calibration curves for α - δ phenylbutazone and β - δ phenylbutazone binary mixtures using intensity ratios at the indicated 2θ values (Matsuda *et al.*, 1984).

workers showed that profile-fitting can be quite useful in the study of α - and δ -prazosin hydrochloride α . They found that they had a surprisingly good detection sensitivity of 0.5% and that the relative amounts of the two polymorphs could be determined with an accuracy of 0.5 to 1.0% depending on the amount of peak overlap. The use of peak-profile fitting, which has also been used to quantitate mixtures by FT-IR spectroscopy, appears to have significant potential for improving the accuracy of X-ray powder diffraction analysis of mixtures.

Mixtures of crystalline and amorphous materials have also been studied using powder diffraction. In early studies, Pikal *et al.* (1977) determined the percentages of amorphous and crystalline forms in antibiotics but found the errors using this procedure were large. Ryan (1986) has shown that X-ray powder diffraction can be used to determine the crystallinity of imipenem:cilastatin sodium mixtures using the peak intensity of the crystalline component. Crocker and McCauley (1995) measured the X-ray diffraction intensity of amorphous imipenem at a diffraction angle where crystalline imipenem peaks did not occur.

REFERENCES

- Cernik, R. J., A. K. Cheetham, C. K. Prout, D. J. Watkin, A. P. Wilkinson, and B. T. M. Willis (1991) "The structure of cimetidine ($C_{10}H_{16}N_6S$) solved from synchrotron-radiation X-ray-powder diffraction data" *J. Appl. Crystallogr.* **24** 222-224.
- Crocker, Louis S. and James A. McCauley (1995) "Comparison of the crystallinity of imipenem samples by X-ray diffraction of amorphous material, *J. Pharm. Sci.*, **84**, 226-227.
- Fogan, Paul G., Robert B. Hammond, Kevin J. Roberts, Robert Docherty, Alan P. Chorlton, William Jones, and Graham D. Potts (1995) "An *ab initio* approach to crystal structure determination using high-resolution powder diffraction and computational chemistry techniques: application to 6,13-dichlorotriphenldioxazine" *Chem. Mater.* **7** 2322-2326.

- Hanawalt, J. D., H. W. Rinn, and L. K. Frevel (1938) "Chemical analysis by X-ray diffraction—classification and use of X-ray diffraction patterns" *Ind. Eng. Chem., Anal. Ed.* **10**, 457–512.
- International Centre for Diffraction Data (1998) 12 Campus Boulevard, Newtown Square, PA 19073-3273 USA.
- Matsuda, Yoshihisa, Etsuko Tatsumi, Etsuko Chiba, and Yukie Miwa (1984) "Kinetic study of the polymorphic transformations of phenylbutazone" *J. Pharm. Sci.* **73**, 1453–1460.
- Pikal, M. J., A. L. Lukes, John E. Lang, and K. Gaines (1977) "Quantitative crystallinity determinations for β -lactam antibiotics by solution calorimetry: correlations with stability" *J. Pharm. Sci.* **67**, 767–773.
- Ryan, James Arthur (1986) "Compressed pellet X-ray diffraction monitoring for optimization of crystallinity in lyophilized solids: imipenem:cilastatin sodium case" *J. Pharm. Sci.* **75**, 805–807.
- Suryanarayanan, Raj (1989) "Determination of the relative amounts of anhydrous carbamazepine ($C_{15}H_{12}N_2O$) and carbamazepine dihydrate ($C_{15}H_{12}N_2O \cdot 2H_2O$) in a mixture by powder X-ray diffraction" *Pharm. Res.* **6**, 1017–1024.
- Suryanarayanan, Raj (1990) "Determination of the relative amounts of α -carbamazepine and β -carbamazepine in a mixture by powder X-ray diffractometry" *Powder Diff.* **5**, 155–159.
- Suryanarayanan, Raj, and Craig S. Herman (1991) "Quantitative analysis of the active tablet ingredient by powder X-ray diffractometry" *Pharm. Res.* **8**, 393–399.
- Tanninen, V. P. and J. Yliruusi (1992) "X-ray powder diffraction profile fitting in quantitative determination of two polymorphs from their powder mixture" *Int. J. Pharm.* **81**, 169–177.

182
82

Anexo 2

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NF 25

THE NATIONAL FORMULARY

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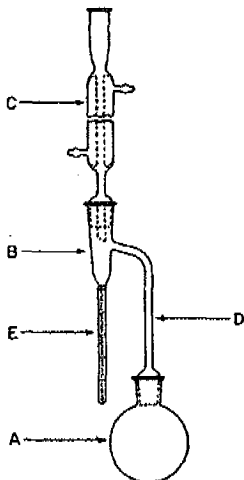
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THE UNITED STATES PHARMACOPEIAL CONVENTION
12601 Twinbrook Parkway, Rockville, MD 20852

METHOD II (AZEOTROPIC—TOLUENE DISTILLATION)

Apparatus—Use a 500-mL glass flask *A* connected by means of a trap *B* to a reflux condenser *C* by ground glass joints (see Figure).



Toluene Moisture Apparatus

The critical dimensions of the parts of the apparatus are as follows. The connecting tube *D* is 9 to 11 mm in internal diameter. The trap is 235 to 240 mm in length. The condenser, if of the straight-tube type, is approximately 400 mm in length and not less than 8 mm in bore diameter. The receiving tube *E* has a 5-mL capacity, and its cylindrical portion, 146 to 156 mm in length, is graduated in 0.1-mL subdivisions, so that the error of reading is not greater than 0.05 mL for any indicated volume. The source of heat is preferably an electric heater with rheostat control or an oil bath. The upper portion of the flask and the connecting tube may be insulated.

Clean the receiving tube and the condenser with chromic acid cleansing mixture, thoroughly rinse with water, and dry in an oven. Prepare the toluene to be used by first shaking with a small quantity of water, separating the excess water, and distilling the toluene.

Procedure—Place in the dry flask a quantity of the substance, weighed accurately to the nearest centigram, which is expected to yield 2 to 4 mL of water. If the substance is of a pasty character, weigh it in a boat of metal foil of a size that will just pass through the neck of the flask. If the substance is likely to cause bumping, add enough dry, washed sand to cover the bottom of the flask, or a number of capillary melting-point tubes, about 100 mm in length, sealed at the upper end. Place about 200 mL of toluene in the flask, connect the apparatus, and fill the receiving tube *E* with toluene poured through the top of the condenser. Heat the flask gently for 15 minutes and, when the toluene begins to boil, distill at the rate of about 2 drops per second until most of the water has passed over, then increase the rate of distillation to about 4 drops per second. When the water has apparently all distilled over, rinse the inside of the condenser tube with toluene while brushing down the tube with a tube brush attached to a copper wire and saturated with toluene. Continue the distillation for 5 minutes, then remove the heat, and allow the receiving tube to cool to room temperature. If any droplets of water adhere to the walls of the receiving tube, scrub them down with a brush consisting of a rubber band wrapped around a copper wire and wetted with toluene. When the water and toluene have separated completely, read the volume of water, and calculate the percentage that was present in the substance.

METHOD III (GRAVIMETRIC)

Procedure for Chemicals—Proceed as directed in the individual monograph preparing the chemical as directed under *Loss on Drying* (731).

Procedure for Biologics—Proceed as directed in the individual monograph.

Procedure for Articles of Botanical Origin—Place about 10 g of the drug, prepared as directed (see *Methods of Analysis* under *Articles of Botanical Origin* (561)) and accurately weighed, in a tared evaporating dish. Dry at 105° for 5 hours, and weigh. Continue the drying and weighing at 1-hour intervals until the difference between two successive weighings corresponds to not more than 0.25%.

(941) X-RAY DIFFRACTION

Every crystal form of a compound produces its own characteristic X-ray diffraction pattern. These diffraction patterns can be derived either from a single crystal or from a powdered specimen (containing numerous crystals) of the material. The spacings between and the relative intensities of the diffracted maxima can be used for qualitative and quantitative analysis of crystalline materials. Powder diffraction techniques are most commonly employed for routine identification and the determination of relative purity of crystalline materials. Small amounts of impurity, however, are not normally detectable by the X-ray diffraction method, and for quantitative measurements it is necessary to prepare the sample carefully to avoid preferred orientation effects.

The powder methods provide an advantage over other means of analysis in that they are usually nondestructive in nature (specimen preparation is usually limited to grinding to ensure a randomly oriented sample, and deleterious effects of X-rays on solid pharmaceutical compounds are not commonly encountered). The principal use of single-crystal diffraction data is for the determination of molecular weights and analysis of crystal structures at the atomic level. However, diffraction established for a single crystal can be used to support a specific powder pattern as being truly representative of a single phase.

Solids—A solid substance can be classified as being crystalline, noncrystalline, or a mixture of the two forms. In crystalline materials, the molecular or atomic species are ordered in a three-dimensional array, called a lattice, within the solid particles. This ordering of molecular components is lacking in noncrystalline material. Noncrystalline solids sometimes are referred to as glasses or amorphous solids when repetitive order is nonexistent in all three dimensions. It is also possible for order to exist in only one or two dimensions, resulting in mesomorphic phases (liquid crystals). Although crystalline materials are usually considered to have well-defined visible external morphologies (their habits), this is not a necessity for X-ray diffraction analysis.

The relatively random arrangement of molecules in noncrystalline substances makes them poor coherent scatterers of X-rays, resulting in broad, diffuse maxima in diffraction patterns. Their X-ray patterns are quite distinguishable from crystalline specimens, which give sharply defined diffraction patterns.

Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

In addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its own characteristic X-ray patterns, so does every solvate. Sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached. In some instances, these poly-

morphs and/or solvates show varying dissolution rates. Therefore, on the time scale of pharmaceutical bioavailability, different total amounts of drug are dissolved, resulting in potential bioequivalence of the several forms of the drug.

Fundamental Principles—A collimated beam of monochromatic X-rays is diffracted in various directions when it impinges upon a rotating crystal or randomly oriented powdered crystal. The crystal acts as a three-dimensional diffraction grating to this radiation. This phenomenon is described by Bragg's law, which states that diffraction (constructive interference) can occur only when waves that are scattered from different regions of the crystal, in a specific direction, travel distances differing by integral numbers (n) of the wavelength (λ). Under such circumstances, the waves are in phase. This condition is described by the Bragg's equation:

$$\frac{n\lambda}{2 \sin \theta} = d_{hkl}$$

in which d_{hkl} denotes the interplanar spacings and θ is the angle of diffraction.

A family of planes in space can be indexed by three whole numbers, usually referred to as Miller indices. These indices are the reciprocals, reduced to smallest integers, of the intercepts that a plane makes along the axes corresponding to three nonparallel edges of the unit cell (basic crystallographic unit). The unit cell dimensions are given by the lengths of the spacings along the three axes, a , b , c , and the angles between them, α , β , and γ . The interplanar spacing for a specific set of parallel planes hkl is denoted by d_{hkl} . Each such family of planes may show higher orders of diffraction where the d values for the related families of planes nh , nk , nl are diminished by the factor $1/n$ (n being an integer: 2, 3, 4, etc.). Every set of planes throughout a crystal has a corresponding Bragg's diffraction angle associated with it (for a specific λ).

The amplitude of a diffracted X-ray beam from any set of planes is dependent upon the following atomic properties of the crystal: (1) position of each atom in the unit cell; (2) the respective atomic scattering factors; and (3) the individual thermal motions. Other factors that directly influence the intensities of the diffracted beam are: (1) the intensity and wavelength of the incident radiation; (2) the volume of crystalline specimen; (3) the absorption of the X-radiation by the specimen; and (4) the experimental arrangement utilized to record the intensity data. Thus, the experimental conditions are especially important for measurement of diffraction intensities.

Only a limited number of Bragg's planes are in a position to diffract when monochromatized X-rays pass through a single crystal. Techniques of recording the intensities of all of the possible diffracting hkl planes involve motion of the single crystal and the recording media. Recording of these data is accomplished by photographic techniques (film) or with radiation detectors.

A beam passing through a very large number of small, randomly oriented crystals produces continuous cones of diffracted rays from each set of lattice planes. Each cone corresponds to the diffraction from various planes having a similar interplanar spacing. The intensities of these Bragg's reflections are recorded by either film or radiation detectors. The Bragg's angle can be measured easily from a film, but the advent of radiation detectors has made possible the construction of diffractometers that read this angle directly. The intensities and d spacings are more conveniently determined with powder diffractometers employing radiation detectors than by film methods. Microphotometers are frequently used for precise intensity measurements of films.

An example of the type of powder patterns obtained for four different solid phases of ampicillin are shown in the accompanying figure. These diffraction patterns were derived from a powder diffractometer equipped with a Geiger-Müller detector; nickel-filtered Cu K α radiation was used.

Radiation—The principal radiation sources utilized for X-ray diffraction are vacuum tubes utilizing copper, molybdenum, iron, and chromium as anodes; copper X-rays are employed most

commonly for organic substances. For each of these radiations there is an element that will filter off the K β radiation and permit the K α radiation to pass (nickel is used, in the case of copper radiation). In this manner the radiation is practically monochromatized. The choice of radiation to be used depends upon the absorption characteristics of the material and possible fluorescence by atoms present in the specimen.

Caution—Care must be taken in the use of such radiation. Those not familiar with the use of X-ray equipment should seek expert advice. Improper use can result in harmful effects to the operator.

Test Preparation—In an attempt to improve randomness in the orientation of crystallites (and, for film techniques, to avoid a grainy pattern), the specimen may be ground in a mortar to a fine powder. Grinding pressure has been known to induce phase transformations; therefore, it is advisable to check the diffraction pattern of the unground sample.

In general, the shapes of many crystalline particles tend to give a specimen that exhibits some degree of preferred orientation in the specimen holder. This is especially evident for needle-like or plate-like crystals where size reduction yields finer needles or plates. Preferred orientation in the specimen influences the relative intensities of various reflections.

Several specialized handling techniques may be employed to minimize preferred orientation, but further reduction of particle size is often the best approach.

Where very accurate measurement of the Bragg's angles is necessary, a small amount of an internal standard can be mixed into the specimen. This enables the film or recorder tracing to be calibrated. If comparisons to literature values (including compendial limits) of d are being made, calibrate the diffractometer. NIST standards are available covering to a d -value of 0.998 nm. Tetradecanol¹ may be used (d is 3.963 nm) for larger spacing.

The absorption of the radiation by any specimen is determined by the number and kinds of atoms through which the X-ray beam passes. An organic matrix usually absorbs less of the diffracted radiation than does an inorganic matrix. Therefore, it is important in quantitative studies that standard curves relating amount of material to the intensity of certain d spacings for that substance be determined in a matrix similar to that in which the substance will be analyzed.

In quantitative analyses of materials, a known amount of standard usually is added to a weighed amount of specimen to be analyzed. This enables the amount of the substance to be determined relative to the amount of standard added. The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed. Under these conditions a linear relationship between intensity and concentration exists. In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices.

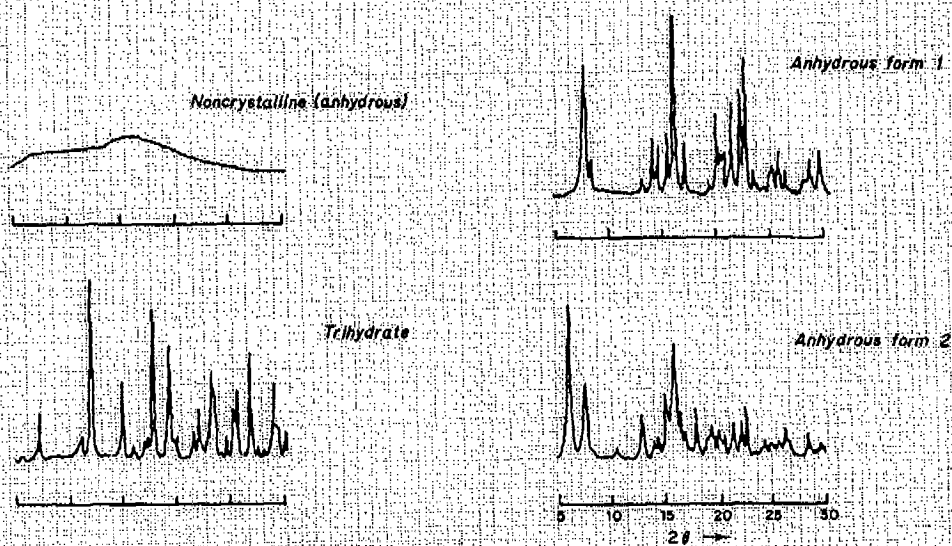
Identification of crystalline materials can be accomplished by comparison of X-ray powder diffraction patterns obtained by known materials with those of the unknown. The intensity ratio (ratio of the peak intensity of a particular d spacing to the intensity of the strongest maxima in the diffraction pattern) and the d spacing are used in the comparison. If a reference material (e.g., USP Reference Standard) is available, it is preferable to generate a primary reference pattern on the same equipment used for running the unknown sample, and under the same conditions. For most organic crystals, it is appropriate to record the diffraction pattern to include values in 2θ that range from as near zero degrees as possible to 40 degrees. Agreement between sample and reference should be within the calibrated precision of the diffractometer for diffraction angles (2θ values should typically be reproducible to ± 0.10 degrees) while relative intensities between sample and reference may vary considerably. For other types of samples (e.g., inorganic salts), it may be necessary to extend the 2θ region scanned to well beyond 40 degrees. It is generally sufficient to scan past the ten strongest reflections identified in the Powder Diffraction File.²

¹ Brindley, GW and Brown, G, eds., *Crystal Structures of Clay Minerals and Their X-ray Identification*, Mineralogical Society Monograph No. 5, London, 1980, pp. 318 ff.

² The International Centre for Diffraction Data, Newtown Square Corporate Campus, 12 Campus Boulevard, Newtown Square, PA 19073, maintains a file on more than 60,000 crystalline materials, both organic and inorganic, suitable for such comparisons.

184
184

185
185



Typical Powder Patterns Obtained for Four Solid Phases of Ampicillin

186
186

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. DC-015766-00008-0000

RECIBO OFICIAL DE CAJA : 7 - 98,202
FECHA : DICIEMBRE 3 DE 2007

Dep. 2020 NUECRLACIONE
Lvs. 379 FASENACIONALII
Folios: 37

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	48825361	03/12/2007	68,286,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	99,000.00
		TOTAL :	\$ 99,000.00

SON: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

060 4058-841001-3

82
187

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

✓ Abogado
EMILIO FERRERO

ASUNTO Radicación 04 - 016766
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 6 - 1852
 Folios 6

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒
No. Sol. Internacional PCT/EP02/08466
Fecha de Presentación Internal. Julio 30 de 2002

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 le comunica:

1. Documentos estudiados

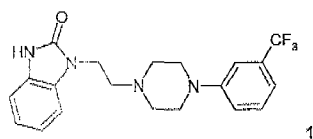
- 1.1. Descripción: Folios: 60 a 72 como se radico originalmente
1.2. Reivindicaciones: Folios: 73 a 75 como se radico originalmente
 Folios: 162 a 164 modificadas
1.3. Prioridad: EP 01118593.1 del 02 de Agosto de 2001
 EP 01130180.1 del 19 de Diciembre de 2001
1.4. Respuesta del solicitante Folios: 148 a 185

2. Objeto de la invención

Título de la solicitud: "POLIMORFO DE FLIBANSERINA Y PROCEDIMIENTO INDUSTRIAL PARA SU PREPARACION". Modificado en folio No. 152.

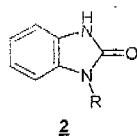
El objeto de la solicitud de la presente invención consiste en:

- En las Reivindicaciones 1 y 2: Un Polimorfo de Flibanserina 1:

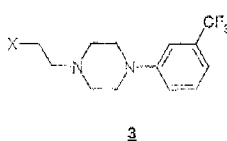


- En las Reivindicaciones de la 3 a la 6: Un procedimiento para la preparación industrial de la Flibanserina 1, caracterizado por:

(a) Reacción de una benzoimidazolona 2, de fórmula:



(b) Con una Piperazina de fórmula 3:



- En la Reivindicación 7: Composiciones farmacéuticas de un polimorfo A de la Flibanserina 1

El problema planteado en esta solicitud es proporcionar una nueva forma cristalina y estable del compuesto de Flibanserina que satisfaga los requisitos impuestos a sustancias farmacéuticamente activas.

Para solucionar este problema técnico la solicitud en estudio presenta un polimorfo de Flibanserina 1, un procedimiento para su preparación y sus composiciones farmacéuticas.

El objeto de la invención definido anteriormente se clasifico de acuerdo con la IPC: A61K 31/495, A61P 15/10, A61P 25/00

3. Respuesta a los argumentos del solicitante

- El solicitante pasa un nuevo capítulo reivindicatorio, y esta oficina lo acepta.

4. De la solicitud de Patente

4.1 Descripción (artículo 28 D. 486)

Esta Oficina se permite señalar que dentro de la descripción se encontró falta de sustento debido a que:

- No hay evidencia que permita concluir que el polimorfo de Flibanserina 1, su composición farmacéutica y su proceso de preparación, son explícitos y concretos en cuanto a las ventajas y/o el salto tecnológico de la solicitud con respecto al estado de la técnica.

4.2 Reivindicaciones (artículo 30 D 486)

- La Reivindicación 7 comprende una Composición Farmacéutica, la cual no se encuentra sustentada en el capítulo descriptivo.
- En las Reivindicaciones 3 y 5 las palabras y/o expresiones: "adecuado", "aproximadamente"; no son concisas y son muy amplias; por tanto no permiten delimitar la materia, allí a proteger.

Por lo anteriormente expuesto, es preciso requerir al interesado para que señale el verdadero alcance de su invención.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: Agosto 02 de 2001

Teniendo en cuenta la fecha indicada se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud; aclarando, que esta búsqueda se realizó únicamente para aquellas partes que parecen ser claras y/o concisas:

Nº	Documento	Título	Fecha de publicación
D1	EP 0526434	BENZIMIDAZOLONE DERIVATES AS 5-HT1A AND 5-HT2 ANTAGONISTS	Febrero 03 de 1993

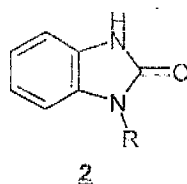
6. Análisis de patentabilidad (artículo 14 D486)

6.1 Novedad (artículo 16 D486)

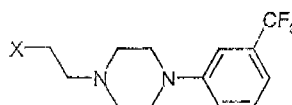
La Novedad se evaluó por comparación entre lo solicitado y lo encontrado en el estado de la técnica.

- En las Reivindicaciones de la 3 a la 6: Un procedimiento para la preparación industrial de la Flibanserina 1, caracterizado por:

(a) Reacción de una benzoimidazolona 2, de fórmula:



(b) Con una Piperazina de fórmula 3:



3

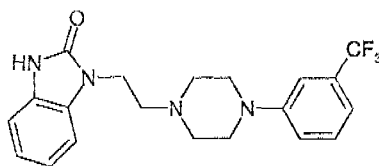
CARACTERISTICAS ESENCIALES DE LA SOLICITUD COLOMBIANA No. 04-016766	D1 = EP 0526434
Un procedimiento para la preparación industrial de la Flibanserina <u>1</u>, caracterizado por: (a) Reacción de una benzoimidazolona <u>2</u>, de fórmula: <chem>O=C1NC2=CC=CC=C2N1R</chem> <u>2</u> (b) Con una Piperazina de fórmula <u>3</u>: <chem>XCCN1CCN(C1)c2ccc(C(F)(F)F)cc2</chem> <u>3</u>	Un procedimiento para preparar compuestos de fórmula (I); el cual comprende: (a) Reacción de una benzoimidazolona (b) Con una Piperazina Folios 137

Teniendo en cuenta el objeto de la invención y la materia descrita en la anterioridad D1, esta dependencia se permite señalar que existe afectación al requisito de Novedad, ya que en la anterioridad se divulga el procedimiento para preparar compuestos de fórmula (I), el cual cubre la reivindicación independiente de la presente solicitud, resultando idéntico al publicado en el estado de la técnica. Es decir que el procedimiento para preparar a nivel industrial la Flibanserina 1, no es nuevo y ya se encuentra revelado en el estado de la técnica.

6.2 Nivel inventivo (artículo 18 D486)

El Nivel Inventivo se evaluó por comparación entre lo solicitado y lo encontrado en el estado de la técnica.

- En las Reivindicaciones 1 y 2: Un Polimorfo de Flibanserina 1:



1

- En la Reivindicación 7: Composiciones farmacéuticas de un polimorfo A de la Flibanserina 1

CARACTERÍSTICAS ESENCIALES DE LA SOLICITUD COLOMBIANA No. 04-016766	D1 = EP 0526434
Un Polimorfo de Flibanserina <u>1</u>: Máximo endotérmico: 161°C	Un compuesto de fórmula (I): En donde: R1, R2, R3: Hidrógeno A: ausente B: Alquilo C2-6 m: 2 n: 2 R4: Arilo opcionalmente sustituido por CF3 Punto de fusión: 230-231°C Folios 138, 140 y 141
Composiciones farmacéuticas del polimorfo de Flibanserina <u>1</u>	Composiciones farmacéuticas de acuerdo a los compuestos de fórmula (I) Folios 139 y 140

Un polimorfo de Flibanserina 1:

Comparando las características esenciales de la solicitud, las cuales corresponden a un polimorfo de Flibanserina 1; el documento del estado de la técnica más cercano es D1, ya que divulga un compuesto de fórmula (I) el cual es específicamente la Flibanserina de fórmula 1-[2-(4-(3-Trifluoromethyl-phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one la cual se encuentra en los folios 138 y 141; el cual presenta una actividad tanto agonista como antagonista de los receptores 5-HT1a y 5-HT2 y la cual se usa para la depresión, esquizofrenia, enfermedad de Parkinson, ansiedad, alteraciones del sueño, trastornos sexuales y mentales, deterioro de la memoria asociado con la edad, trastornos del deseo sexual.

La única diferencia con D1 de la presente solicitud es, que en la solicitud el polimorfo de Flibanserina 1 presenta un máximo endotérmico de 161°C; mientras que en D1 el punto de fusión de la Flibanserina de fórmula 1-[2-(4-(3-Trifluoromethyl-phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one es de 230-231°C. Pero esto no parece conceder un efecto técnico inesperado ya que el objeto de la solicitud corresponde simplemente a una forma cristalina específica de una molécula conocida desde el inicio de la década de los 90; por lo tanto no hay evidencia que permita concluir que el polimorfo de Flibanserina 1 y sus composiciones farmacéuticas, presentan una ventaja inesperada con respecto al estado de la técnica y además, que para el experto en la materia basándose en este documento y en los fundamentos de la química orgánica, sabe que una sustancia es capaz de cristalizar en diferentes formas, pues resulta indiscutible que al variar las condiciones de cristalización de un producto – como los solventes utilizados – se producirán cristales que presentan características de difracción de rayos X distintas a la forma física cristalina normal o a la presentación amorfa; además la obtención de estos cristales es una habilidad intrínseca de las sustancias que se deriva directamente de las condiciones de cristalización, por ello, el separar y caracterizar dichos productos por todas las variables que intervienen en el proceso de elaboración de la mencionada forma cristalina son conocidas y hacen parte del estado de la técnica; de manera que un experto en la materia lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

102

192

Puesto que el Problema Técnico Objetivo fundamental de la Invención es proporcionar una nueva forma cristalina y estable del compuesto de Flibanserina que satisfaga los requisitos impuestos a sustancias farmacéuticamente activas; la invención presenta una alternativa a los compuestos del estado de la técnica en (D1), por falta de datos que evidencien el nivel inventivo.

Así que, el problema planteado en la solicitud, sería solucionado fácilmente por el experto en la materia ya que hubiese sido obvio obtener un polimorfo de Flibanserina 1 similar y/o alternativo teniendo en cuenta D1. Por tanto, Carece de Nivel Inventivo: el polimorfo de Flibanserina 1 y sus Composiciones Farmacéuticas.

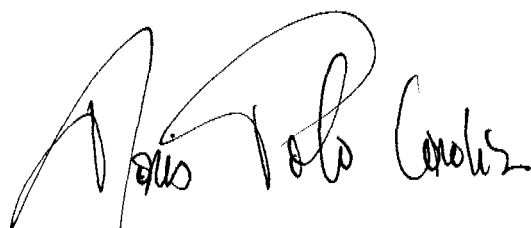
7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	EP 0526434	De la 3 a la 6 y la 1, 2 y 7	Novedad y 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 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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



DORIS ELENA POLO CORDOBA
Jefe de División de Nuevas Creaciones (E)

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

14/05/2011

CONCEPTO TÉCNICO No. 3550	EXAMINADOR TÉCNICO Código No. 202080
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