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

M. Grčman[1], *F. Vrečer*[1] *and A. Meden*[2]

[1]Krka, d.d., Novo mesto, Research and Development Division, Novo mesto, Slovenia
[2]University 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°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

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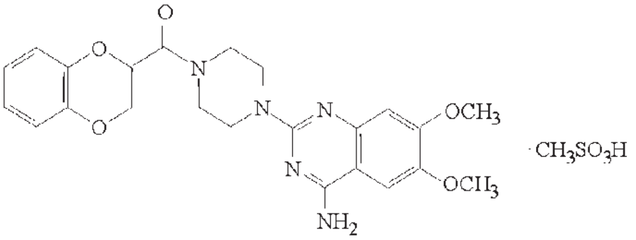
glass transition point [2]. It is well known from the literature that polymorphism of drugs must be considered as an important preformulation parameter, especially because of a different biopharmaceutical and stability properties exhibited by different polymorphic forms. The results of the study of physico-chemical 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 cystallization 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 (λ=1.54178 Å). The 2θ range was 5–32°, 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 (5–25° 2θ), 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 μm 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.

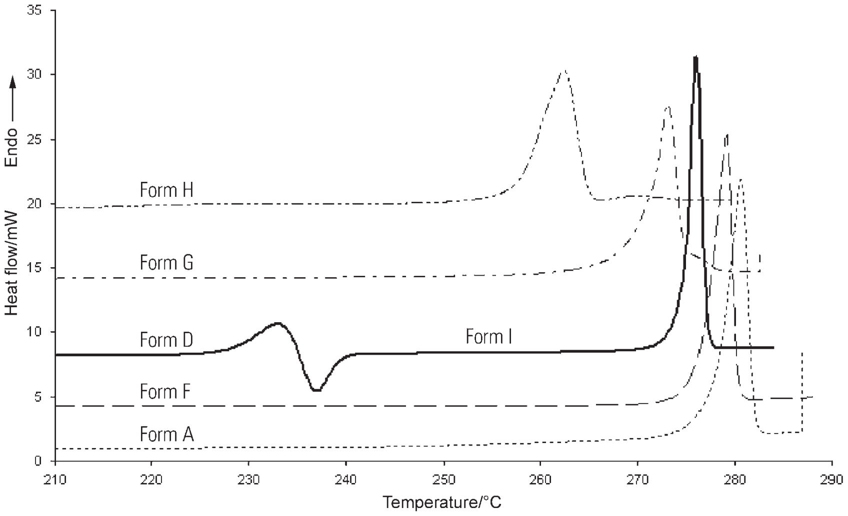


Fig. 1 DSC curves of polymorphic forms A, D, F, G, H and I in the temperature range from 210 to 280°C

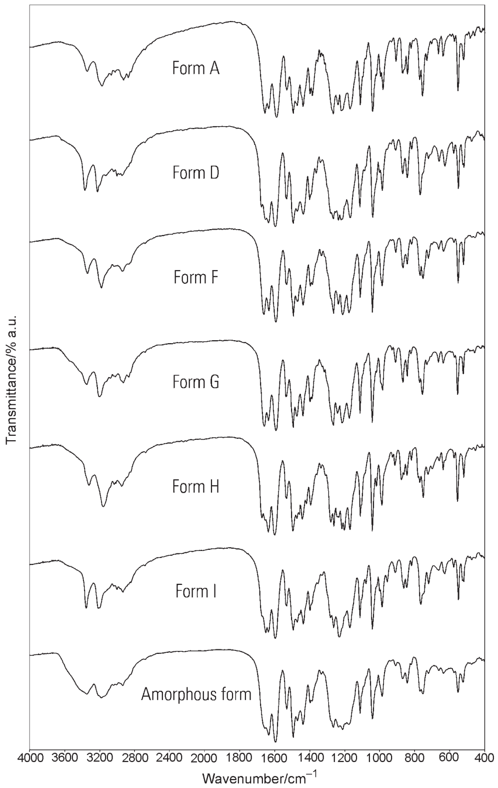


Fig. 2 FT-IR spectra of polymorphic forms A, D, F, G, H, I and the amorphous form

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
	T_{onset}/°C ±95% c.i.	ΔH/kJ mol^{-1} ±95% c.i.	T_{onset}/°C ±95% c.i.	Δm (30–200°C)/%
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-

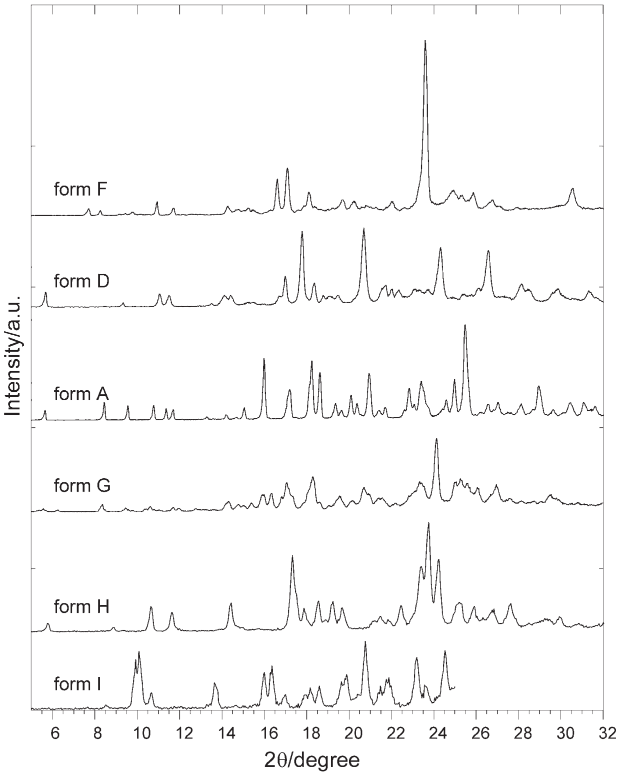


Fig. 3 X-ray powder diffraction patterns of polymorphic forms A, D, F, G, H and I at room temperature. Form I was measured after the transformation and cooling in the HTK chamber at a shorter range

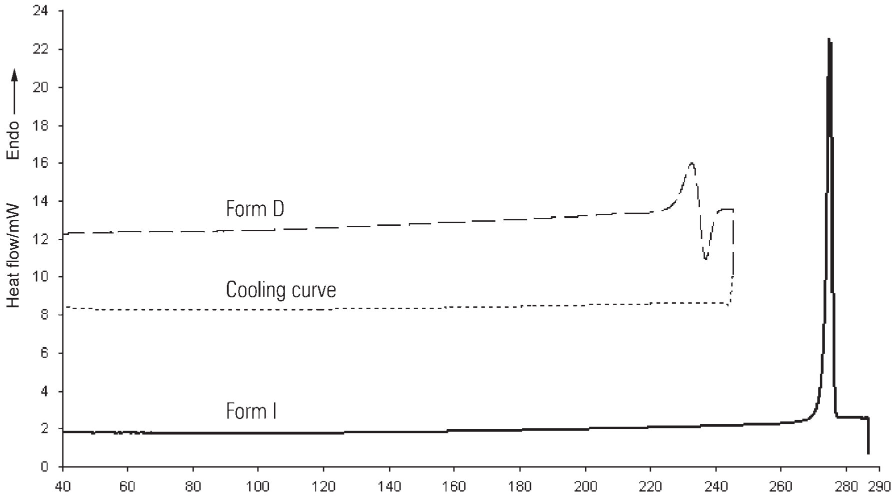


Fig. 4 DSC curves of polymorphic forms D and I

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

2θ/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 temperature 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

2θ/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 endotheric 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 athmosphere (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

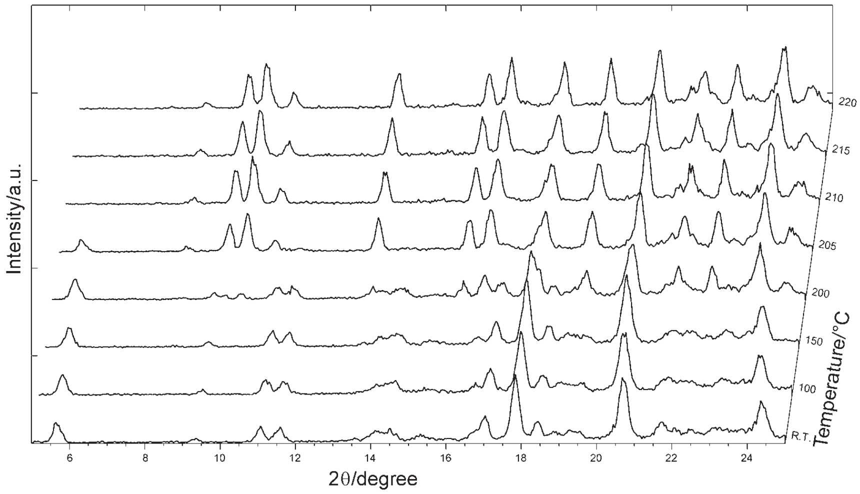


Fig. 5 *In situ* X-ray powder diffraction patterns collected during heating of form D in the HTK chamber

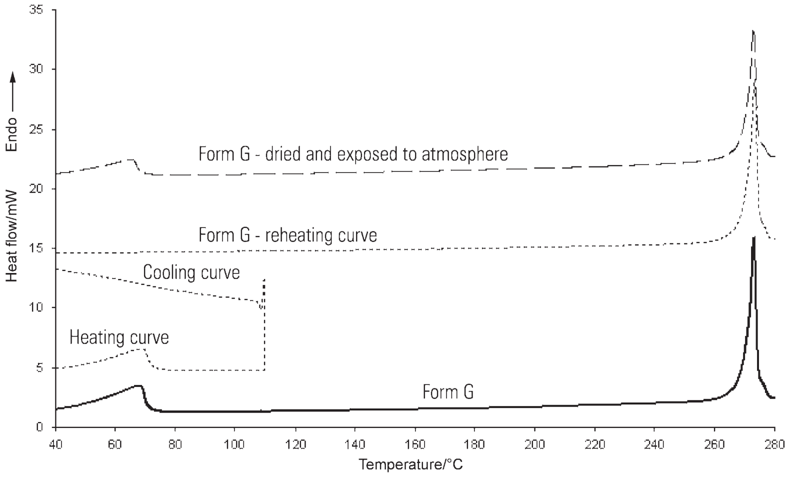


Fig. 6 DSC curve of form G, heating-cooling curves of form G and DSC curve of form G previously dried in DSC and then exposed to the atmosphere

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.

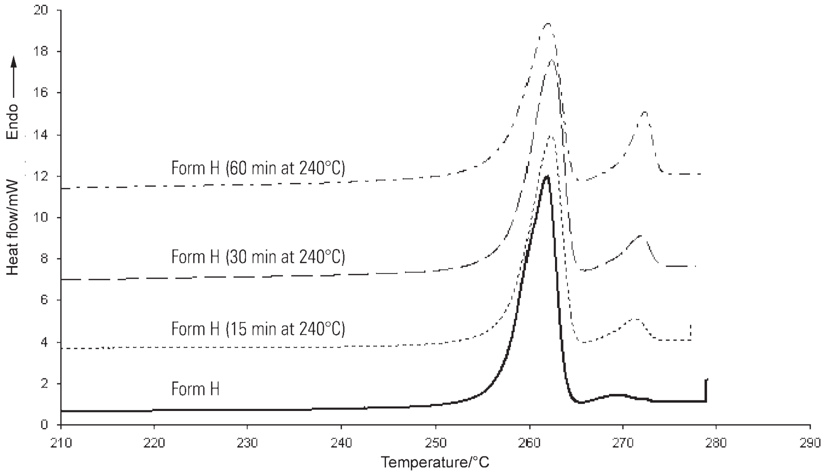


Fig. 7 DSC curve of the form H compared to DSC curves of the form H previously kept 15, 30 and 60 min at 240°C in the temperature range from 210 to 290°C

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 wavenumbers 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

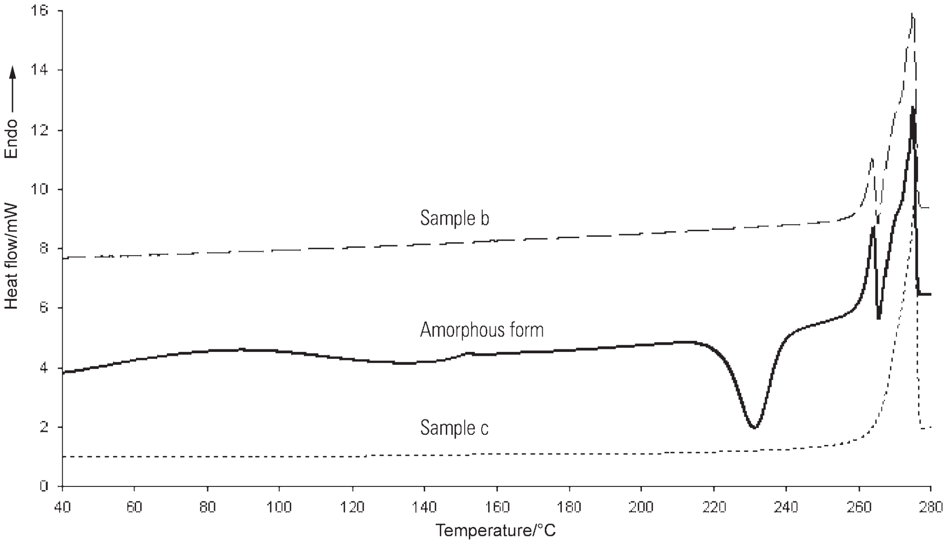


Fig. 8 DSC curves of sample b, sample c and of the amorphous form

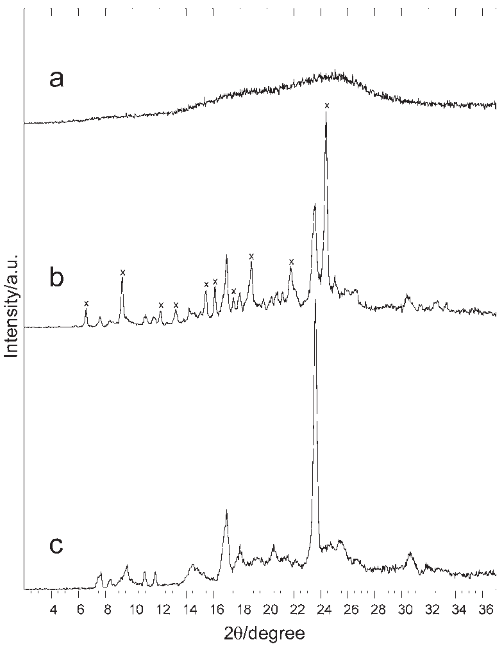


Fig. 9 X-ray powder diffraction patterns of samples a, b and c at room temperature. Marked reflections (*) are characteristicof the new polymorph E

(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

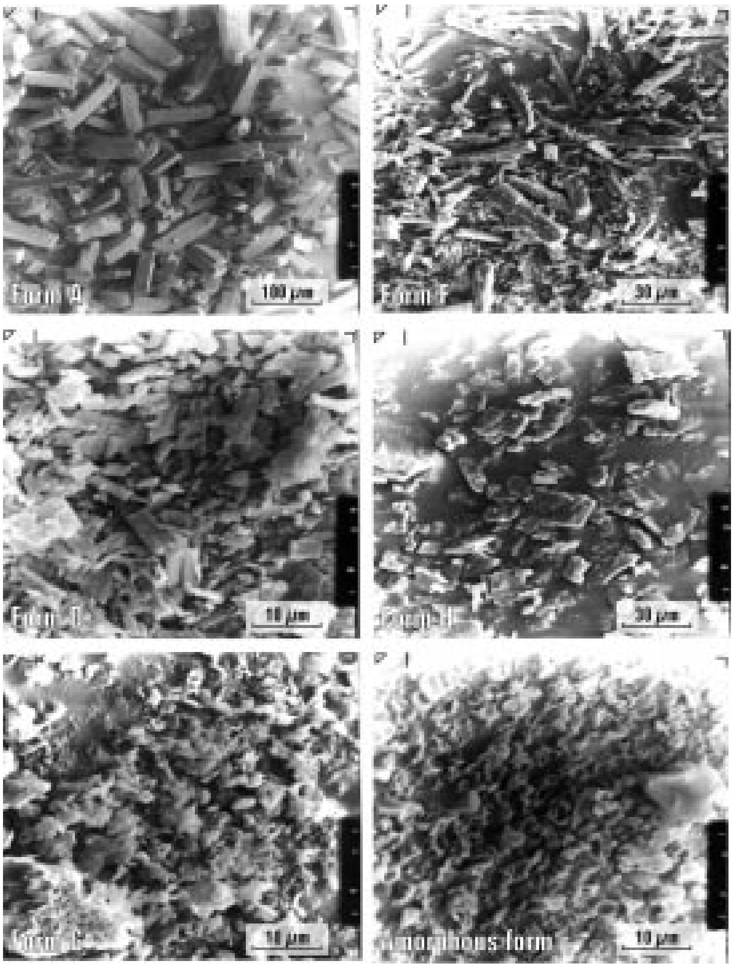


Fig. 10 SEM micrgpaphs forms A, D, G, F, H and of the amorphous form

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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