ELSEVIER

Thermochimica Acta 321 (1998) 43–52

thermochimica acta

Thermal studies on the polymorphic modifications of (R,S) propranolol hydrochloride

M. Bartolomei*, P. Bertocchi, M. Cotta Ramusino, E. Ciranni Signoretti

Laboratorio di Chimica del Farmaco, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy

Received 5 March 1997; accepted 5 October 1997

Abstract

The polymorphism of (R,S) propranolol hydrochloride was investigated by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-ray powder diffractometry (XRPD) and thermomicroscopy (HSM) coupled with FT-IR spectroscopy.

Propranolol hydrochloride existed in three different crystalline forms, denoted as forms I, II and III, according to their decreasing melting temperatures. Modification II was the commercial product. The forms I and III were obtained by melting form II in different experimental conditions. Form III was obtained only by solidification of the melt in the presence of an alkali halide matrix (as a crystalline film on an alkali halide window or as powder dispersion in a KBr pellet). Forms I and II were also obtained by crystallization from 95% aqueous ethanol and acetone, respectively. The three forms were easily differentiated by their IR spectra in the 3400–2000 cm^{-1} range. The different crystalline structures of forms I and II were characterized by means of their X-ray powder diffraction patterns. © 1998 Elsevier Science B.V.

Keywords: DSC; Hot-stage microscopy; Polymorphism; Propranolol hydrochloride; Thermal behaviour

1. Introduction

The identification and characterization of polymorphic behaviour are essential aspects of drug development. The presence of metastable crystalline forms can influence the physicochemical properties of bulk powders (batch to batch reproducibility) and the bioavailability of the preparations by affecting the dissolution rate [1].

Propranolol hydrochloride (±1-[(2-methylethyl)-amino]-3-(1-naphthalenyloxy)-2-propanol hydrochloride), is a non-selective, β-adrenergic antagonist of the β_1 and β_2-receptors, mainly used in the treatment of systemic hypertension. The solid-state properties of this drug with regard to the relationships between the racemic mixture and the (+) and (−) enantiomers have been previously investigated by DSC [2,3]. Kuhnert-Brandstatter and Vollenklee [4] reported that propranolol hydrochloride exists in more than one solid form. By observing crystalline films (obtained by solidification of the melt) with thermomicroscopy, two crystalline modifications (which were designated I and II) were noted and their IR spectra reported. Poorly-defined melting points and discrepancies in the IR spectra have also been reported [5]. Nevertheless, no reference of propranolol hydrochloride polymorphism is made in the most recent European Pharmacopoeia, despite the compound being included in lists of drugs exhibiting polymorphism [6,7].

*Corresponding author.

PII: S0040-6031(98)00438-9

The purpose of the present work was therefore to re-examine the different crystalline forms of propranolol hydrochloride in more detail and to elucidate their thermal behaviour with particular regard to polymorphism by DSC, TGA, X-ray powder diffraction and hot stage microscopy coupled with FT-IR.

2. Experimental

2.1. Material

(R,S) Propranolol hydrochloride was purchased from Sigma (99.5% purity by the Ph. Eur. HPLC assay procedure) and used without further purification.

2.1.1. Preparation of polymorphic forms

The commercial product consisted of modification II. The polymorphic forms I and III of propranolol hydrochloride were prepared by melting form II directly on the hot-stage compartment of the thermomicroscope. The glassy material obtained was recrystallized under different experimental conditions. Modification I was obtained in an aluminum DSC pan by cooling at room temperature, reheating and holding the glassy solid at a temperature of 100°C for several min (usually 15 min) up to complete crystallization. Modification III was prepared by cooling the melt at room temperature on an alkali halide window.

Form II was easily produced by evaporation of solutions from several solvents like methanol, water, propanol and acetone. The crystallization from a saturated solution of the drug in acetone on an ice bath produced form II crystals consisting of fine particles of homogeneous size. Efforts were made to obtain form I by solvent crystallization with a variety of solvents. Form I was obtained by vacuum evaporation of a 95% aqueous ethanol solution and by heating the residual glassy product at 100°C for at least 60 min (to permit complete crystallization) in a Heraeus vacutherm oven. Evaporation from 95% aqueous ethanol solution at room temperature gave mixtures of form I and III.

It was impossible to obtain form III by solvent evaporation. Form III was obtained by crystallization of the melt on a rectangular alkali halide window (4×5 cm) in an oven. As the glassy product exhibited a pronounced inertia towards crystallization, the sample was reheated and held at 100°C to increase the process rate. On removing the layer of the crystalline film from the surface of the alkali halide window with a spatula, form III tended to be transformed to a mixture of forms I and III.

UV and HPLC analysis (by the Ph. Eur. assay procedures) performed on polymorphs I and II obtained by crystallization, either from solvents or from the melt, indicated that no degradation had taken place.

In order to obtain good infrared spectra, the forms I and II were pre-ground with a pestle in an agate mortar, while modification III was pressed and rubbed with a spatula and a Perkin–Elmer roller knife (a device which consists of a razor knife at one end and a roller wheel device for pressing samples at the other end) directly on to KBr window. The crystalline structures did not seem to alter in these experimental conditions.

2.1.2. Preparation of forms II and III dispersions in KBr pellets for DSC analysis

KBr pellets of form II were prepared by accurately weighing 4 mg of the commercial sample which had been previously gently ground. This sample was dispersed in 200 mg of dried KBr (IR grade), placed in an evacuable stainless-steel die and pressed in a Perkin–Elmer manual hydraulic press to obtain a KBr pellet (13 mm diameter ×1 mm thickness).

The same KBr pellets, heated in a hot-stage apparatus at 170°C and then cooled to room temperature, resulted in the formation of KBr pellets of form III. In these conditions, propranolol hydrochloride recrystallized completely as form III. This was confirmed by FT-IR spectroscopy.

Each pellet was accurately weighed and divided into four parts. Each part was accurately weighed and placed in a sample pan. The theoretical contents of form II and III of each fragment were obtained by calculation.

2.1.3. Preparation of forms I and II mixtures

The mixtures of forms I and II at 10/90, 50/50 and 90/10 w/w ratios were prepared by mixing and grinding, for 1 min, accurately weighed quantities of each polymorph, with an agate mortar and pestle.

2.2. Methods

2.2.1. Thermomicroscopy coupled with FT-IR spectroscopy

Thermomicroscopy experiments were performed on an *i*-Series Perkin–Elmer hot-stage microscope (HSM) coupled with a Perkin-Elmer system 2000 FTIR spectrometer, employing a MCT (mercury-cadium-telluride) detector. The apparatus was set to collect both transmittance and reflectance spectra. A small amount of pre-ground sample was placed into the hot stage compartment either on a KBr or NaCl window or on a DSC aluminum pan in order to collect reflectance spectra. Large crystals were pulverized and distributed by lightly pressing and rubbing with a spatula or the roller knife. The HSM experiments were performed at 0.5, 2, 5 and 10°C min^{-1} to enable a correct comparison with DSC experiments. The heating and cooling rate of 5°C min^{-1} was suitable for the microscopic observation of thermal phenomena. Furthermore, the observed melting and cooling ranges almost completely overlapped at these different rates.

Room-temperature and variable-temperature infrared spectra were recorded from 4000 to 580 cm^{-1}; 32 scans were collected for each sample at a resolution of 4 cm^{-1}.

2.2.2. Differential scanning calorimetric studies

DSC curves were recorded using a Perkin–Elmer DSC7 instrument, calibrated using indium and zinc standards. Samples (≈1.5 mg) were accurately weighed into DSC pans; the DSC profiles were recorded at 0.5, 2, 5, 10°C min^{-1} rate, from 40° to 175°C, under nitrogen flux. Heating rates lower than 10°C min^{-1} were time-consuming and did not permit a better resolution of the melting peaks. The DSC experiments were run using pans that were open, closed or closed with a cover hole. As it was impossible to obtain a better resolution of overlapping thermal events from these different modifications, open pans were used for meaningful comparison with the thermomicroscopy data.

DSC curves of forms II and III dispersed in KBr disks were also recorded at a scanning rate of 10°C min^{-1}, using as reference an aluminum pan containing a fragment of KBr pellet, as similar as possible in weight to the sample.

The programmed heat–cool cycles were repeatedly performed at 10°C min^{-1}, heating the sample from 40° to 170°C, cooling to 40°C and reheating. Cyclic DSC studies were also performed using scanning rates ranging from 0.5 to 20°C min^{-1}. The rate found suitable to permit the most complete recrystallization of the melt on reheating the sample was 10°C min^{-1}. Each experiment was repeated at least three times.

2.2.3. Thermogravimetric analyses

Thermogravimetric curves were recorded from 40° to 180°C with a Perkin–Elmer TGA7 instrument, under nitrogen flux, at a heating rate of 10°C min^{-1}. Samples (≈5 mg) were weighed on a platinum crucible. Temperature calibration was performed using two standards, Alumel and nickel, whose magnetic transition temperatures are 163° and 354°C, respectively.

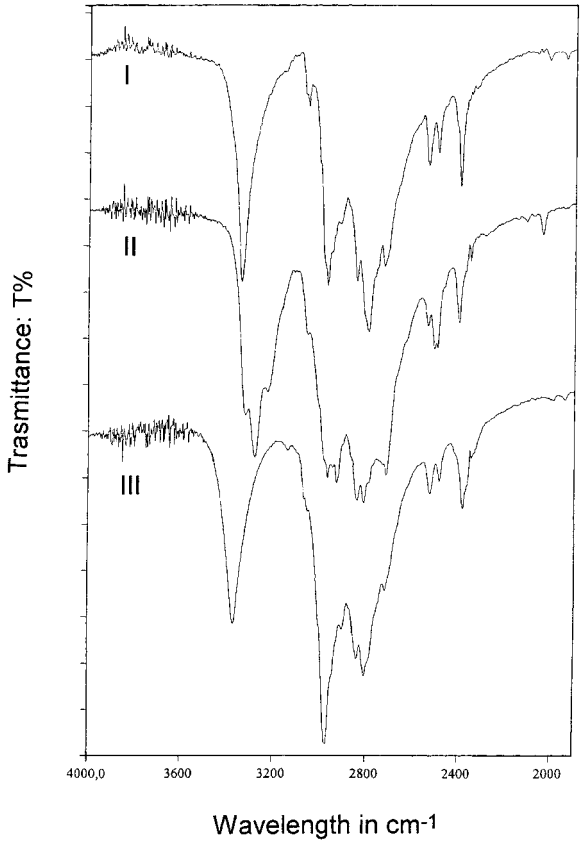

Fig. 1. FT-IR spectra in the 4000–2000 cm^{-1} range of polymorphs I, II and III of propranolol hydrochloride at room temperature.

2.2.4. X-ray powder diffraction measurements

XRPD patterns were obtained with a Philips P.W. 1710 diffractometer in the $2<2\vartheta<60^\circ$ range, using CuK_α radiation-Ni filtered (40 kV; 40 mA). The step scan mode was performed with a step width of 0.02°, at a rate of 1 step/s.

3. Results and discussion

Modification II, heated by HSM on an alkali halide window, melted inhomogeneously at ~161°C with occasional separation of crystals of form I that melted rapidly at ~163°C. Modifications I and III showed sharper melting at ~163° and ~154°C, respectively. All three modifications heated above their melting point and cooled at room temperature did not immediately crystallize, but formed a glassy solid. It exhibited a pronounced reluctance to crystallize and the use of different cooling conditions was not helpful in increasing the crystallization rate. The glassy solid, cooled to room temperature, spontaneously gave rise to form III, whereas by scratching or grinding it was rapidly transformed into form II. Crystallization to form III could be improved by holding the glassy solid at a temperature of 100°C. The glassy solid obtained on an alkali halide window never crystallized into form I. The alkali halide matrix played a major role in the preferred crystallization of form III. The influence of the alkali halide was confirmed by variable temperature experiments, using HSM on forms I and II dispersions in KBr disks. The drug was transformed into form III by heating to above 170°C and cooling.

Spontaneous cooling of the glassy solid obtained by melting forms I or II on a DSC aluminum pan mainly afforded form I crystals, but crystals consisting of form II or a mixture of forms I and III also showed up in small amounts; modification III only formed jointly with I and was not separable from it.

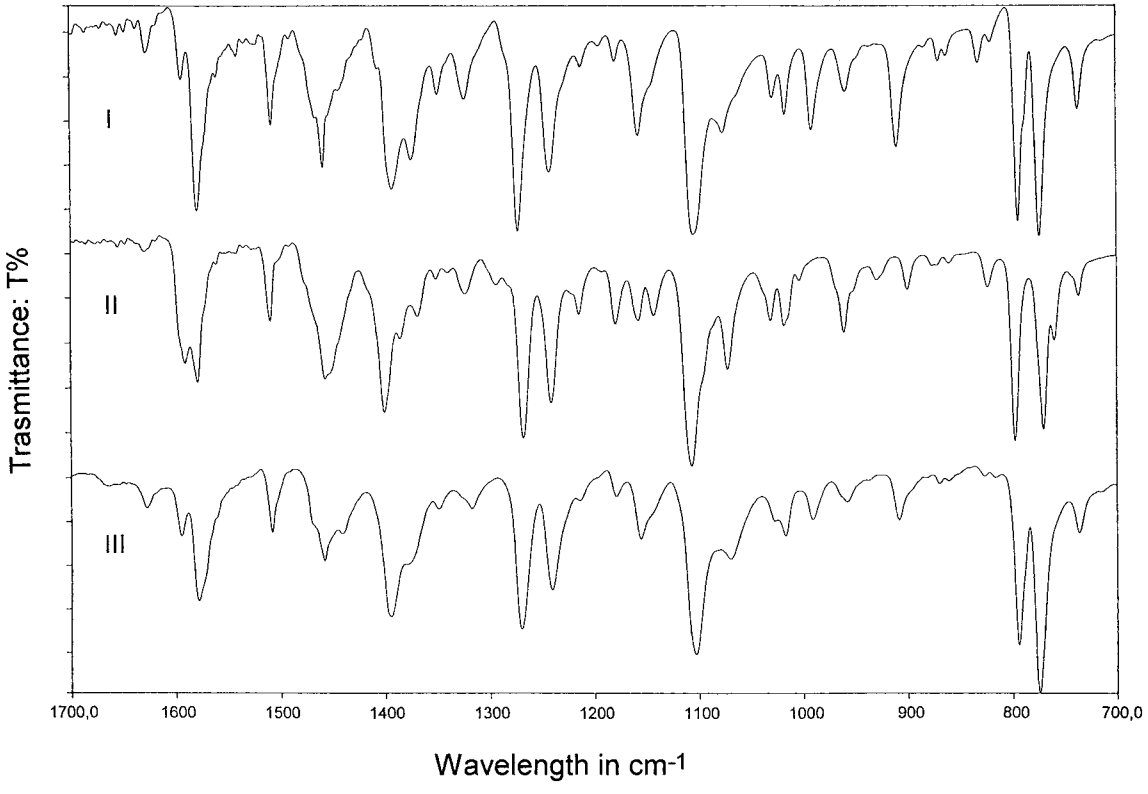

Fig. 2. FT-IR spectra in the fingerprint region of polymorphs I, II and III of propranolol hydrochloride at room temperature.

The solidified melt kept at a temperature of 100°C, always gave rise only to form I. Microscopic observation showed only subtle morphological differences between the crystal habits of the three polymorphs, but they were easily differentiated by their IR absorption bands in the 3400–2000 cm^{-1} range (Fig. 1). Moreover forms I and II were distinguishable over the whole 3400–700 cm^{-1} range of frequencies, while form I and III fingerprint regions showed few subtle differences (Fig. 2).

The spectrum of modification II was in agreement with that previously reported by Kunhert-Brandstatter and Vollenklee [4] for form II, while the spectrum of modification I reported [4] is actually representative of a mixture of forms I and III. DSC, combined with thermomicroscopy, permitted a better interpretation of thermal events. The DSC profiles of forms I, II and III, containing seed crystals of form I (III impure of form I), obtained at a heating rate of 10°C min^{-1}, are shown in Fig. 3. The DSC data of forms I and II are summarized in Table 1. The DSC curve of form III (impure of form I) was recorded on the sample obtained by removing the crystalline film from the surface of the KBr window with a spatula. Fig. 3 showed a wide melting range for form III that could be attributed to a concomitant solid–solid transition to form I (onset temperature of ∼154°C, peak temperature of ∼159°C and heat of fusion of ∼91 J g^{-1}). As form III, removed from alkali halide surface, tended to

Table 1
DSC data of forms I and II of propranolol hydrochloride

Form	T_e/°C [a]	T_p/°C [b]	ΔH_f/(J g^{-1}) [c]
I	163.0±0.3	166.0±0.5	106.0±0.8
II	161.8±0.1	163.6±0.2	123.8±1.6

[a] Extrapolated onset temperature.
[b] Peak temperature.
[c] Fusion temperature.

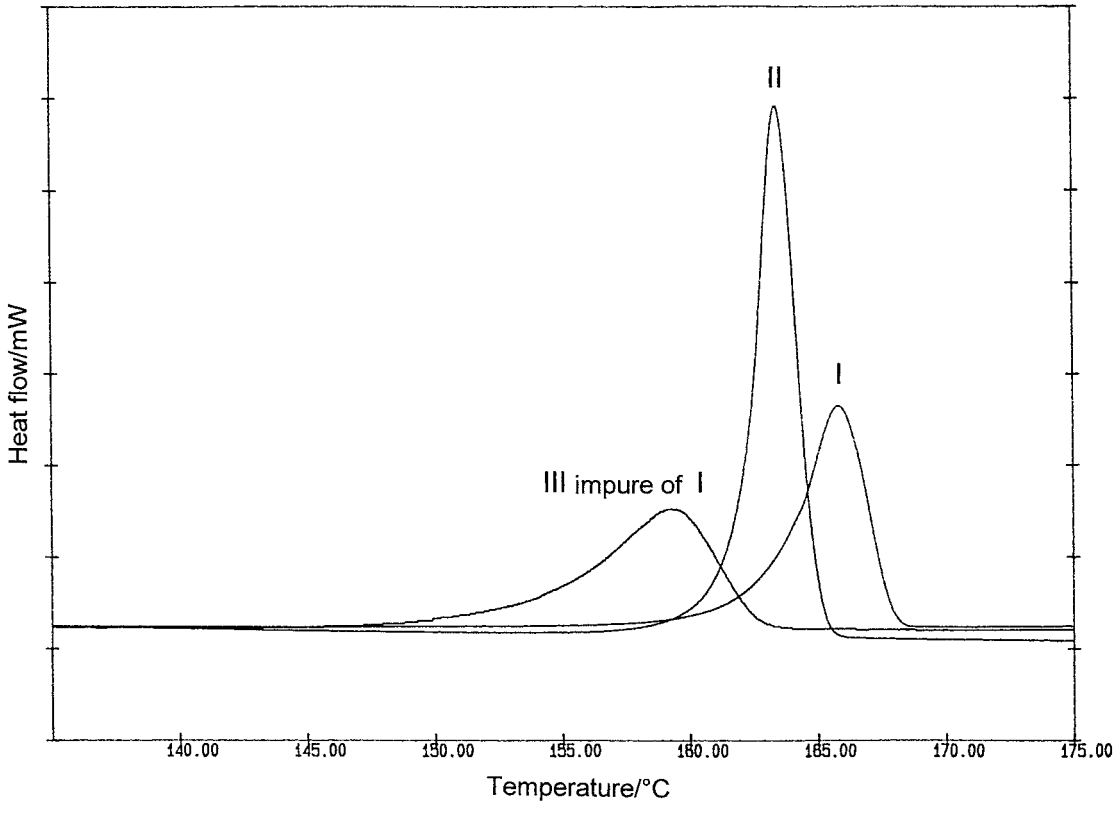

Fig. 3. DSC curves for propranolol hydrochloride polymorphs I, II and III impure of I (III with seed crystals of form I); 10°C min^{-1} scan rate; heat flow, endothermic scale.

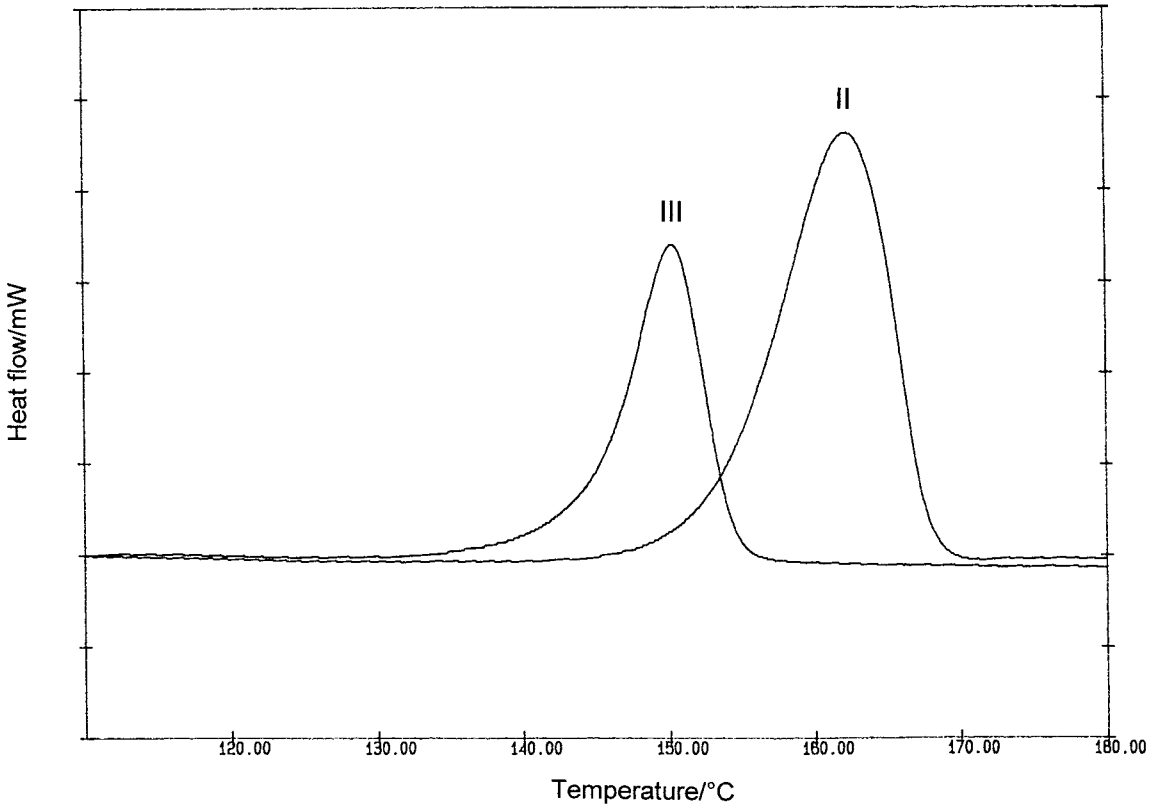

Fig. 4. DSC curves of propranolol hydrochloride forms II and III (dispersions in KBr disks) 10°C min^{-1} scan rate; heat flow, endothermic scale.

be transformed into form I, it was impossible to accurately measure the melting point and heat of fusion of form III.

As it was only possible to isolate form III from form I in the presence of an alkali halide matrix, the thermal behaviour of form III was investigated by running the DSC experiments as KBr pellets at 10°C min^{-1}. The scan (Fig. 4) showed a fusion endotherm with an onset temperature of 144.9°C (±0.4) and a heat of fusion of 77.4 J g^{-1} (±3.4). A DSC scan of form II as a KBr pellet gave an onset temperature of 152.6°C (±0.7) and a heat of fusion of 108.4 J g^{-1} (±5.9). These experiments qualitatively confirmed that modification III was the lowest melting polymorph with the lowest heat of fusion.

DSC curves of form II sometimes showed a wider melting range or a variable peak shape of the fusion endotherm. This indicates the presence of overlapping thermal events which could be attributed to the incomplete transition of form II into form I after fusion. This was in agreement with the HSM results, as well as to previous reports [4]. Unfortunately, no DSC curves were shown [4] and, therefore, it was impossible to make a comparison with the present results.

Cyclic DSC heating–cooling studies were also performed to clarify further the thermal behaviour. In this way, the melt was found to recrystallize slowly on an open pan in the 90–130°C range, either by cooling or by reheating the solidified melt. Reheating caused the crystallization to proceed more rapidly and completely. These results were consistent with the occurrence of a melt–solid transition. The cooling and reheating studies confirmed that the transition of form II into form I was incomplete and reversible. Although the temperature of spontaneous crystallization was not

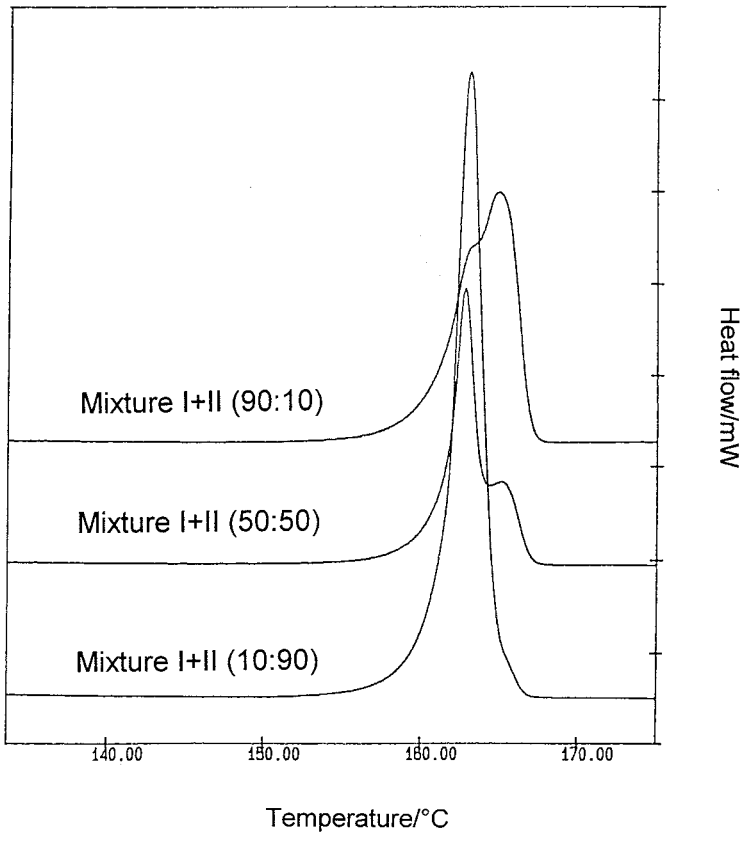

Fig. 5. DSC curves of propranolol hydrochloride mixtures of forms I and II, in 10 : 90, 50 : 50, 90 : 10 w/w ratios; 10°C min^{-1}, scan rate; heat flow, endothermic scale.

constant, the heating–cooling DSC experiments were helpful in choosing a suitable temperature range for obtaining polymorphs I and III, using isothermal holding [8].

In order to assess the efficiency of DSC in detecting the various polymorphs, mixtures were prepared containing known amounts of forms I and II; some mixtures of forms I and III, obtained by melting and cooling experiments and by crystallization from solvents, were also analyzed. Fig. 5 shows the curves obtained with 10 : 90, 50 : 50, 90 : 10 w/w mixtures of forms I and II. The curve of the 10 : 90 (I : II) mixture was practically superimposable on that of pure form II, making it difficult to detect the presence of form I when present at <10% w/w. The DSC profile of the I–III mixture (obtained by evaporation from 95% aqueous ethanol at room temperature) was also not clearly distinguishable from that of pure form II, the only remarkable difference being in the value of the heat of fusion (Fig. 6).

To exclude the possibility of solvent being present, the isolated polymorphs I and II were investigated by TGA: no weight loss was detected in the 40–180°C temperature range. These results confirmed that the differences between the two polymorphic forms I and II in the DSC curves and FT-IR spectra were not due to the presence of solvates.

Finally, polymorphism was clearly confirmed by XRPD patterns of the two isolated polymorphs, forms I and II: their profiles were sufficiently distinct to characterize each crystalline form (Fig. 7). The XRPD pattern of form II corresponded to that previously reported [9,10]. The XRDP profile of form I was clearly different. These differences, both in the

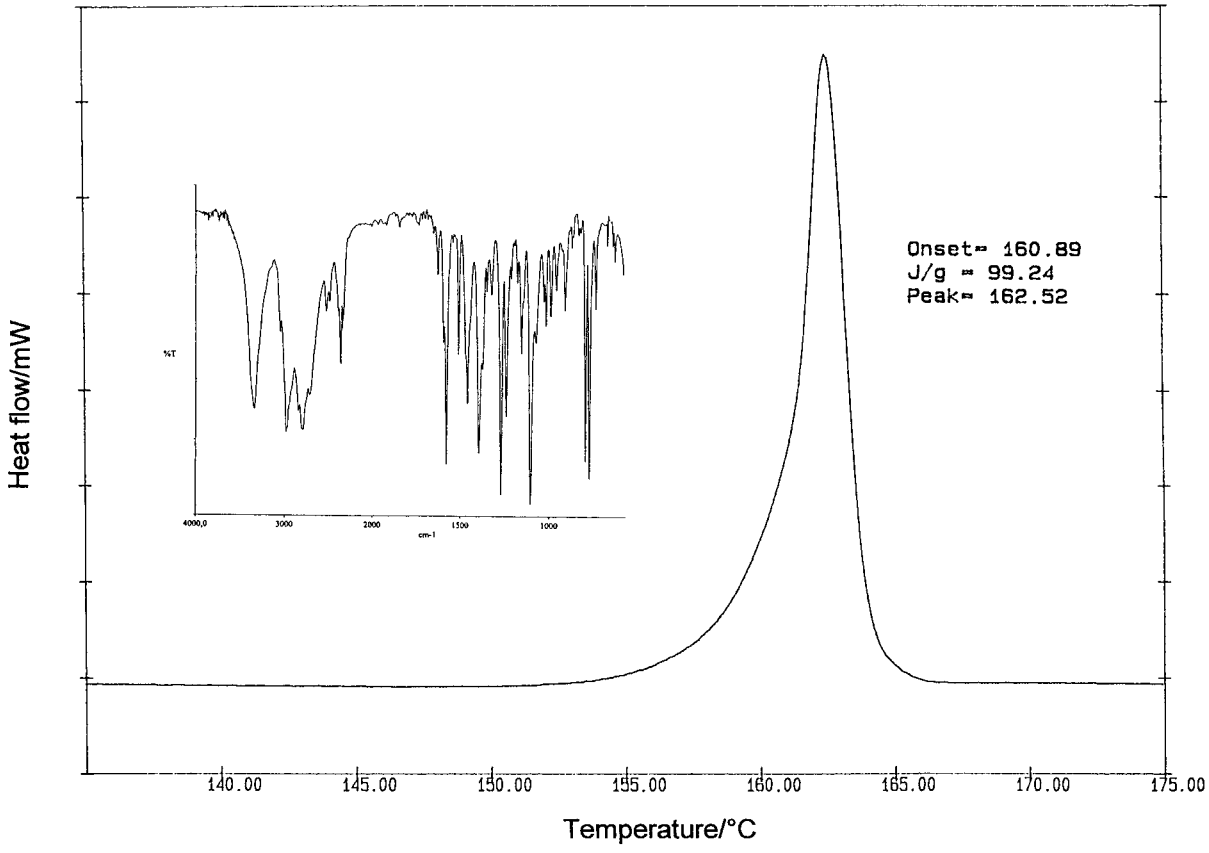

Fig. 6. DSC curve of propranolol hydrochloride form I–III mixture obtained by evaporation of 95% aqueous ethanol solution at room temperature; scan rate, 10°C min^{-1}; heat flow, endothermic scale. Inset showed the corresponding IR spectrum.

positions and in the intensity ratios of the peaks, could not be attributed to a preferred orientation of crystal growth. The presence of a peak at 2ϑ=7.09 could not be accounted for by the unit cell and space group symmetry reported for form II [10] and was, therefore, a conclusive proof for the presence of a polymorphic modification.

4. Conclusions

Propranolol hydrochloride existed in three crystalline forms with unique physical and spectroscopic properties: modification II (which was found in the commercial sample), is the stable form at room temperature. Form II showed little tendency to transform into form I after melting, but probably the transition temperature was so close to the fusion temperature that it was difficult to follow dynamically the heat induced changes by both, FT-IR thermomicroscopy and DSC.

Modification I, the highest melting form, was enantiotropically related to form II, in agreement with previous reports [4] and with the heat-of-fusion thermodynamic rule [11].

Modification III, the lowest melting polymorph, was found only on the alkali halide surface or in the KBr pellets. The alkali halide matrix seemed to catalyze recrystallization of the melt into form III.

According to the thermodynamic infrared rule, form III, which absorbs at higher frequencies, may be assumed to have the largest entropy and to be also the least stable at 0°K [11].

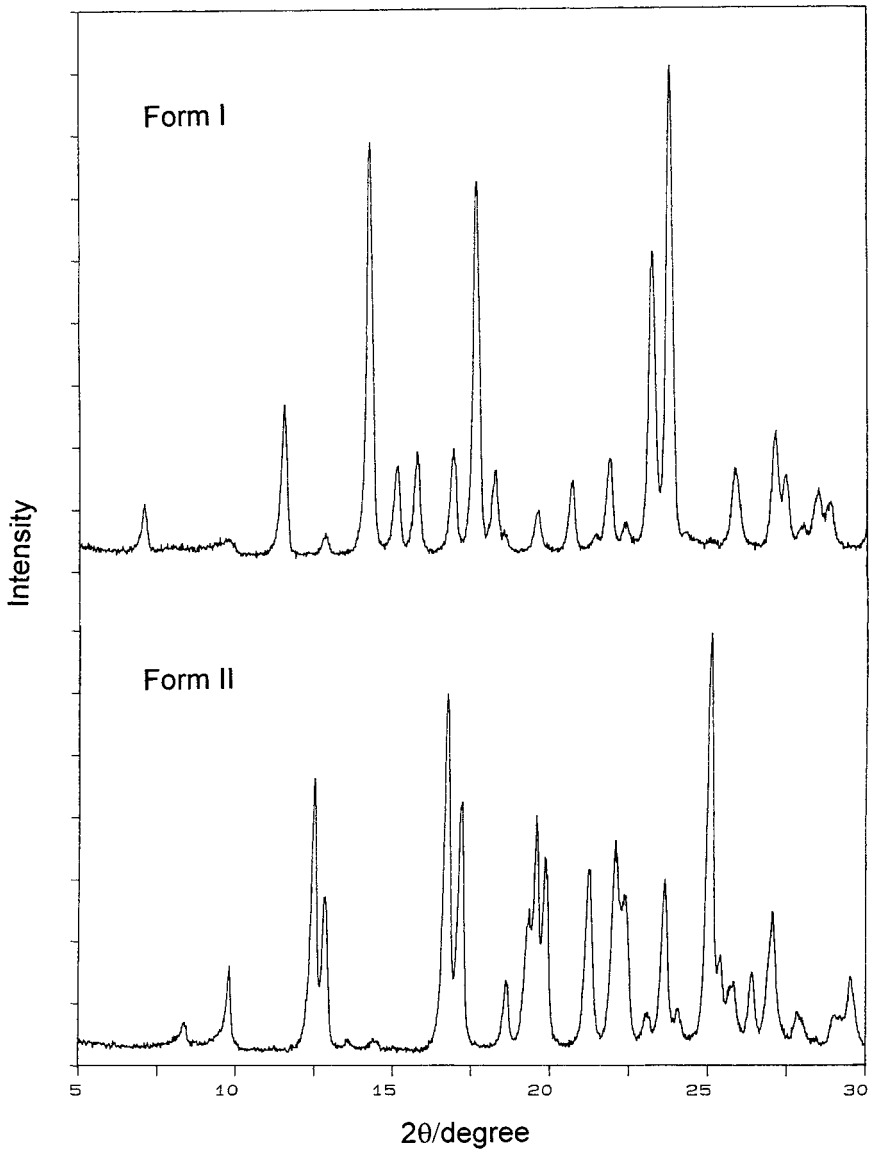

Fig. 7. XRPD patterns for propranolol hydrochloride forms I and II.

These experimental findings are in agreement with the fact that more polymorphic modifications can be obtained by crystallization from the melt than by solvent evaporation. Moreover, crystallization from the melt tended to promote the formation of unstable modifications. [12]

Although systematic stability studies have not been carried out, the crystalline structures of forms I and II seemed to be neither modified nor destroyed by both, mild grinding for 1 min and pelleting. Furthermore, forms I and II had their crystal structures altered by hard grinding (with mortar and pestle for 15 min) and gave rise to the glassy solid that rapidly crystallized into form II. Form I in KBr pellets tended to be transformed into form III fully on heating and cooling the pellet and partially by ageing. The presence of seed crystals enhanced the interconversion process as checked by IR spectroscopy.

Form III was able to exist for at least nine months at room temperature on a KBr window or in KBr pellet. If form III was not removed from the alkali halide surface, its IR spectrum was not modified by mild grinding for 1 min.

Acknowledgements

We are grateful to Dr. G. Moretti for help in acquiring the XRPD data and to Dr. L. Manna for HPLC data.

References

[1] J.K. Haleblian, W. McCrone, J. Pharm. Sci. 58(8) (1969) 911.
[2] M. Elsabee, R.J. Prankerd, Int. J. Pharm. 86 (1992) 221.
[3] S.H. Neau, M.K. Shiwari, E.W. Hellmuth, Int. J. Pharm. 99 (1993) 303.
[4] M. Kuhnert-Brandstatter, R. Vollenklee, Fresenius Z. Anal. Chem. 322 (1985) 164.
[5] Clarke's Isolation and Identification of Drugs, the Pharmaceutical Press, London, 1996, pp. 936.
[6] L. Borka, Pharm. Acta Helv. 66(1) (1991) 16.
[7] L. Borka, Pharmaeuropa 7(4) (1995) 586.
[8] D. Giron, Thermochim. Acta 248 (1995) 1.
[9] R.J. Roberts, R.C. Rowe, Int. J. Pharm. 109 (1994) 83.
[10] K. Shankland, K.S. Knight, Int. J. Pharm. 137 (1996) 255.
[11] A. Burger, R. Ramberger, Mikrochim. Acta II (1979) 259.
[12] M. Kuhnert-Brandstatter, Thermomicroscopy of organic compounds, in G. Svehla (Ed.) Comprensive Analytical Chemistry, Vol. XVI, Elsevier Scientific Publishing Company, Amsterdam, Oxford, New York, 1982, p. 410.