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Physico-chemical characterisation of the modifications I and II of (R,S) propranolol hydrochloride: solubility and dissolution studies

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Abstract

The crystallisation conditions and the physicochemical properties of the modifications I and II of (R,S) propranolol hydrochloride were investigated. Detailed methods of preparation of the two forms were described. Data from FTIR spectroscopy, X-ray powder diffraction, thermal analysis, solubility and dissolution studies were used for the identification and the characterisation of the two forms. The forms I and II were easily differentiated by their IR spectra, X-ray patterns and thermal behaviour. The two polymorphs were found to be enantiotropically related to each other. Their stability was followed at room temperature over a period of 1 year and under different conditions of temperature, grinding and compression to verify the tendency to solid–solid transition and to study the existence range of the two forms. The equilibrium solubilities of the two polymorphs in *n*-octanol were determined as well as their dissolution profiles as pellets in aqueous medium. These studies showed that form I, the less thermodynamically stable, was more soluble (by more than 34%) and dissolved faster than form II in agreement with the thermodynamic rules (A. Burger, R. Ramberger, Mikrochim. Acta II (1979) 259–271).

Keywords: Propranolol hydrochloride; Polymorphism; Infrared spectroscopy; Physical stability; Equilibrium solubility; Intrinsic dissolution

1. Introduction

Propranolol hydrochloride (± 1-[(2-methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol hydrochloride) is an adrenergic beta-receptor blocking drug, marketed as a racemic mixture. It

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is a non-selective antagonist of the β_1 and β_2 receptors, mainly used in the treatment of systemic hypertension. It is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration, but undergoes extensive first-pass metabolism with considerable inter-subject variations [1,2].

The importance of polymorphism on the therapeutic effectiveness of a drug and the pharmaceutical implication of the presence of metastable crystalline forms in the bulk powder are well-recognised [3,4]. It was also shown that the crystal structure could affect tablet porosity and density, the mechanism of disintegration and aggregation, as well as the plastic and elastic properties of solid dosage form [5].

The solid state properties of propranolol hydrochloride have been the subject of a great deal of investigation. Thermal behaviour of propranolol hydrochloride with regard to the relationships between the (+) and (−) enantiomers in the racemic mixture have been previously investigated by differential scanning calorimetry (DSC) [6,7]. Kuhnert–Brandstatter and Vollenklee [8] reported that (R,S) propranolol hydrochloride existed in two crystalline forms, designated I and II. The two modifications were distinguished by means of thermomicroscopy, but no further details on the preparation methods or on their characterisation have been reported. As a part of a recent study on the thermal behaviour of (R,S) propranolol hydrochloride [9] its solid state properties were re-examined and it was found to exist in three polymorphic forms, denoted as I, II and III, according to their decreasing melting temperatures. Modification II represented the commercial form.

The present work summarises the available data on the polymorphism of propranolol hydrochloride, including the preparation, the characterisation in more detail of the two isolated forms I and II, their relative equilibrium solubilities and intrinsic dissolution profiles. The stability of the two polymorphic forms under different experimental conditions and their physico-mechanical properties were investigated to forecast the tendency of crystalline structural changes under grinding, compression and tabletting conditions.

It was impossible to perform the same studies on modification III of propranolol hydrochloride as it could not be obtained pure by solvent crystallisation; it only formed jointly with form I and was not separable from it in a suitable grade of purity. Pure form III was obtained by melting forms I or II on KBr window and cooling and re-heating the melt at 110°C [9]. Due to the poor stability of form III when removed from the KBr surface, its solid state properties have not been investigated in detail. Some aspects of physico-chemical properties of form III crystals have been reported in the aforementioned paper.

2. Materials and methods

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

All solvents were of analytical grade.

2.1. Preparation of the polymorphs: crystallisation procedures

Propranolol hydrochloride was recrystallised from various organic solvents of different polarity in order to check its capacity to give different crystalline modifications, either polymorphs or solvates.

In each experiment about 50 mg were dissolved in an appropriate amount of water, acetone, methanol, absolute ethanol, 95% aqueous ethanol, *n*-propanol, ethyl acetate and dioxane/water mixtures in different ratio.

Recrystallisation was firstly obtained by evaporation of solvent at room temperature, then it was forced by evaporating the solvent in water-bath and in vacuum-oven at various temperatures or by crystal precipitation on ice-bath.

Solvate forms have never been obtained, as confirmed by thermogravimetric experiments. An amorphous glasslike solid was obtained by lyophilisation from a water solution. This form was so unstable that by scratching, touching or heating it gave rise to form II. The glassy solid could be stabilised for 1 month by storing it at −18°C.

Form I was prepared by vacuum evaporation of a 95% aqueous ethanol solution and by heating the residual glassy product at 100°C for at least 60 min in a Heraeus vacutherm oven. This method occasionally led to production of the forms I and II from the same solution. Therefore it was often necessary to repeat this crystallisation more than once. However crystal aggregates of form I could be physically separated by those of form II.

Evaporation of 95% aqueous ethanol solution at room temperature or in water-bath at 100°C gave mixtures of form I and III.

Form I was also obtained by crystallisation of a saturated absolute ethanol solution on ice-bath, but this method was found to give less reproducible results.

Form II was easily produced by evaporation of methanol, water, *n*-propanol and acetone solutions at room temperature. Crystallisation from a saturated solution of the drug in acetone on an ice-bath produced form II consisting of fine particles of homogeneous size.

The resulting samples were stored in a desiccator for 3 h and tested by TGA for solvent loss.

UV and HPLC analysis (by the Eur. Ph. assay procedures) performed on polymorphs I and II obtained by crystallisation indicated that no degradation had taken place.

2.2. Polymorphs characterisation

FTIR spectra of the two crystal forms were obtained using a mull in liquid paraffin (nujol), a dispersion (0.5%) in alkali halide (KBr) disk and directly on untreated powder by means of i-series Perkin Elmer microscopy coupled with a FTIR spectrometer. Spectra were recorded at room temperature from 4000 to 650 cm^{-1} on a Perkin Elmer System 2000 spectrometer. For each sample 32 scans were collected at a resolution of 4 cm^{-1}.

X-ray powder diffraction (XRPD) patterns were obtained with a Philips P.W. 1710 diffractometer in the 2θ range between 3 and 60° using Cu Kα radiation-Ni filtered (40 KV; 40mA). The step scan mode was performed with a step width of 0.02° at a rate of 1 step s^{-1}.

DSC thermograms were recorded using a Perkin Elmer DSC7 instrument. Approximately 1.5 mg of sample were accurately weighed into a DSC open pan. The use of open pan allows for pressure release and permits a correct comparison with TGA experiments. The DSC profiles were recorded at 10°C min^{-1}, under nitrogen flux, from 40 to 180°C. The DSC temperature scale was calibrated using extrapolated onset temperatures of the fusion endotherms of indium and zinc pure standards, heated at the same rates used for the samples.

The thermogravimetric curves were recorded with a Perkin Elmer TGA7 instrument coupled with a System 2000 FTIR spectrometer, at a heating rate of 10°C min^{-1}. For TGA determinations, approximately 10 mg of sample were used. A temperature calibration of the thermogravimetric apparatus was performed 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.

2.3. Stability studies

Samples of propranolol hydrochloride form I and II were stored at room temperature for 1 year on open air ($\approx$ 55% RH) and in a desiccator, to test the stability of the different crystalline forms in such conditions and to check the different ability of the two forms to uptake water from the environment.

Aliquots of the two forms were also stored in oven at 70, 110 and 140°C up to 48 h to test the effect of temperature on the polymorphic system. DSC, TG, FTIR analyses were carried out on each sample.

2.4. Physico-mechanical property studies: grinding and compression effects.

The two crystalline forms (about 10 mg) were manually ground and milled in an agate mortar with a pestle, separately for 1, 5 and 15 min.

Their DSC profiles and IR spectra were recorded after these processes.

About 30 mg of the two forms were placed in the Specamill ball mill and samples were withdrawn at 5, 30 and 60 min and tested for polymorphic transition.

Pellets of the two crystalline forms were prepared by accurately weighing 50 mg of the samples which were placed in an evacuable stainless steel die and pressed in a Perkin Elmer manual hydraulic press to obtain a 13 mm diameter sample pellet. Three levels of pressure were applied: 2 tons cm^{-2} for 5′ and 90′; 5 tons for 5′ and 90′ and 10 tons for 5′, 15′ and 90′.

Samples were taken from the core of each tablet and were screened for polymorphic transition using DSC and FTIR. Compressed disks obtained by 10 tons cm^{-2} of pressure for 15′ were used for intrinsic dissolution studies.

2.5. Equilibrium solubility studies

The solubility of each polymorph was investigated in various solvents like water, *N*,*N*-dimethylformamide, methanol, ethanol, 2-propanol, *n*-butanol, 3-methyl-1-butanol, and *n*-octanol. As propranolol hydrochloride is very soluble in water and in most of the aforementioned solvents, *n*-octanol was chosen, allowing use of a lesser amount of substance.

Saturated solutions were prepared by introducing excess amounts of form I and II (10 mg) into 1 ml of *n*-octanol in screw cap vials. The samples were placed in a thermostatic water-bath maintained at 20 and 37 ± 0.5°C for 15, 30, 45, 60 min and subjected to magnetic stirring. Aliquots of the solutions were withdrawn with a syringe, filtered through a 0.45-μm membrane filter (Millipore type HV) and appropriately diluted with *n*-octanol (1:50; 100 μl in 5 ml of solvent). The concentration of the drug was measured and spectrophotometrically analysed at 292 nm (λ_{MAX} of absorption of propranolol hydrochloride in *n*-octanol) by a Hewlett Packard model 8452A diode array spectrophotometer. The state of true equilibrium was reached when the concentrations of the samples fell to constant values.

The equilibrium solubility value was confirmed by preparing saturated solutions in glass vials by adding an excess of each form into an appropriate volume of *n*-octanol so that a sediment was left either after 1 h of vigorous shaking or after 24 h without agitation at 20°C. The samples were centrifuged and filtered through a 0.45 μm membrane filter, diluted in the solvent and then quantitatively determined by UV absorption at 292 nm. The solids remaining after the solubility studies were analysed by DSC and FTIR. All reported data represented the mean values of at least three separate experiments that always showed a good reproducibility.

2.6. Intrinsic dissolution studies

Dissolution studies were carried out by stationary disk method [10], using Dissotest Prolabo, a rotating paddle apparatus. 50 mg of the samples were compressed into constant surface pellets as described above. The compressed disk was not ejected from the die; the die cavity was stoppered so that only one planar surface was exposed to the dissolution medium. The die carrying the compressed disk was placed into the dissolution apparatus in a fixed position relative to the stirrer: the distance of the paddles from the sample surface was set at 25 mm. The samples compressed as disk (13 mm diameter) under 10 tons cm^{-2} of pressure for 15 min were tested under the following conditions: 0.1 N HCl solution as dissolution medium (900 ml); at 20 and 37°C; 50 rpm stirrer velocity.

The dissolution medium was continuously pumped through a Beckman flow-through cell at a constant flow rate by means of a peristaltic pump. The flow-through cell was enclosed in a Hewlett Packard 89100A temperature controller, held at 20 and 37°C. The amount of propranolol hydrochloride dissolved per time unit was followed spectrophotometrically at 290 nm [2] with a Hewlett Packard Model 8450A diode array spectrometer.

3. Results and discussion

Efforts were made to obtain form I in a suitable amount to perform solubility and dissolution studies by crystallisation with a variety of solvents, but it was very difficult to produce it rather than the other more stable form.

The crystallisation experiments clearly indicated that the simple crystallisation at room tempera-

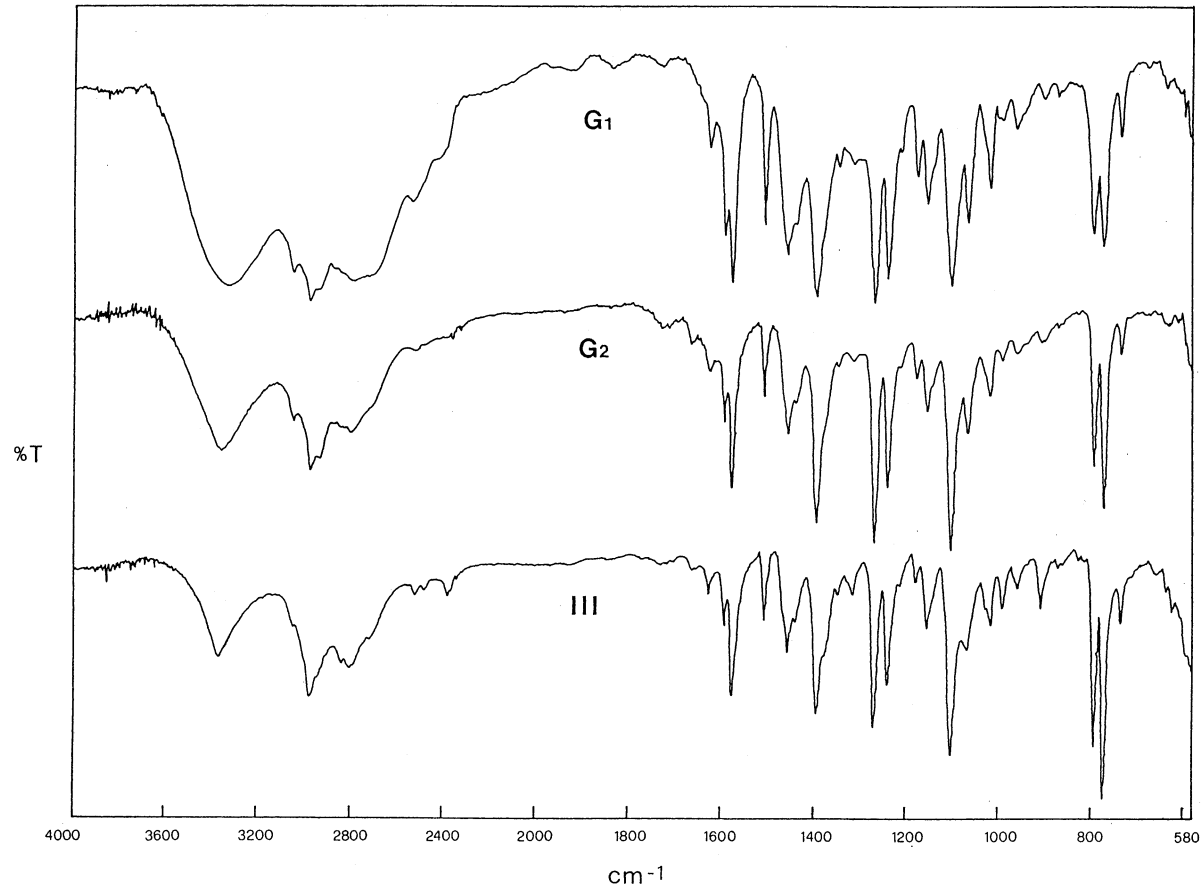


Fig. 1. FTIR spectra in the 4000–580 cm^{-1} range of the glassy solid obtained by solidification of the melt (G_1), the first material obtained from aqueous ethanol solution evaporation (G_2) and form III.

ture from the selected organic solvents always gave rise to the starting material, form II. In many instances the temperature at which the solvent was removed affected the form of the resulting solid. Isolation of pure form I was successful by vacuum evaporation of a 95% aqueous ethanol solution until a glassy solid was obtained which was held at 100°C up to complete crystallisation. This temperature was chosen taking into account the thermomicroscopy and heating–cooling experiments results [9]. In fact, during the crystallisation experiment the first material to separate from solution was in the form of droplets of melt, a glassy transparent material, which subsequently crystallised. This suggested that the conditions of crystallisation from solution would be the same as those for crystallisation from the melt. This could be supported by the fact that the glassy material separated from solutions was similar, in the appearance but also in the IR spectrum (Fig. 1) and in thermal behaviour, to the melt. The nucleation step from the glassy material was the critical point of the crystallisation process. In fact, touching the glassy solid with a needle was sufficient to induce crystallisation of form II: the imperfections on the container surface or the presence of dust particles could practically provide a stimulus to crystallisation. It was often necessary to repeat this crystallisation many times under controlled and reproducible conditions and to accurately check all the experimental conditions, such as the oven cleaning, to avoid the unintentional seeding with form II crystals.

The repeatability of form I formation was verified by FTIR and DSC on each batch. Form II or III traces were easily detected by DSC and IR. However crystal aggregates of form I and form II could be visually distinguished and physically separated. Both the forms took the habit of spherulites, disk-shaped crystal aggregates in which crystals are distributed with a different degree of roundness about a centre, but a fine structure of opaque needle-like crystals and of transparent thinner prismatic crystals was seen for form I and form II, respectively.

Solvate forms of propranolol hydrochloride were never obtained. 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.

FTIR spectroscopy was a useful tool to distinguish the two polymorphic forms. The two forms as previously reported [9] exhibited significant differences in the observed vibrational transitions. The crystalline structures seemed to be neither altered nor destroyed by pelletting. For each form the FTIR spectra obtained directly on the powder by infrared microscopy or using a mull in liquid paraffin and a dispersion in KBr pellet were not markedly different from each other with respect to the positions, sharpness and intensity ratio of the bands. The two forms were easily differentiated by their IR absorption bands in the 3600–2000 cm^{-1} range, but were distinguishable over the whole 3600–650 cm^{-1} range of frequencies. In the 3600–3300 cm^{-1} range (OH and NH stretching vibrations) a single band at 3337 cm^{-1} was seen in the spectrum of form I, while a band with a bigger intensity at 3280 cm^{-1} with two shoulders at 3325 and 3321 cm^{-1} was observed for form II. These spectra distinctly differed in the location and intensity as well as in fine structure of some major absorption bands. In the 2000–650 cm^{-1} range the fundamental frequencies positions were nearly the same, the differences consisting in the relative intensity ratio of the bands and the presence of specific peaks for each form. The frequencies of the fundamental bands attributed to propranolol hydrochloride by Clarke [1] compared to those reported in the present work for form I and II are shown in Table 1. The frequencies reported by Clarke are closer to the ones of form I, which are shifted to higher frequencies. The fingerprint region of the spectrum differentiated each form and could be used for the characterisation and identification of the different crystalline modifications.

Fig. 2 shows the form I and II spectra in the 1700–700 cm^{-1} range. The specific bands for each form, also suitable for identification in mixture, are marked in the figure with arrows.

As previously reported [9] the XRPD patterns of the two forms were sufficiently distinct to characterise each crystalline form: they showed differences both in the positions and in the intensity ratios. Differences in X-ray diffraction patterns indicated different arrangements of propranolol hydrochloride molecules in the crystal lattice of the two forms. The X-ray diffraction patterns for form II were consistent with those previously reported [11–13]. The polymorph I exhibited numerous different peak positions distinguishing itself from the known crystal form. The characteristic angles of diffraction together with the four main peak intensities for the two crystal forms are listed in Table 2.

The thermal behaviour of the propranolol hydrochloride polymorphs has already been extensively reported [9]. The DSC profiles of form I and II, recorded at a heating rate of 10°C min^{-1}, showed quite sharp fusion endotherms: form I with an onset temperature of 163.0 ± 0.3°C (peak temperature: 166.0 ± 0.5°C) and an enthalpy of fusion of 106 ± 0.8 J g^{-1}, while form II showed an onset temperature of 161.8 ± 0.1°C (peak temperature: 163.6 ± 0.2°C) and an enthalpy of fu-

Table 1
IR specific major bands for propranolol hydrochloride reported by Clarke [1] compared with the related bands obtained for forms I and II (wavenumber given in cm^{-1})

Literature data	I	II
1103	1102.9	1106.8
1270	1271.8	1267.5
772	773.9	770.2
1580	1579.1	1578.9
795	794.4	797.6
1240	1241.9	1241.1

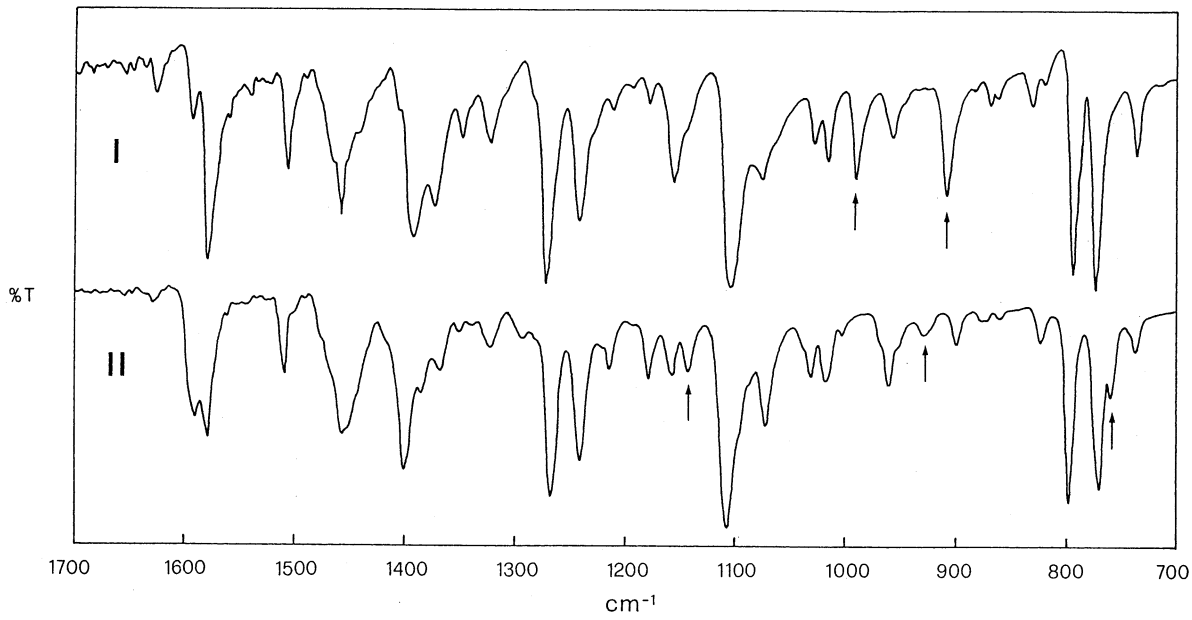


Fig. 2. FTIR spectra in the fingerprint region (1700–700 cm^{-1}) of forms I and II of propranolol hydrochloride (0.5% in potassium bromide disk). Specific peaks for each form are pointed with arrows.

sion of 123.8 ± 1.6 J g^{-1}. The different enthalpy fusion values were very useful to distinguish form I and II in mixture. Since forms I and II showed onset temperatures quite close to each other, this made difficult to detect the presence of form I when present at a level lower than 10% in mixture with form II [9], the only remarkable difference being the value of the heat of fusion. The good reproducibility of the fusion enthalpy value of form I also allowed to detect the presence of little amount of contaminant polymorph III in mixture with it. According to the heat of fusion rule [14], form I, the higher melting form with the lower heat of fusion, should be in an enantiotropic relationship with form II. An enantiotropic relationship implies that each form has a range of temperature over which it is stable with respect to the other and a transition point at which the forms are equistable and in principle interconvertible. Thermomicroscopy and heating–cooling experiments by DSC, reported in the aforementioned paper, showed that there is no observable transition point but only hardly detectable tendency of form II to convert in form I above the melting point.

Table 2
X-ray powder diffraction data for forms I and II of propranolol hydrochloride

Form	I/I_0	2θ (°)
I	100	23.765
	85	14.255
	77	17.650
	61	23.220
II	100	25.085
	86	16.735
	66	12.510
	60	17.195

Stability of form I and II of propranolol hydrochloride depended significantly on the grinding conditions. In fact, both forms seemed unaffected by mild grinding in a mortar for 5 min and in a ball mill up to 90 min. Vigorous grinding in a mortar for 15 min altered the crystalline structure, giving rise for both the forms to an amorphisation of the crystals, followed by their recrystallisation into form II. It is noteworthy that hard grinding (grinding about 1 mg of both the forms in a mortar with a pestle) for 5 min could also gave

rise to a transition to form II, mediated by the amorphous form. The influence of compression on polymorphic transition was also investigated: pressing forces up to 10 tons cm^{-2} for 90 min did not alter the crystalline modifications of propranolol hydrochloride. In fact no differences in the IR spectra and DSC profiles could be detected after compression.

Both the polymorphic forms did not show tendency to uptake water as checked by thermogravimetric experiments.

The crystalline structures of forms I and II did not show any polymorphic transition after a year at room temperature. Heating also for a long period (48 h up to 140°C) did not cause conversion of form I into polymorph II. These results, which were also in agreement with the previous theoretical considerations on the thermodynamic relationship of the two polymorphs, suggested that both the forms had a wide range of stability.

Equilibrium solubilities of forms I and II were investigated by comparison of several experimental results. In butanol solution no differences between the two polymorphs could be detected. In this medium both polymorphs showed an extremely high solubility.

3-Methyl-1-butanol showed at 20°C a certain discriminant power (form I about 18% more soluble than form II), but the solubility values were not reproducible. The saturation conditions for the two crystal forms were determined in *n*-octanol at 20°C and at 37°C. *n*-Octanol, being much less polar than butanol and 3-methyl-1-butanol, discriminated between the two polymorphic forms.

At 20°C both the forms reached saturation within 60 min. The equilibrium solubility value at 20°C was confirmed by comparison of the results obtained at 20°C by stirring for 1 h and storing without stirring for 24 h saturated solutions of the two forms. The results of equilibrium solubility studies are reported in Table 3. It can be seen that form I attained a higher concentration than form II, the form thermodynamically more stable at 20°C. The amount dissolved from form I was about 34% higher than that from form II. The thermodynamically less stable form I resulted more soluble than form II in agreement with what has been previously reported [8] and with the thermodynamic rules [14].

Table 3
Equilibrium solubilities of form I and II measured at $T = 20$ °C

Form	Equilibrium solubility after 1 h in mg ml^{-1} [a]	Equilibrium solubility after 24 h in mg ml^{-1} [b]
I	7.36 ± 0.09	7.20 ± 0.09
II	5.43 ± 0.08	5.39 ± 0.12

[a] Subjected to a constant stirring rate.
[b] Without stirring.

No difference in solubility was found between the polymorphic forms in *n*-octanol at 37°C. In fact within few minutes the two forms reached a common constant value of 7.5 mg ml^{-1}.

FTIR and DSC studies were performed on the solid remaining after solubility studies had been completed: in all cases the solid phases isolated at the end of each experiment corresponded to the initial form, demonstrating that a solvent–mediated phase transformation did not occur.

The free energy difference ($\Delta G_{I,II}$) between the two polymorphs at a particular temperature (20°C) is an indication of their relative stability and can be obtained by means of solubility measurements according to the formula:

$$\Delta G_{I,II} = RT \ln \frac{\text{solubility of form I}}{\text{solubility of form II}}$$

where T is the temperature (K) at which the solubilities were determined and R is the gas constant [15–17]. The solubility ratio between form I and form II at 20°C subjected to magnetic stirrer for 1 h in *n*-octanol was found to be 1.35 and the free energy difference between the polymorphs was 0.73 $kJmol^{-1}$.

Due to the high solubility of propranolol hydrochloride, particle size distribution for the two polymorphs was initially not investigated. However, in order to obtain good infrared spectra by infrared microscopy and X-ray powder diffraction patterns, the two forms were pre-ground with a pestle in an agate mortar and large crystals comminuted. In order to complement solubility studies results, microscopic observation was performed by scanning electron microscopy

(SEM): crystals of the two forms were very similar in their morphology and the main proportion of the crystals showed a particle size below 10 μm, while single crystals could show a particle size up to 50 μm.

The dissolution properties of the different modifications were studied by determining the relative intrinsic dissolution in 0.1 N chloridric acid at 20 and 37°C. It is well-known that the dissolution rate of a drug is only important where it is the rate-limiting step in the absorption process from a solid dosage form. The water solubility of propranolol hydrochloride exceeded 10 mg ml^{-1}, so bioavailability related problems were not expected. These studies were performed to further characterise the two polymorphic forms and to evaluate their different dissolution in an aqueous medium.

According to the Nelson assumption [18], for a dissolving disk with an essentially constant surface area, under sink conditions, the dissolution process can be described by:

$$W = kC_s t$$

where W is the amount dissolved, C_s is the solubility of the substance at time t, and the constant k includes the surface area of the dissolving disk, the diffusion coefficient and the diffusion layer thickness. The advantage of the constant surface area method is evident in that its profiles are linear with the time and more easily compared. Additional information about the relative surface areas or particle size distributions of the two materials is not required, since these differences were eliminated when analyte disk was prepared.

Pellets of the two forms were checked before the dissolution test: a scrap was obtained from the protected side of the pellet to perform DSC and FTIR analysis. No transformation associated with compression was found in the disks in agreement with stability studies. A comparison between the dissolution profiles of the two polymorphs at 20°C is shown in Fig. 3. The increase in the slopes of the straight lines should follow the order of their saturated solubilities: it can be seen that the initial dissolution rates within 10 min were in the order form I > form II. Concentration plateaus were reached within 15 min. Dissolution at 37°C showed the same profiles, but saturation was attained within few minutes. As expected from theoretical consideration, form I dissolved faster than stable form II in an aqueous medium.

The intrinsic dissolution profiles suggested that no conversion to other phases takes place during the dissolution experiment. To exclude that the conversion of metastable form I to stable form II did occur at the surface of the disks exposed to the dissolution medium, the pellets were withdrawn before the end of some selected dissolution runs. No changes were observed in the DSC patterns and FTIR spectra of the two forms.

4. Conclusions

Propranolol hydrochloride was showed to exist in three crystalline forms with unique physical and spectroscopic properties. Form I and II were obtained by crystallisation from solvents and could be isolated in a suitable grade of polymorphic purity to permit a complete physico-chemical characterisation of each form. Form III was obtained by melting form I or II on an alkali halide disk, cooling at room temperature and reheating the melt at 110°C. The alkali halide surface

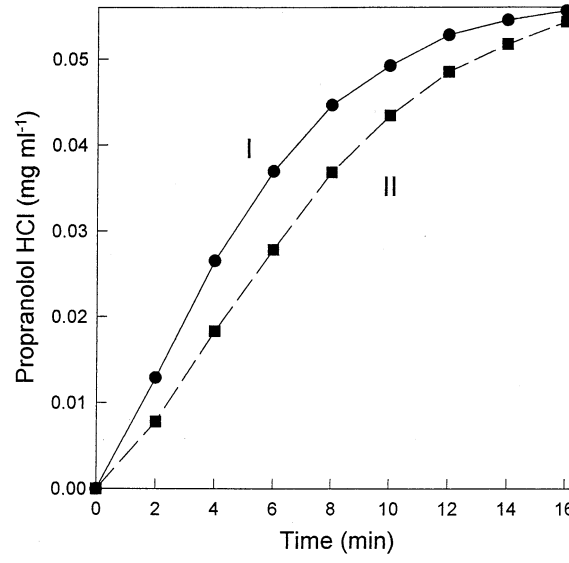
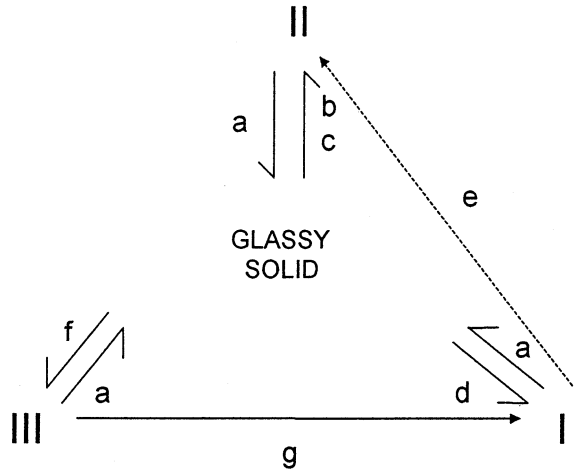


Fig. 3. Dissolution profiles of form I and II pellets at 20°C.



a = heating above melting point
b = crystallisation at room temperature from solvents
c = touching with a needle or scratching
d = vacuum evaporation of 95% aqueous ethanol solution and heating at 100 °C the residual glassy product
e = hard grinding
f = crystallisation at room temperature or at 110 °C on KBr disk
g = by ageing and on removing the crystalline film from KBr window surface

solid-solid transition

transition mediated by an amorphous glasslike intermediate

Scheme 1.

played a major role in the preferred crystallisation of form III; in fact the glassy solid obtained on this surface never crystallised into form I. Form III could be obtained by crystallisation from solvent only in mixture with form I [9].

Infrared spectroscopy provided a useful mean of identifying the three polymorphs. Thermal analysis is not recommended as a primary tool for identifying propranolol hydrochloride modifications, but the knowledge of their thermal behaviour was found to be helpful in determining the crystallisation conditions of the three polymorphs and in evaluating their polymorphic purity.

Form I, the highest melting form, showed a higher solubility and a faster dissolution than polymorph II and results enantiotropically related to form II with decreasing stability in the order II > I at room temperature. All the experimental evidences confirmed that the commercial product, modification II, was the more thermodynamically stable at room temperature. Form II showed a little tendency to be transformed into I after the melting, but this transition was difficult to observe by DSC and thermomicroscopy.

Both the forms were shown to have good physical stability: in fact the two forms were able to exist for at least 1 year at room temperature; no change in crystalline form by mild grinding, compression up to 10 tons cm^{-2} and storage in oven at temperatures up to 140°C for 24 h were observed. No interconversion between the polymorphs mediated by dissolution medium was detected even after storing the saturated solution for 24 h. No solid–solid transition was observed between the two forms before melting temperature: the conversion into each other can only be produced in the melt.

Form III showed the lowest melting point (≈ 154°C) [9] and the highest frequencies in the IR spectrum (Fig. 1). 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 [14]. Therefore the stability order for the three polymorphs should be II > I > III at room temperature. This conclusion is in agreement with the fact that crystallisation from the melt tends to promote the formation of unstable modifications and with the experimental evidence. In fact, although systematic stability studies on form III could not be carried out, 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 into a mixture of form I and III. Form III was able to exist for at least 10 months on a KBr window, but after this time the sample stored on KBr window showed form I traces, checked by infrared microscopy. These results suggested that by ageing form III converts into form I by a solid–solid transition.

The phase relationships among the propranolol hydrochloride polymorphs are summarised in Scheme 1.

As a general conclusion, it could be postulated that form III was an important intermediate in the formation of form I, although this step was not detectable unless in presence of the alkali halide. This supposition was supported by the fact that the glassy material and form III are very similar in their IR spectra (Fig. 1) and that mixtures of form I and III were easier to obtain by crystallisation from solvents than pure form I.

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