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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 07063490
Asunto : Solicitud de patente para: **FORMAS DE DOSIFICACIÓN FARMACÉUTICA SÓLIDA ADMINISTRABLES POR VÍA ORAL CON LIBERACIÓN MODIFICADA**
Solicitante : BAYER SCHERING PHARMA AG
Clase : A61K 009/020, A61K 009/028, A61K 031/5377, A61P 007/002
Fecha solicitud : 22 de junio de 2007

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **8761** notificado por fijación en lista del 27 de mayo de 2011.

2. Mediante oficio No. **8761** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio son las siguientes:

2.1 Reivindicaciones

Considera el Examinador que el término "sal inorgánica soluble en agua" presente en la reivindicación 1 da lugar a un alto número de posibilidades, lo cual no permite limitar la invención. Se solicita restringir el alcance a una generalización razonable.

2.2 Nivel inventivo

Para la evaluación de este requisito, el Examinador ha citado tres documentos D1: ES 2237497, D2: US 6294201 y D3: US 4765989. Se considera que la combinación de los

documentos D1 y D3 afecta el nivel inventivo de la reivindicación 1 y que la combinación de los documentos D1 y D2 afecta el nivel inventivo de la reivindicación 9.

3. Respuesta a las objeciones

Con el ánimo de superar las objeciones formuladas por el Examinador, se presenta en esta oportunidad las siguientes modificaciones, aclaraciones y argumentos:

3.1 Modificación a una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 8 reivindicaciones.

Así, siguiendo las amables sugerencias del Examinador se ha modificado la reivindicación 1 para indicar que la capa de ósmosis contiene de 10% a 40% de una sal inorgánica soluble en agua tal como cloruro de sodio. Las demás alternativas para la sal inorgánica no han sido incluidas.

Por otra parte, no se incluye en esta oportunidad el grupo de reivindicaciones 9 a 16.

Consecuentemente, la reivindicación 1 constituye una generalización razonable del contenido de la descripción y la objeción formulada en este sentido se ve superada.

Finalmente, deseamos poner de presente, que a pesar de eliminar materia del pliego reivindicatorio, mi representada no renuncia a la protección que pueda obtener sobre la misma y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

3.2 Argumentos a favor del nivel inventivo de la solicitud

Tal como se indicó anteriormente, el grupo de reivindicaciones 9 a 16 no se incluye en esta oportunidad, por lo que la objeción por falta de nivel inventivo formulada con base en el documento D2, se debe tener por superada.

Por otra parte, respetuosamente nos apartamos de la posición del Examinador cuando afirma que la combinación de las enseñanzas de los documentos D1 y D3 afecta el nivel

inventivo de las reivindicaciones 1 a 8. Lo anterior, por cuanto la forma de de dosificación farmacéutica sólida de liberación modificada reivindicada en la presente solicitud no resulta obvia, para la persona medianamente versada en la materia, en vista de las enseñanzas D1 y D3.

Los argumentos del Examinador se basan en una posibilidad de éxito razonable, teniendo en cuenta que D3 enseña que los sistemas de liberación son útiles para la entrega de un agente activo, soluble o escasamente soluble. D3 dirige el uso del dispositivo de manera general, a medicamentos insolubles en agua y revela muchos agentes benéficos con un amplio rango de tasas de liberación. En las columnas 3 y 4, D3 discute los objetivos de la invención pero no revela datos científicos que demuestren que una persona medianamente versada en la materia puede esperar razonablemente que todos los objetivos de la invención son obtenidos.

Cuando se toma en consideración los resultados experimentales de D3, la persona medianamente versada en la materia observa que solamente se prueban tres medicamentos. Consecuentemente, una expectativa razonable de éxito para el 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida (rivaroxaban) no puede ser concluida a partir de las enseñanzas de D3, el cual comprende objetivos de gran alcance soportados en pruebas experimentales llevadas a cabo con sólo 3 medicamentos. La obviedad de un objeto requiere una expectativa de éxito razonable que se extienda a medicamentos no nombrados en la anterioridad.

D3 además no revela datos que permitan predecir el comportamiento del rivaroxaban. D3 solamente reporta resultados experimentales para tres medicamentos en donde dos de ellos -prazosin clorhidrato y doxazosin mesilato- son sales con una solubilidad significativamente mayor respecto a la solubilidad del rivaroxaban. Estos dos medicamentos revelados en D3 son aproximadamente **200 a 1000 veces más soluble** en agua que el rivaroxaban. Específicamente mientras el rivaroxaban es soluble en agua aproximadamente 7 mg **por litro**, el prazosin clorhidrato es soluble en agua aproximadamente 1,4 mg **por mililitro** a un pH de 3,5 y el doxazosin mesilato es soluble en agua aproximadamente 3,8-6,2 mg **por mililitro**. Evidencia de estas solubilidades de encuentra en el Sigma Product Information para el prazosin clorhidrato (July 12, 1997) y Grcman et al., J Thermal Analysis and Calorimetry, vol. 68 (2002), 373-387 (ver resumen, última línea par la solubilidad del doxazosin mesilato).

Es posible asumir el éxito de un sistema de liberación osmótico a partir las características de solubilidad del medicamento. En este sentido, dado que dos de los tres medicamentos probados en D3 tienen una solubilidad mucho mayor respecto al rivaroxaban,

los resultados con estos dos medicamentos no resultan razonablemente predecibles para dicho compuesto.

Por lo anterior, el único ejemplo en D3 en el cual el compuesto tiene baja solubilidad es aquel llevado a cabo con nifedipina. Tal como puede establecer el Examinador, un único ejemplo no puede resultar suficiente para la persona medianamente versada en la materia y ésta no podría predecir de manera obvia el éxito con cada medicamento insoluble. Por consiguiente, D3 no establece una probabilidad razonable de éxito de la modificación del arte previo para obtener la presente invención.

De otro lado, D1 no provee la expectativa de éxito faltante. Este documento no contiene ninguna enseñanza o sugerencia que conlleve a una expectativa razonable para un sistema osmótico de dos cámaras.

D1 describe de manera general y amplia medicamentos y composiciones farmacéuticas que contienen uno de los compuestos allí descritos y uno o más auxiliares farmacológicamente aceptables. No se hace referencia a una composición farmacéutica especial que contenga rivaroxaban. Adicionalmente, D1 no enseña o sugiere un sistema osmótico de liberación.

Consecuentemente, aunque la persona medianamente versada en la materia combinase las enseñanzas de los documentos D1 y D3 no podría derivar de manera obvia la presente invención, ya que no podría establecer el éxito de un sistema osmótico como el reivindicado para el compuesto rivaroxavan, cuando dichos documentos no comprenden enseñanzas o sugerencias claras sobre esta solución técnica.

En conclusión, ni D1 ni D3 resultan anterioridades válidas capaces de afectar el nivel inventivo de la presente solicitud al no contener enseñanzas claras que individualmente o en combinación, le permitan a una persona medianamente versada en la materia, obtener de manera obvia la presente invención.

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

5. Anexos

- Nuevo pliego reivindicatorio conformado por 8 reivindicaciones
- Formulario de modificaciones en solicitud pendiente

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- Sigma Product Information para el prazosin clorhidrato (July 12, 1997)
- Grcman et al., J Thermal Analysis and Calorimetry, vol. 68 (2002), 373-387

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-15846-845-019-8

COLO-14033-841-046-1

 JMS\JMS\ID-198980\WPC15846

No. M-2011-198980\JMS



Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1

SOLICITUD DE:

☐ Corrección de Error Material

☒ Modificación a una solicitud

2

SOLICITANTE

Nombre: **BAYER SCHERING PHARMA AG**
Sociedad constituida y existente bajo las leyes de Alemania.

Dirección: **Muellerstrasse 178,
13353 Berlín,
Alemania**

Domicilio: **Berlín,
Alemania**

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: **LUZ CLEMENCIA DE PÁEZ**
Dirección: **Carrera 4ª. No. 72-35**
Teléfono: **347 36 11**
Fax: **211 86 50**
E-mail: **clientes@cavelier.com**
Domicilio: **Bogotá, Colombia.**

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Cual _____
Número **35.456.344** T. P. **23.555**

4

Número de expediente: 07.063.490

5

Descripción de la corrección o modificación solicitada:

Presento nuevo capítulo reivindicatorio compuesto por 8 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

6

Comprobante de pago No. Fecha:

7

Anexos

☐ Comprobante de pago de la tasa por \$118.000, por concepto de modificaciones.

☐ Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por

☐ Poderes, si fuere el caso

☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8

NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA: Luz Clemencia De Páez

C.C. 35.456.344 de Usaquén T.P.A. 23.555

JMS

Reivindicaciones

1. Forma de dosificación farmacéutica sólida de liberación modificada administrable por vía oral, compuesta por un sistema osmótico bicameral que comprende

un núcleo con una capa de principio activo, que contiene:

- 1 a 40% de 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida (I),
- 50 a 95% de óxido de polietileno;

una capa de ósmosis que contiene:

- 40 a 90% de óxido de polietileno,
- 10 a 40% de una sal inorgánica soluble en agua tal como cloruro de sodio.

y una cubierta compuesta de acetato de celulosa o una mezcla de acetato de celulosa y polietilenglicol, donde la cubierta es permeable al agua e impermeable para los componentes del núcleo; y presenta al menos un orificio.

2. Forma de dosificación farmacéutica según la reivindicación 1, caracterizada porque el ingrediente activo (I) está presente en forma cristalina.

3. Forma de dosificación farmacéutica según la reivindicación 2, caracterizada porque el ingrediente activo (I) está presente en forma micronizada.

4. Forma de dosificación farmacéutica según la reivindicación 2, caracterizada porque el ingrediente activo (I) está presente en forma hidrofílica.

5. Forma de dosificación farmacéutica según la reivindicación 3, caracterizada porque el ingrediente activo (I) está presente en forma amorfa.

6. Forma de dosificación farmacéutica según las reivindicaciones 1 a 5, caracterizada en que el óxido de polietileno en la capa del ingrediente activo presenta una viscosidad de 40 a 100 mPa·s (solución acuosa al 5%, 25°C), y el óxido de polietileno en el núcleo en la capa de ósmosis presenta una viscosidad de 5000 a 8000 mPa·s (solución acuosa al 1%, 25°C).

7. Forma de dosificación farmacéutica según las reivindicaciones 1 a 6, caracterizada por que la capa de ósmosis comprende cloruro de sodio.

8. Procedimiento para la fabricación de un sistema osmótico bicameral como se define en las reivindicaciones 1 a 7, caracterizado porque:

- los componentes de la capa de principio activo se mezclan y se granulan; y
- los componentes de la capa de ósmosis se mezclan y se granulan;
- subsecuentemente ambos granulados se comprimen en una prensa de comprimidos bicapa hasta formar un comprimido bicapa;
- se recubre después el núcleo así formado con la cubierta; y
- se proporciona a la cubierta uno o varios orificios en su parte del principio activo.



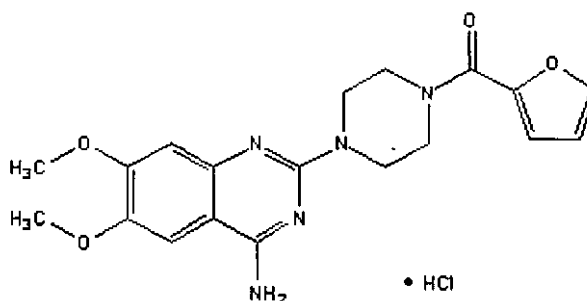
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Product Information

PRAZOSIN HYDROCHLORIDE
Sigma Prod. No. P7791

CAS NUMBER: 19237-84-4

SYNONYMS: CP-12299-1; Deprazolin;
Furazosin Hydrochloride; Hypovase;
Hypovasole; 1-(4-Amino-6,7-Dimethoxy-
2-Quinazolinyl)-4-(2-
Furanylcarbonyl)Piperazine
Hydrochloride; 1-(4-Amino-6,7-
Dimethoxy-2-Quinazolinyl)-4-(2-
Furoyl)Piperazine Monohydrochloride;
Minipress; Peripress; Sinetens¹



PHYSICAL DESCRIPTION:

Appearance: White with a yellow cast powder.²

$E^{1\%}_{1\text{cm}}$ (247 nm) = 1470 (aqueous acid)⁴

$E^{1\%}_{1\text{cm}}$ (331 nm) = 281 (aqueous acid)⁴

$E^{1\%}_{1\text{cm}}$ (252 nm) = 1642 (aqueous alkali)⁴

$E^{1\%}_{1\text{cm}}$ (345 nm) = 150 (aqueous alkali)⁴

$E^{mM}_{1\text{cm}}$ (329.5-330 nm) = 11.3⁵

$E^{mM}_{1\text{cm}}$ (246.8-248 nm) = 57.3⁵

pK_a = 6.5⁴

Fluorescence Spectroscopy (acid): 330 nm (excitation),

390 nm (emission); 335 nm (excitation), 415 nm (emission).⁶

Melting Point: 264°C (with decomposition)⁷

Molecular Formula: $C_{19}H_{21}N_5O_4 \cdot HCl$

Molecular Weight: 419.9

METHOD OF PREPARATION:

Prazosin HCl is synthetically prepared.⁸ Methods of analysis including, Thin-Layer chromatography, HPLC, IR, NMR and mass spectrometry have been reported.^{3,4,6,9} Methods of synthesis have been reported.^{3,9}

STABILITY / STORAGE AS SUPPLIED:

Prazosin Hydrochloride should be stable for at least two years when stored desiccated at room temperature and protected from the light.²

PRAZOSIN HYDROCHLORIDE
Sigma Prod. No. P7791

SOLUBILITY / SOLUTION STABILITY:

Prazosin Hydrochloride is slightly soluble in isotonic saline¹⁰; The approximate solubilities in various

solvents (mg/ml, ambient temperature) is: water (about pH 3.5), 1.4; ethanol, 0.84; methanol, 6.4; dimethylformamide, 1.3; dimethylacetamide, 1.2; chloroform, 0.041; acetone, 0.0072.³ It can be dissolved in deionized water at 1 mg/ml with the application of heat (clear, colorless to very slightly hazy solutions results).² Clear solutions of 50 mg/ml each were prepared in ethanol plus 1 drop of 4 N ammonium hydroxide and in methanol plus 6 drops of 1 N hydrochloric acid with application of heat for both.² Prazosin hydrochloride is not soluble in DMSO.⁸ Solutions up to 11.9×10^{-5} M in 0.2 M Tris-HCl buffer, pH 7.4 were stored at 4°C for one day.¹¹ Since no other solution stability information may be available, solutions are recommended to be freshly prepared and protected from light.

USAGE / APPLICATIONS:

Prazosin suppressed the clinical and histological expression of experimental autoimmune encephalomyelitis (EAE) in the Lewis rat supporting the idea that antagonists of adrenergic receptors can modulate the expression of this disease in the Lewis rat.¹²

GENERAL NOTES:

Prazosin hydrochloride, a quinazole derivative, is the first of a new chemical class of antihypertensive compounds. It is a very potent and selective α_1 -adrenergic antagonist (affinity for α_1 receptors is about 1000-fold greater than for α_2). It reduces peripheral resistance and blood pressure by vasodilation of peripheral vessels (by blockade of α_1 -adrenergic receptors) in arterioles and veins without increasing the heart rate or significantly impairing sympathetic functions.¹³⁻¹⁶ The vasodilator effect may be related not only to the direct relaxant action on vascular smooth muscle but to the blockade of postsynaptic α -adrenoceptors.¹⁰ Prazosin is a potent inhibitor (1 mM-0.1 mM) of cyclic nucleotide phosphodiesterases.¹⁶ The effects of prazosin may be related to its increase of intracellular levels of cyclic AMP at vascular sites and intracellular levels of cyclic GMP at cholinergic receptor sites in the heart.¹⁶ Doses for injection and for oral administration for laboratory animals with cited references have been reported.¹⁷ Prazosin is highly bound (92-97%) to human plasma proteins, i.e. albumin and α_1 -acid glycoprotein; the extent of binding is independent of drug concentration.⁶ The pharmacokinetics, metabolism and pharmacology have been reported.^{3,6,9,14-16,18,19}

REFERENCES:

1. Sigma Material Safety Data Sheet
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PRAZOSIN HYDROCHLORIDE
Sigma Prod. No. P7791

REFERENCES: (continued)

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SOME PHYSICO-CHEMICAL PROPERTIES OF DOXAZOSIN MESYLATE POLYMORPHIC FORMS AND ITS AMORPHOUS STATE

M. Grčman¹, F. Vrečer¹ and A. Meden²

¹Krka, d.d., Novo mesto, Research and Development Division, Novo mesto, Slovenia

²University of Ljubljana, Faculty of Chemistry and Chemical Technology, Ljubljana, Slovenia

Abstract

Seven polymorphic modifications of doxazosin mesylate, designed as forms A, D, E, F, G, H, I, and the amorphous state were studied by thermal methods (TG and DSC), temperature resolved X-ray powder diffractometry, hot stage and scanning electron microscopy and by FT-IR spectroscopy. Amorphous form was obtained either by fast evaporation of the solvent or by fast cooling of the melt in the DSC. Polymorphs A and F were found to be stable in the temperature range from room temperature to their melting points at 277.9 and 276.5°C, respectively. Form G, which melts at 270.8°C, was found to be hygroscopic. Polymorph D undergoes irreversible solid–liquid–solid phase transition at 235.5°C to polymorph I which melts at 274.9°C. Form H, which melts at 258.0°C, was found to be unstable at high temperatures. DSC examinations revealed that form H is irreversibly transformed to polymorph F during heating above the temperature of about 240°C. The amorphous state was found to be stable at room temperature but when heating above the glass transition ($T_g=144.1^\circ\text{C}$) it crystallizes at 221.6°C, what leads into a mixture of polymorphic forms. The new polymorphic form designed as E was identified in the mixture. The polymorph E is converted by heating to the more stable form F. The solubilities at 25°C for forms A, and F in methanol are 3.5 and 7.7 mg mL⁻¹ and in water they are 3.8 and 6.2 mg mL⁻¹, respectively.

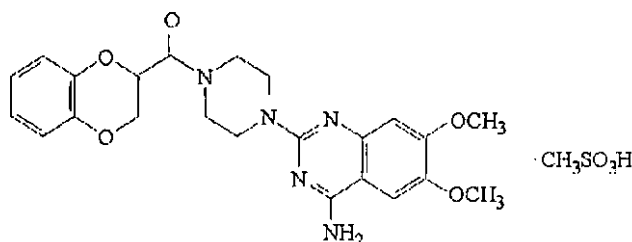
Keywords: amorphous state, doxazosin mesylate, polymorphic forms, stability, thermal characterization

Introduction

Polymorphism is the ability of the substance to crystallize in different crystalline states. Different crystalline forms of the same compound are called polymorphs or crystalline modifications. The expression pseudo-polymorphism applies to hydrates and solvates as the result of compound formation with the solvent [1]. Many pharmaceutical solids can exist also in the amorphous physical state. The amorphous state is characterized by solidification in a non-ordered, liquid-like state. Amorphous substances are generally hygroscopic, have a higher solubility and bioavailability, but they are very often chemically less stable and they tend to be transformed into crystalline forms upon storage. The transitions are generally fast at temperatures above the

glass transition point [2]. It is well known from the literature that polymorphism of drugs must be considered as an important preformulation parameter, especially because of a different biopharmaceutical and stability properties exhibited by different polymorphic forms. The results of the study of physico-chemical parameters of different polymorphic forms of certain substance enable us to predict and explain different behaviour of substances during the technological processing. Different strategies for a systematic study of polymorphism can be applied. They usually involve a combination of techniques such as DSC, TG, thermomicroscopy, X-ray diffraction, solid state NMR, IR and Raman spectroscopy [3–5].

The compound 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl piperazine monomethanesulfonate (DM) Scheme 1, which is known under the international name as doxazosin mesylate, is a new generation of α_1 receptor blocking agent and is used for the treatment of various type of hypertension.



Scheme 1 Chemical structure of DM

Literature data show that DM can crystallize in different polymorphic forms [6–12]. Polymorphic forms described in literature are designed differently: form A [6, 11]; B, C [11]; form D [6], crystalline form [10]; Form I [7]; Form II [8]. Polymorphic forms described in this study are designed as follows: A and D [6], F for crystalline form [10], G for Form I [7], H for Form II [8], E and I for new polymorphs detected during our thermal investigations.

In the present study we investigated the polymorphism of DM, together with the ranges of stability of the relevant crystalline forms and of the amorphous form. The DM polymorphs were characterized by determining their melting points, IR spectra, X-ray powder diffraction patterns, thermal behaviour, microscopic techniques and also by some solubility measurements.

Experimental

Preparation of the forms

Commercial samples from Supplier 1 (forms A and D), Supplier 2 (form F), Supplier 3 (form G) and Supplier 4 (form H) were used. Form I was obtained by thermal method.

Sample a: Amorphous form of DM – obtained by spray drying or freezing

Sample b: Amorphous form after heating under controlled conditions in the DSC furnace through the crystallization exotherm (245°C) and cooling back to the room temperature (Fig. 8)

Sample c: Amorphous form after heating under controlled conditions in the DSC furnace through the crystallization exotherm and to the end of the first endotherm (265°C) and cooling back to the room temperature (Fig. 8)

The amorphous form was prepared as follows:

Fast cooling in the DSC

Crystalline doxazosin mesylate was heated in an open aluminium sample pan under dynamic nitrogen atmosphere just above the melting temperature and the melt was solidified by fast cooling to room temperature.

Spray drying method

Crystalline doxazosin mesylate was dissolved in methanol, clear solution was filtered through a 0.5 µm membrane filter (Millipore type FH), the solution was spray dried using Büchi 190 Mini Spray Dryer at the following conditions: the flow rate of air was 800 mL min⁻¹, the inlet air temperature was 92 and the outlet air temperature was 56°C. All the samples were chromatographically pure.

Methods

Thermal analysis

DSC scans were recorded with a Perkin Elmer DSC-7 Thermal Analyzer–Pyris Software. Samples of approx. 3 mg were heated between 30 and 290°C under nitrogen atmosphere in aluminium DSC open pans at the heating rate of 10°C min⁻¹. The instrument was calibrated using extrapolated onset temperatures and associated heat of the fusion endotherms of indium and zinc pure standards, heated at the same conditions, as used for the samples.

TG curves were recorded with a Perkin Elmer TGA 7 Thermogravimetric Analyser–Pyris Software. Samples of approx. 20 mg were heated under the nitrogen atmosphere between 30 and 270°C. The instrument was calibrated by using two standards, alumel and nickel, whose magnetic transition temperatures are 163 and 354°C, respectively.

Each thermoanalytical experiment was repeated at least three times.

Hot stage microscopy

A Mettler FP-90 Central Processor with Mettler FP82HT–Hot Stage Cell were used. Microscopic observations of glassy doxazosin mesylate exposed under selected temperature program were performed with a polarized light microscope Olympus BX 50 coupled with equipment for recording microphotographs (PM-20 Olympus). FP82HT–Hot Stage Cell was calibrated by using two standards, benzoic acid and caffeine.

FT-IR spectrometry

FT-IR spectra were recorded over a wavenumber range from 4000 to 400 cm^{-1} with a Perkin Elmer FT-IR Spectrometer 1720 X, at a resolution of 4 cm^{-1} . Drift accessory with a micro sampling cup was used for scanning the spectra. In the diffuse reflectance (Drift) technique the sample to be examined is dispersed in a matrix of a powdered alkali halide and placed in a sample cup in the diffuse reflectance accessory.

X-ray powder diffraction

X-ray powder diffraction patterns under ambient conditions were collected on a Siemens D-5000 θ - θ diffractometer using graphite monochromatized (secondary side) CuK_α radiation ($\lambda=1.54178 \text{ \AA}$). The 2θ range was $5\text{--}32^\circ$, step size 0.02° , integration time 10 s/step, divergence and receiving slit set to constant (6 mm) length of the illumination of the sample and the receiving slit was 0.2 mm. The X-ray powder diffraction patterns at elevated temperatures were performed on the same instrument equipped with a HTK-16 high-temperature chamber. The instrumental settings were the same as those of the ambient temperature measurements except for the range ($5\text{--}25^\circ 2\theta$), step size (0.04°) and integration time (4 s/step). Data collection at a given temperature thus took about 33 min and the samples were heated at 5°C min^{-1} between the measurements.

Scanning electron microscopy

The shape and the surface appearance of the amorphous and crystalline forms of DM were observed with a scanning electron microscope (SEM, JSM-U2; Jeol, Tokyo, Japan). The samples were prepared by shadowing with carbon and gold/palladium and observed with the secondary electron technique.

Solubility measurement

Solubility in methanol and in water of the polymorphic forms A and F was determined as follows: an excess amount of each form (1000 mg) and 50 mL of purified water or methanol were placed in an Erlenmeyer flask with a glass stopper. The flasks were placed on a shaker and mechanically shaken for 30 h at a rate of 120 strokes per min. An aliquot of each solution was withdrawn and filtered through a $0.5 \mu\text{m}$ Millipore filter. The solubility of each polymorphic form was determined by measuring the absorbance at a wavelength of 246 nm using an UV spectrophotometer Perkin Elmer. Under these conditions no degradation of the drug was observed by HPLC.

Results and discussion

DSC curves of six doxazosine mesylate polymorphs are presented in Fig. 1. By TG curves of the crystal modifications A, D, F, H and I (not shown) it was proved that these DM polymorphs were non-solvated forms.

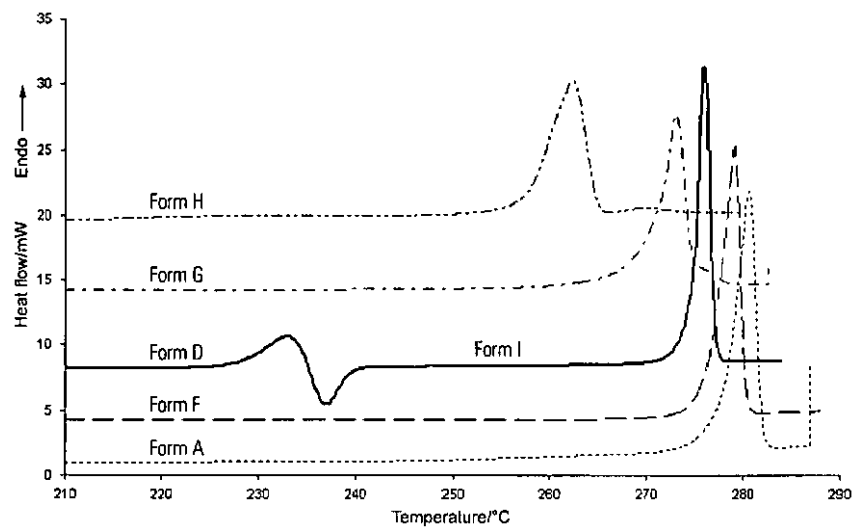


Fig. 1 DSC curves of polymorphic forms A, D, F, G, H and I in the temperature range from 210 to 280°C

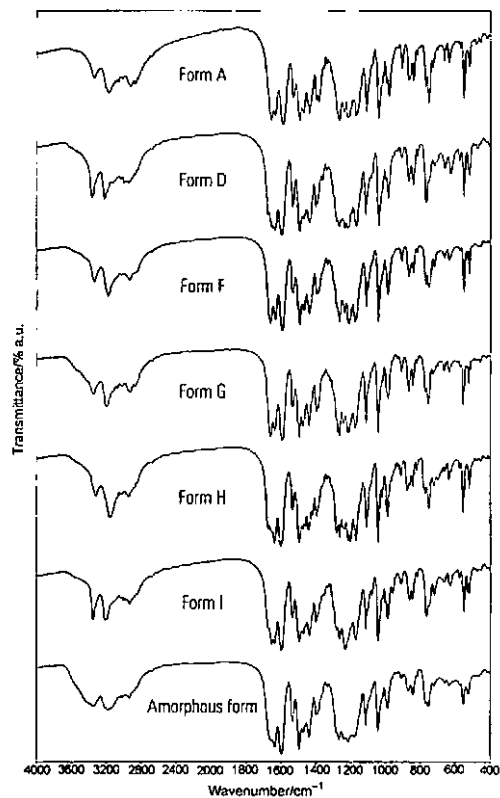


Fig. 2 FT-IR spectra of polymorphic forms A, D, F, G, H, I and the amorphous form

FT-IR spectra of different polymorphs were scanned in KBr pellets and they were also acquired by DRIFT technique which excludes practically any mechanical stress during preparation of the samples and scanning. FT-IR spectra (Fig. 2) show differences among different polymorphic forms in the whole spectral region; characteristic peaks in the FT-IR spectrum of individual crystalline modifications are listed in Table 1.

Table 1 Characteristic FT-IR peaks of DM different polymorphic forms

Modification	Characteristic peaks/cm ⁻¹
A	3347, 1357, 1328, 998, 983
D	3374, 3228, 1677, 1364, 769
F	3343, 3183, 1663, 1178
G	3349, 3209, 1661, 985
H	3324, 3164, 1460, 1444, 1396, 1203, 878
I	3355, 3219, 1233, 958, 766
E	3340*, 1666*, 1176*, 746

*Shifted peaks characteristic of the form F

X-ray powder diffraction patterns of the crystalline forms A, D, F, G and H (Fig. 3) are similar to those reported in literature [6–8, 10]. Pure crystalline forms A, D, F, G, H and the previously unknown form I were also investigated by high-temperature X-ray powder diffraction. Forms A, F, G, H and I did not show any changes up to 240–250°C when the thermal decomposition started.

Table 2 Thermal data

Modification	Melting		Transition	Residual solvents/water Δm (30–200°C)/%
	$T_{onset}/^{\circ}\text{C}$ ±95% c.i.	$\Delta H/\text{kJ mol}^{-1}$ ±95% c.i.	$T_{onset}/^{\circ}\text{C}$ ±95% c.i.	
A	277.9±0.2	60.1±0.3		0.2
D	228.0±0.3		235.5±0.3	0.4
F	276.5±0.2	55.1±0.3		0.1
G	270.8±0.2	55.8±0.5		2.8
H	258.0±0.2	50.4±0.5		0.1
I	274.9±0.3	43.8±0.2		
E	260.5±0.2			

DSC curves of forms A and F show only melting peaks at 277.9 and at 276.5°C, respectively. The heat of fusion of form A is by 5.0 kJ mol⁻¹ higher than that of form F (Table 2). The higher melting point of form A indicates that it is the more thermody-

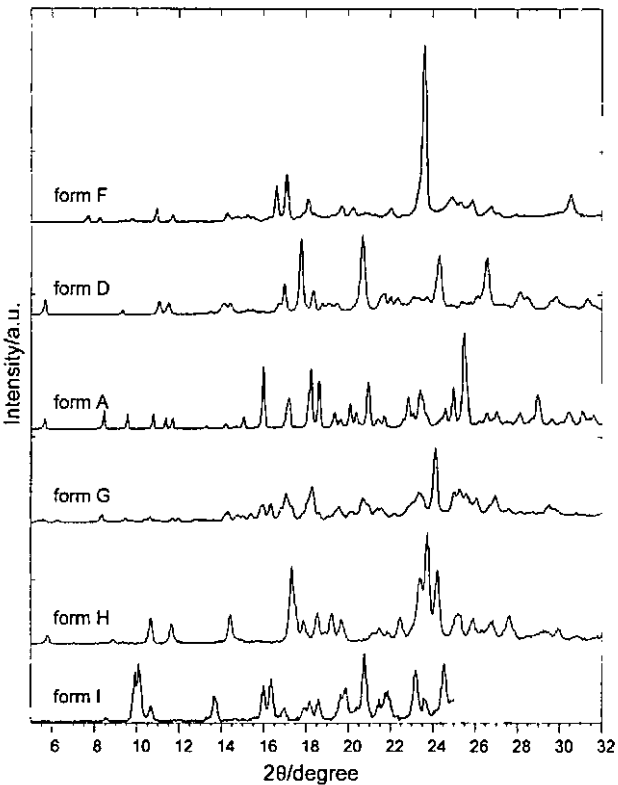


Fig. 3 X-ray powder diffraction patterns of polymorphic forms A, D, F, G, H and I at room temperature. Form I was measured after the transformation and cooling in the HTK chamber at a shorter range

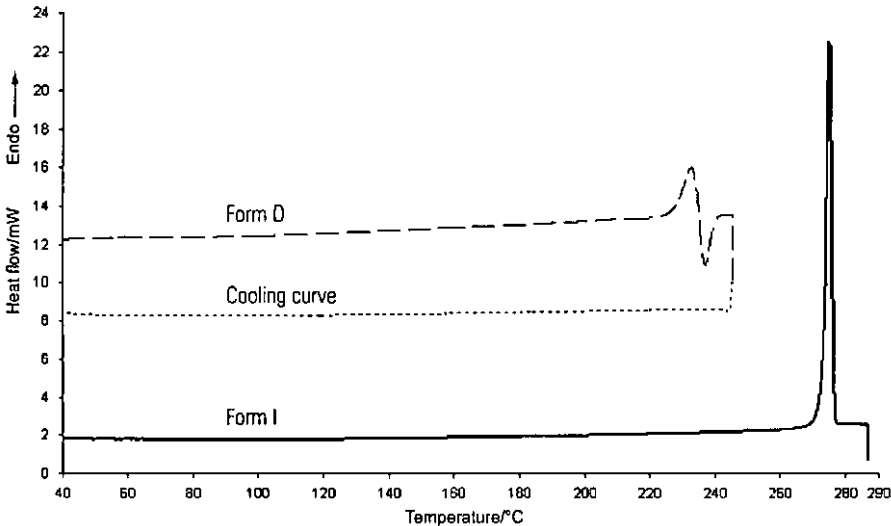


Fig. 4 DSC curves of polymorphic forms D and I

namically stable polymorph in the temperature region of the melting points. The higher heat of fusion also supports this statement. The room temperature solubility measurements in water and in methanol show that form F is the more soluble polymorph. Solubility of form A and F in water is 3.8 and 6.2 mg mL⁻¹, respectively and in methanol 3.5 and 7.7 mg mL⁻¹. The polymorph with the lower solubility is the more thermodynamically stable form at temperature of the solubility measurement, so the polymorph A is the more thermodynamically stable polymorph at room temperature. These data suggest that the two forms are monotropic polymorphs.

Table 3 Characteristic diffraction peaks of form I up to 25° θ

2 θ /degree	Rel. int./%
8.50	5
9.90	62
10.08	77
10.66	21
13.26	5
13.72	37
14.63	3
15.97	53
16.33	62
16.97	20
17.93	19
18.14	25
18.59	30
19.63	33
19.86	45
20.41	14
20.75	100
21.40	22
21.71	38
21.86	36
23.16	77
23.58	31
24.52	72

DSC curve of form D shows two endothermic peaks separated by an exothermic peak (Figs 1 and 4). After melting of the lower melting form (form D) at 228.0°C, crystals of the higher melting form (form I) grow from the melt, giving rise to an exothermic peak at 235.5°C. Then the higher melting form (form I) melts, giving a second endothermic peak at 274.9°C. TG curve shows no change in mass in the tempera-

ture region corresponding to the DSC peaks at 228.0 and 235.5°C. The liquid–solid phase transition at 235°C was also observed by hot stage microscopy investigations. The sample of form D was heated in the DSC furnace just above the end of the crystallization exotherm, cooled at the same rate to room temperature and heated again to the melting point. Only the melting exotherm at 274.9°C was observed from the repeated heating curve. From heating-cooling DSC experiments (Fig. 4) it is evident, that the polymorphic transition from form D to I at 235.5°C is irreversible. The polymorphic transformation from form D to form I was also confirmed by high-temperature X-ray powder diffraction analysis. Form D, however, showed a transformation into the new crystalline form I at about 205–210°C (Fig. 5). The temperature of the phase transition is significantly lower in the HTK chamber compared to the DSC experiment indicating that the heating and sample conditions are important for its transition. Repeated heating-cooling experiments in the HTK chamber also proved that transition from form D to form I phase is irreversible. The room temperature diffraction pattern of form I is shown in Fig. 3 and the reflection list is given in Table 3.

Table 4 Characteristic diffraction peaks for the crystalline phase E

2 θ /degree	Rel. int./%
6.56	9
9.24	24
12.10	8
13.23	8
15.45	17
16.14	20
17.51	14
18.85	31
21.77	29
24.39	100

On the DSC curve of form G, a broad endotherm at 35–75 and a sharp endotherm at 270.8°C were observed. On TG curve of form G (not shown), the mass loss corresponding to the DSC endotherm at 35–75°C was 2.8%, which was not equal to the stoichiometric value calculated for the monohydrate of DM (3.2%). The sample of form G was heated in the DSC furnace to the end of the first endothermic peak (80°C), and without opening the furnace the sample was cooled to room temperature at the same rate and heated again to the melting point. As seen from Fig. 6, only the melting endothermic peak at 270.8°C was observed. But the DSC curve of the sample, which was previously heated in the DSC furnace to the end of the first endotherm and then exposed to the atmosphere (25°C, 45% RH), shows again two endothermic peaks (Fig. 6). From these data it is evident that form G is hygroscopic and at ambient

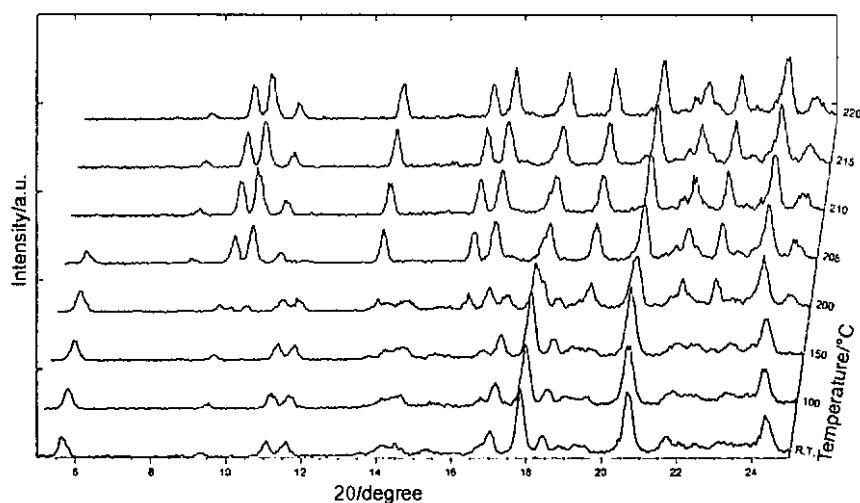


Fig. 5 *In situ* X-ray powder diffraction patterns collected during heating of form D in the HTK chamber

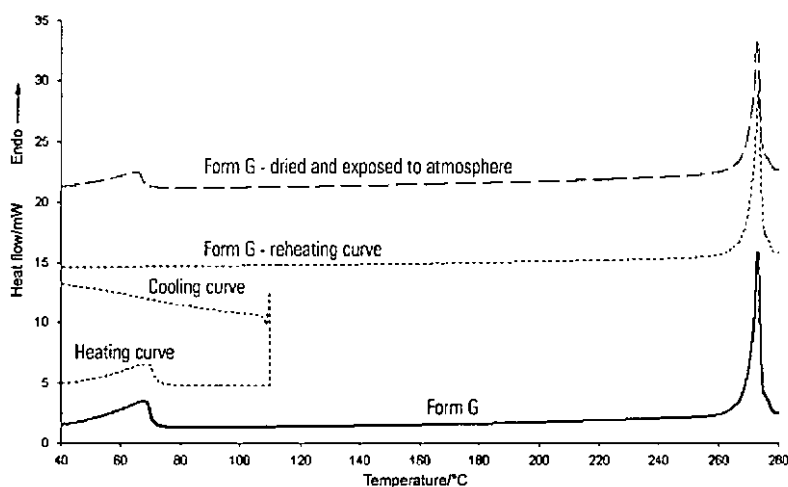


Fig. 6 DSC curve of form G, heating-cooling curves of form G and DSC curve of form G previously dried in DSC and then exposed to the atmosphere

conditions (25°C, 45%) it tends to be in the hydrated form. This was also evident from the results of X-ray analysis. The X-ray powder pattern that was obtained in the HTK chamber at 30°C in the dry nitrogen atmosphere was different from that obtained at ambient conditions (not shown).

DSC curve of the polymorphic form designed as form H exhibits two endothermic peaks. The sharp peak at 258°C is the melting peak of form H which is immediately followed by a minor endotherm. Keeping the samples of form H in the DSC furnace at 240°C for 15, 30 and 60 min, resulted in the increased second endothermic

peaks (Fig. 7). This phenomenon was attributed to the phase transition of form H to another polymorphic form. FT-IR analysis of the sample of form H that was previously held 30 min at 240°C in the DSC furnace under the nitrogen atmosphere, shows characteristic peaks of form H and F; so it can be concluded that the second endotherm on the DSC curve is the melting peak of form F.

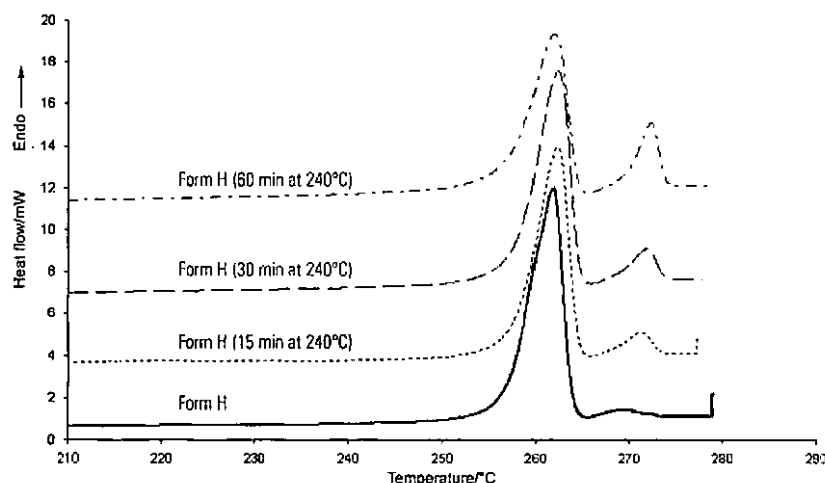


Fig. 7 DSC curve of the form H compared to DSC curves of the form H previously kept 15, 30 and 60 min at 240°C in the temperature range from 210 to 290°C

The DSC curve obtained for the amorphous form shows a broad endotherm at 30–120, a glass transition at 144.1, followed by an exothermic crystallisation peak at 221.6 and subsequent two endothermic peaks at 260.5 and 270.5°C as demonstrated in Fig. 8. The X-ray powder diffraction pattern of the amorphous sample (sample a in Fig. 9) confirms that it is completely amorphous. Individual temperature events of the amorphous form (glass transition, crystallisation and melting) were also observed by hot stage microscopy. The broad endothermic peak on the DSC curve was attributed to the evaporation of adsorbed moisture. This was confirmed by Karl Fisher and TG analysis. On the TG curve, the mass loss corresponding to the DSC endotherm at 30–120°C was 3.5%. The amorphous form was found to be hygroscopic. The amorphous sample was dried under the controlled conditions in the DSC furnace (heated to 120°C) and then exposed for a short period (few min) to ambient conditions and consequently analysed by DSC and TG. These analyses proved that the dried samples take up practically the same quantity of water as released during previous drying process. When the amorphous form was crystallized in the DSC furnace (heated to the end of the exothermic peak – 245°C), the polymorphic mixture was obtained (sample b). The DSC curve of the sample b exhibits the endothermic peaks at 260.5 and 270.5°C (Fig. 8). In the FT-IR spectrum of the sample b there are peaks at wave-numbers that are characteristic of the form F and an additional peak at 746 cm^{-1} . The X-ray powder diffraction pattern of the sample b (Fig. 9) confirms that upon heating

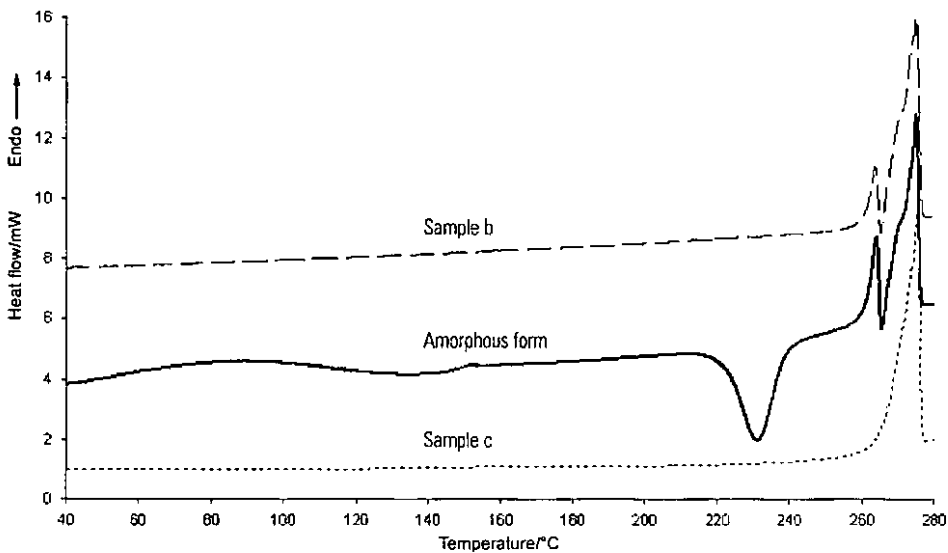


Fig. 8 DSC curves of sample b, sample c and of the amorphous form

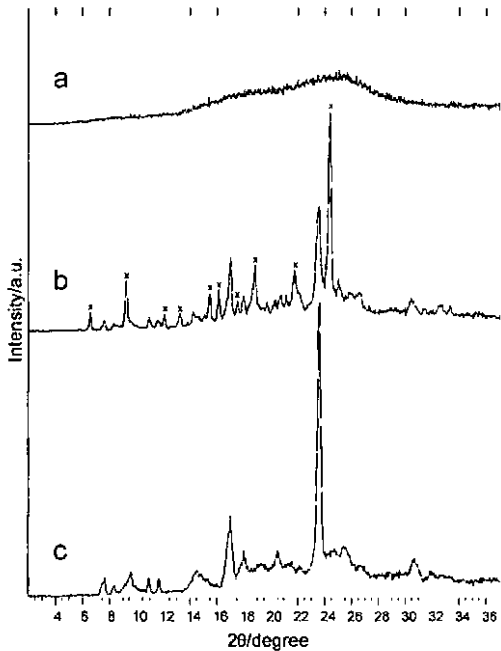


Fig. 9 X-ray powder diffraction patterns of samples a, b and c at room temperature. Marked reflections (*) are characteristic of the new polymorph E

(up to 245°C in the DSC furnace) the amorphous form is transformed to a mixture of at least two crystalline forms one of which is the known form F. The remaining reflections are ascribed to a new polymorphic form designed as form E assuming a mixture of the two polymorphic forms. The characteristic reflections of form E are marked with stars (*) in Fig. 9 and their 2θ values and relative intensities are given in Table 4. The sample b was heated in the DSC furnace to the end of the first endothermic peak (265°C) and cooled at the same rate to the room temperature – thus prepared sample is called sample c. The DSC curve of the sample c shows only the melting peak at 270.5°C (Fig. 8). XRPD and FT-IR analyses of the sample c confirm that the endotherm at 270.5°C on the DSC curve of the sample c is the melting peak of form F. However, in the FT-IR spectrum of the sample c there are only peaks at wave

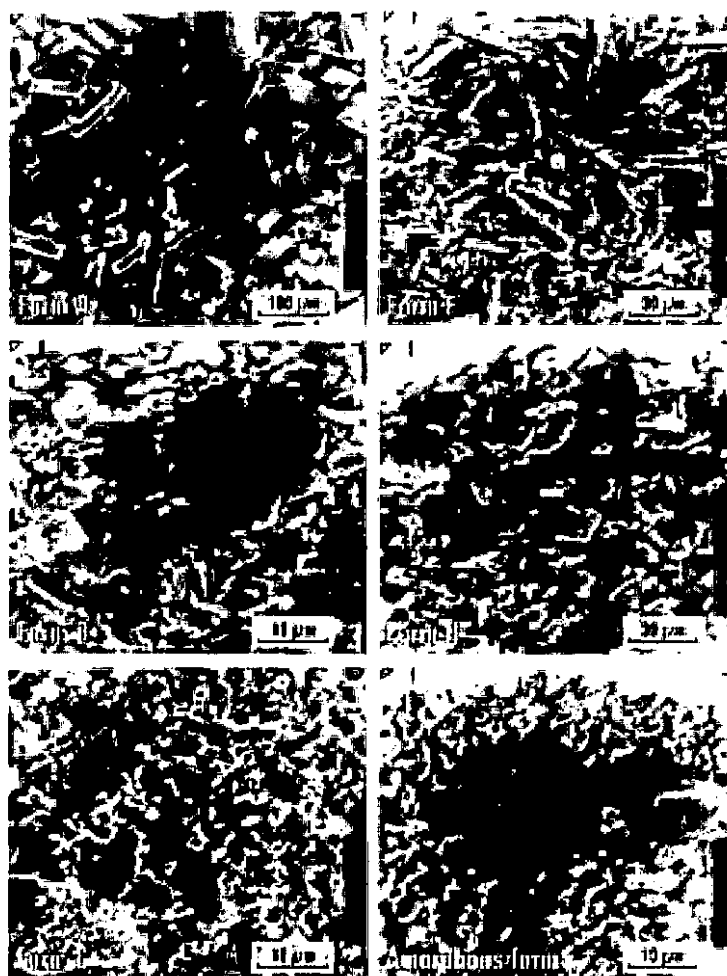


Fig. 10 SEM micrographs forms A, D, G, F, H and of the amorphous form

numbers that are characteristic of the form F and also the X-ray powder diffraction pattern shows only reflections that are characteristic of form F.

SEM micrographs of polymorphic forms A, D, F, G, H and the amorphous form (Fig. 10) show different morphologies among investigated forms: forms A and F with distinctive needle like particles, forms D and H with similar plate like particles, and form G and the amorphous form in a form of aggregates with different and smaller particles.

Conclusions

Seven polymorphic forms of doxazosin mesylate designed as forms A, D, E, F, G, H, I and the amorphous form were investigated in this study by evaluating DSC curves, FT-IR spectra and X-ray powder diffraction patterns. Five of the investigated crystalline forms (A, D, F, G and H) have already been known from the literature, while the polymorphic forms E and I were identified and characterized as new polymorphs. DSC and hot stage microscopic results show the irreversible polymorphic transition from form D to form I at 235.5°C which was confirmed by X-ray temperature dependent investigations. The X-ray powder diffraction reflection list and the FT-IR peaks of the novel form I, which melts at 274.9 °C, were determined to enable its identification.

Thermal data and solubilities measurements for forms A and F suggest that these two forms are monotropic polymorphs.

DSC results for the samples of form H had been previously kept in the DSC furnace at 240°C for 30 min reveal that in this temperature region form H undergoes phase transition into a polymorphic form which was identified by FT-IR analysis as form F.

The amorphous form of doxazosin mesylate was found to be stable at ambient conditions, but at temperatures above the glass transition it is transformed into the mixture of crystalline forms. In the polymorphic mixture, which was obtained by heating the amorphous form in the DSC up to 245°C, a known form F and a new crystalline form (form E) of DM were identified. DSC, FT-IR and X-ray powder diffraction analysis show that, during heating, form E undergoes an irreversible polymorphic transition to the form F.

SEM analyses show different morphologies of the investigated forms.

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