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Solid-state forms of paroxetine hydrochloride

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Summary

Paroxetine hydrochloride exists in two solid state forms differentiated by their degrees of hydration. Form I is a non-hygroscopic hemihydrate and is thermodynamically the more stable. Form II is a hygroscopic anhydrate the moisture content of which is controlled by the prevailing humidity. Form II converts to Form I, if seed crystals of Form I are present, when exposed to humid conditions or if subjected to compression. The rates of transformation were determined by infrared spectroscopy and techniques are described to identify the solid state form in compressed tablets. The transformation follows kinetic models described by diffusion and phase boundary processes and the rate constant (k) is related to temperature by the Arrhenius equation. At constant temperature ln k is related to the reciprocal of the compaction pressure. Thermodynamic measurements of free energy (ΔG_T) and enthalpy (ΔH_T) show the two forms to be energetically similar and measurements of dissolution indicate that both forms would be expected to be bioequivalent.

Introduction

It is well established that many drug entities exist in different solid state forms (Haleblian, 1975) and that these forms can have differing physical, chemical and biological properties (Byrn, 1982). Such differences may have important implications for the stability, processing properties or bioavailability of drug substances. It is important therefore that, when a drug substance is being developed, its propensity to exist in more than one solid state form be investigated. Polymorphs or pseudopolymorphs if shown to exist should be thoroughly characterised so that any necessary steps can be taken to ensure consistent manufacture of the preferred form.

Paroxetine hydrochloride (Lund et al., 1979) is a novel 5-HT uptake inhibitor currently undergoing clinical evaluation. Changes in the conditions of synthesis revealed the existence of two distinct crystalline forms differing in their levels of hydration. They were conventionally defined as pseudopolymorphs I and II. The object of the studies reported here is to evaluate the physicochemical and thermodynamic properties of both forms with a view to identifying a preferred form for subsequent development.

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Materials and Methods

Materials

Paroxetine hydrochloride was prepared by Beecham Pharmaceuticals. Form I was prepared by crystallisation from aqueous propan-2-ol (10% water) and Form II by crystallisation from anhydrous propan-2-ol. Structure and form were confirmed by infrared spectroscopy.

Solubility studies

Aqueous solubilities were determined by shaking an excess of paroxetine hydrochloride with solvent at constant temperature for 24 h. The supernatant liquid was filtered and suitably diluted with water to allow the concentration to be measured spectrophotometrically at 294 nm using an A_1^1 of 120. Solubilities thus determined are expressed in terms of the pure free base. A direct solubility comparison of a representative batch of each form was made by determination of the solubilities at temperatures between 15 and 50 °C; Van't Hoff plots were constructed for both forms by plotting the natural logarithm of the molar solubility ($\ln C_s$) vs reciprocal absolute temperature ($1/T$). Heats of solution (ΔH_s) were calculated from the slopes of the Van't Hoff plot.

Equilibrium moisture contents

Samples of both forms were stored at 20 °C in environments of constant relative humidity ranging from 44% to 100% until there was no further change in sample weight. The equilibrium moisture content was calculated from the sum of the initial moisture content determined by Karl Fischer titration and the net weight change on storage.

Dissolution studies

Intrinsic dissolution rates were determined on compressed discs. Approximately 400 mg of paroxetine hydrochloride were compressed to a force of 2 tons in an infrared die and the compact secured in the stirrer assembly (Fig. 1) with molten stearyl alcohol. The external dimensions of the stirrer assembly were identical to the baskets described in the U.S.P. Excess stearyl alcohol was carefully removed from the plane of the disc face and the whole assembly was placed in the U.S.P. dissolution apparatus. The discs were rotated at 100 rpm in 1000 ml of water maintained at 37 °C. The paroxetine release was monitored for 1 h spectrophotometrically at 294 nm. Each dissolution rate was a mean of 6 determinations and calculated as the slope of the linear plot of mass of paroxetine released vs time divided by the area of the disc face in $\mu g/s/cm^2$. To avoid any possibility of change of crystal form, the measurements were recorded as soon as possible after the preparation of the discs. Additional discs prepared and analysed by IR spectroscopy confirmed that there was no change in form under the conditions of sample preparation. Dissolution rate measurements were also carried out on tablet and capsule formulations employed in the clinical programme utilising U.S.P. apparatus No. 2 with 1000 ml of 0.06 M hydrochloric acid at 37 °C as the dissolution medium and a stirrer speed of 60 r.p.m. The capsules were weighted with a small copper coil to prevent floating. Results were expressed as times taken to attain dissolution of 90% of the nominal drug content in the dosage form.

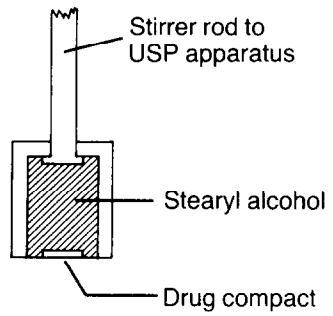

Fig. 1. Intrinsic dissolution rate assembly.

Infrared (IR) measurements

Infrared spectra were recorded as Nujol mulls on a Perkin Elmer 580A spectrophotometer controlled by a Perkin Elmer 3600 Data Station. Identification of solid state form in admixture with excipient materials was achieved by recording the spectra of the sample and the corresponding excipient mixture and storing both in the data

station. Subtraction of the excipient mix spectrum from that of the sample showed sufficient detail for a positive identification.

Transformation studies

Transformation studies were carried out on compressed compacts prepared from a mixture of paroxetine hydrochloride (Form II 13.8%), magnesium stearate (0.5%) and sodium chloride (85.7%). The compacts had a nominal weight of 250 mg and were produced using a Manesty F3 single punch tabletting machine equipped with 7-mm-diameter flat-faced punches. The upper punch was fitted with a strain gauge connected via a Wheatstone Bridge circuit and amplifier to a cathode ray oscilloscope. Using this monitoring device the compressive force on the tablets could be recorded and adjusted by means of the machine hardness control. The compacts were gently ground to a fine powder using a pestle and mortar and the IR spectra were recorded. Absorbance ratios were calculated for the bands at 675 and 665 cm^{-1} representing Forms I and II, respectively. This was performed automatically by a Perkin Elmer OBEY programme or manually by converting transmittance values to those of absorbance and calculating the appropriate ratio. A calibration curve was established for standards containing accurately known ratios of Forms I and II and samples quantified by reference to this plot.

Differential scanning calorimetry (DSC)

DSC was carried out in open pans using a Dupont Model 990 Thermal Analyser. Heats of fusion (ΔH_f) were calculated from the area under the melting endotherm. The areas were determined by graphical square counting and the DSC cell was calibrated with indium as a standard.

Results and Discussion

The existence of two solid state forms was initially evident from a comparison of infrared spectra obtained from Nujol Mulls (Fig. 2). It was significant that these differences were substantially reduced when the samples were prepared as potassium bromide discs since the process of disc preparation tended to reduce the crystallinity of both forms. Further confirmation was obtained from differences in powder X-ray diffraction patterns and from DSC thermograms. The latter showed each form to be monotropic since only the melting endotherms were observed in each case. The fact that the major differences in the IR spectra were located in the hydroxyl stretching region suggested that the forms may be discriminated by their levels of hydration. Certainly the equilibrium moisture contents (Fig. 3) were different when samples were exposed to various relative humidities. Thermogravimetric analysis (TGA) experiments (Fig. 2) showed that the higher melting Form I did not lose weight until the temperature was in excess of 100 °C whereas Form II lost weight steadily between ambient temperature and the melting point. These data are con-

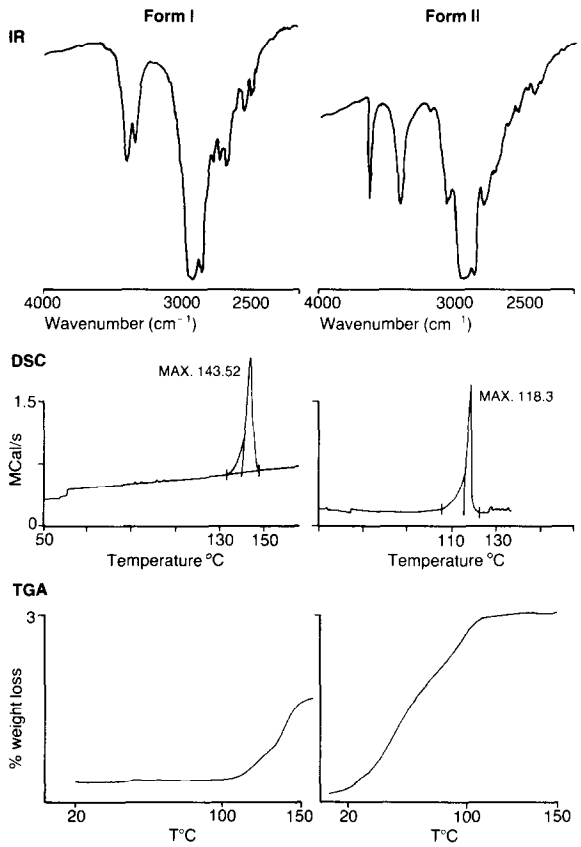

Fig. 2. Comparison of IR, DSC, and TGA for Forms I and II.

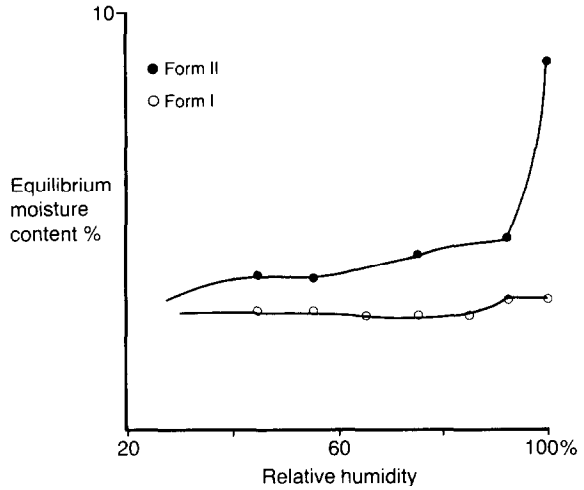

Fig. 3. Equilibrium moisture contents for Form I and II.

sistent with Form I existing as a discrete hemihydrate and Form II as a hygroscopic anhydrate, the water content of which is determined by the prevailing relative humidity.

Solubilities and dissolution rate

In general terms, problems of incomplete absorption are most frequently encountered with drugs of poor solubility. It has been suggested (Florence and Attwood, 1981) that where aqueous solubility is less than 3 mg/ml, dissolution rate in vivo could be rate limiting in the absorption process. The solubilities of both forms of paroxetine hydrochloride at room temperature exceed this threshold albeit by a relatively small margin (Table 1). Furthermore, there is a higher solubility for Form II at all temperatures and the effect that such solubility differences between the crystal forms have on absorption is therefore relevant. In terms of in vitro release, the measurement of intrinsic dissolution rate indicates a greater difference between the two, although the dissolution rates from tablet and capsule formulations were very rapid. Irrespective of crystal form, 90% of the nominal contents appeared in solution in less than 15 min.

Thermodynamic measurements

The free energy change (ΔG_T) associated with the transition between Forms I and II was calculated directly from solubility (C_s) measurements at 20 °C via Eqn. 1:

$$\Delta G_T = RT \ln \frac{C_s(I)}{C_s(II)} \quad (1)$$

The enthalpy of transition (ΔH_T) was determined from both solubility measurements and DSC using Eqns. (2) and (3) respectively:

$$\Delta H_T = \Delta H_s(I) - \Delta H_s(II) \quad (2)$$

$$\Delta H_T = \Delta H_f(I) - \Delta H_f(II) \quad (3)$$

Although heats of solution (ΔH_s) can be measured directly by solution calorimetry (Lindenbaum et al., 1985, Ip et al., 1986) it was convenient to determine the aqueous solubility of each form as a function of temperature and to calculate the heats of solution from the Van't Hoff plots (Fig. 4).

Over the temperature range studied plots for both forms were linear and virtually parallel confirming the monotropic relationship of both forms. Within experimental error the heats of solution were virtually identical indicating that the enthalpy of transition was close to zero (Table 2).

A low enthalpy of transition was confirmed by DSC measurements of heats of fusion. In the case of Form I, quantitation of the area under the melting endotherm was complicated by the slow loss of water from the stable hemihydrate. At normal scanning rates the ΔH_f values determined,

TABLE 1

Solubility-related properties of paroxetine hydrochloride

Property	Form I	Form II
Solubility (mg/ml)		
water 15 °C	5.5	7.0
water 20 °C	4.9	8.2
water 30 °C	7.5	11.8
water 37 °C	9.2	14.4
water 50 °C	12.6	24.2
Intrinsic dissolution rate ($\mu g/s/cm^2$)		
water 37 °C	11.8	30.2
Dissolution rate - T_{90} (min)		
tablets	6.3	9.0
capsules	12.5	8.0

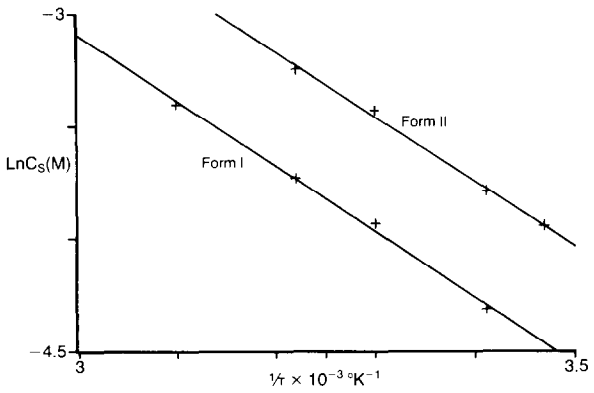

Fig. 4. Van't Hoff solubility plot.

included a contribution from the enthalpy of hydration. This difficulty was overcome by maintaining the DSC cell at 80 °C for 30 min prior to the run. Under these conditions the heats of fusion were found to be identical and the additional energy required to be ca. 3.8 kJ/mol. The interpretation was straightforward for thermograms of Form II which lost water readily on heating.

Aguiar and Zelmer (1969) suggested that when free energy differences between polymorphs are small it is unlikely that there will be differences in bioavailability as it is probable that the forms will interconvert in vivo due to the minimal energy differences. Their statements were based on findings with mefenamic acid and chloramphenicol palmitate. Administration of both forms of these drugs gave rise to similar plasma levels for the polymorphs of mefenamic acid but differing levels for those of chloramphenical palmitate.

Different bioavailability profiles were therefore apparent for polymorphs with high energy differences. The thermodynamic properties of a number of drugs are described in Table 5 where it can be seen that the values for paroxetine hydrochloride are comparable to those of mefenamic acid. Subsequent work (Yokoyama at al., 1979; Kozjek and Golic, 1985) has tended to confirm the hypothesis of Aguiar and Zelmer (1969) and it is therefore unlikely that administration of either form of paroxetine hydrochloride would result in significant differences in bioavailability.

TABLE 2

Heats of solution and fusion for paroxetine hydrochloride

	ΔH_s (kJ/mol)	ΔH_f (kJ/mol)
Form I	24.1	19.7
Form II	24.2	19.7
ΔH_T	0.1	0.0
Form I *	-	23.5

* Sample not equilibrated prior to DSC run.

Interconversion of Forms I and II

DSC data indicated that Form II would not convert to the more thermodynamically stable Form I by heat alone. This was confirmed by examination of a number of batches of paroxetine hydrochloride (II) stored at temperatures up to and including 50 °C for up to 3 years. Only one batch was observed to convert to Form I but conditions of elevated humidity as well as temperature were required. This was probably due to the presence of a small quantity of Form I acting as seed crystals in the humid environment as a batch of Form II which was stable at all conditions showed rapid and complete conversion when 'spiked' with levels from 1% to 5% of Form I and stored at 37 °C/75% RH for 7 days. This phenomenon of seeding also extended to one batch of Form II which dissolved in water to the expected level but crystallised from solution as Form I to give an equilibrium solubility typical of the latter.

In the absence of seeding crystals the only conditions under which transformation could be induced were found to be those of mechanical compression. When Form II was compressed at a force of 10 tons there was immediate conversion of about 50% to Form I and full conversion occurred within 3 days. Compression at 5 tons force had the same effect but at a slower rate, whereas 1 ton failed to initiate the conversion after 2 weeks at ambient temperature. In preparing compacts for intrinsic dissolution rate studies it was therefore necessary to keep the compaction force below 5 tons.

The observation of transformation under compression suggested the possibility of pseudopolymorphic change in tablets containing Form II paroxetine hydrochloride. Before this problem could be addressed it was necessary to devise a

means of identification of the crystal form in the presence of a large excess of excipient material. By storing the IR spectra of both sample and "placebo" formulations in the data station it was possible to identify the crystal form by spectral subtraction. The signal-to-noise ratio of the instrument limited the sensitivity of detection but positive results were obtained for those samples containing 10% or more of paroxetine hydrochloride. In other experiments we have observed that lower levels can be identified by the use of Fourier Transform infrared spectroscopy (FTIR) which is capable of providing a much higher signal-to-noise ratio and consequently less distortion upon spectral subtraction. Examination of stored batches of tablets containing Form II showed qualitatively that there had been no conversion to Form I even at 37 °C/75% RH for 2 years.

However, limitations of sensitivity suggested that some partial conversion could not be ruled out and given the observed transformation of pure drug substance under compression it was desirable to quantify this effect.

Although quantitative IR spectrospcopy in the solid state has been documented (Miller and Stace, 1979) there have been some limitations in this approach. Simple measurements of transmittance or absorbance require accurate and reproducible preparation of discs or mulls, but with careful technique useful quantitation of the polymorphs of copper phthalocyamine was obtained (Ebert and Gottlieb, 1952; Kendal, 1953).

Mixtures of Forms I and II of paroxetine hydrochloride could be quantified by storage of each spectrum in the data station and by trial and error, recreating the sample spectrum from a combination of different percentages of both. This proved to be time consuming and an absorbance ratio method (Moustafa et al., 1974) was adopted. The two bands at 665 and 675 cm^{-1} were chosen since they absorbed in a region free of other bands and showed approximately equivalent transmittance values. Additionally the analysis could be automated by controlling the data station and spectrophotometer with an OBEY programme (Perkin Elmer 1983).

Repetitive analysis of a partially transformed sample of paroxetine gave a coefficient of variation of 4.6% for 7 runs over a period of about 2 h. This was sufficiently precise to examine the transformation in compressed tablets. In order to simplify the analysis, Form II paroxetine hydrochloride was compressed in a matrix of sodium chloride and a calibration curve was constructed (Fig. 5) from samples containing known proportions of Forms I and II. Tablets were then prepared at different compaction forces and the Form I/II ratio determined periodically at 20 °C. Tablets compressed to the highest force were also stored at 30, 37 and 50 °C to examine the effect of temperature on the compression-induced transformation.

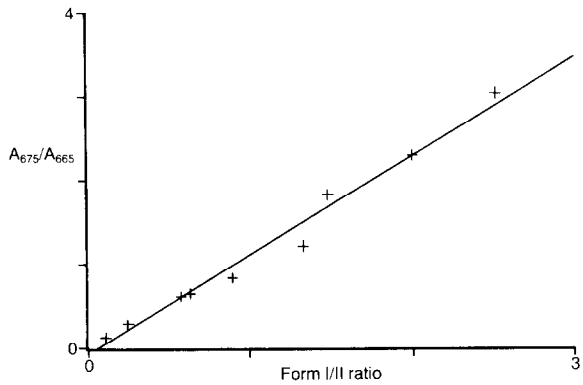

Fig. 5. Calibration curve for absorbance ratio measurements.

The fractional conversion (α) (Fig. 6) versus time plot was analysed by the method of Hancock and Sharp (1972). This analysis produces a plot of $\ln [-\ln(1-\alpha)]$ versus $\ln t$ from which values of

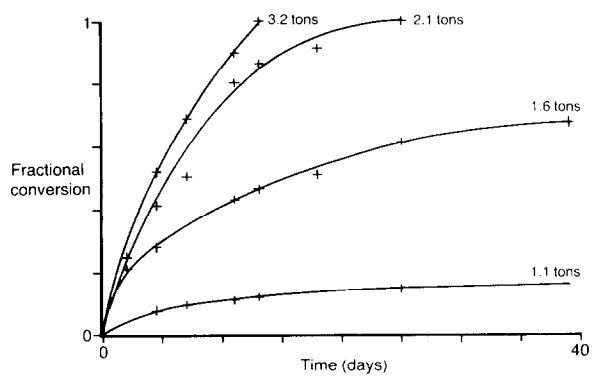

Fig. 6. Conversion of paroxetine Form II to I in tablets at 20 °C.

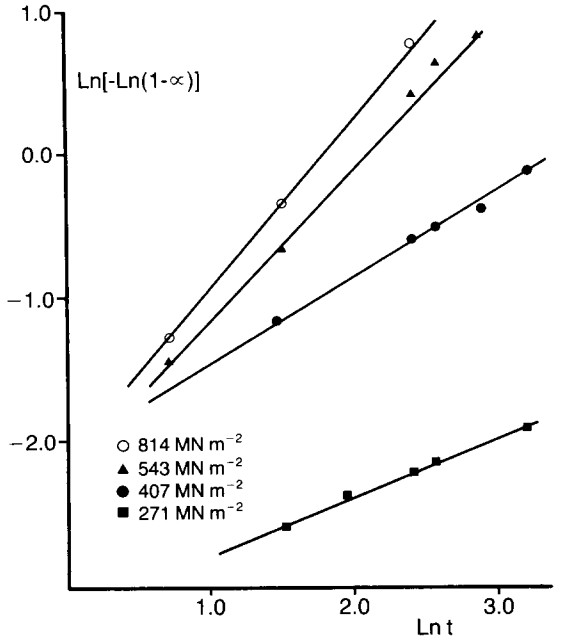

Fig. 7. Kinetic model analysis for Form II transformation.

the slopes (m) can be obtained (Fig. 7). The numerical values of m indicate the appropriate solid state model to which the kinetic data applies. A summary of the 20 °C data is given in Table 3. As the compaction pressure increases the kinetic model changes from a diffusion controlled process described by the Jander equation to a phase boundary controlled system (Fig. 8).

A possible explanation for this is that the number of crystal dislocations increases with increasing compaction pressure and the greater density of the compact makes a diffusion process less favourable.

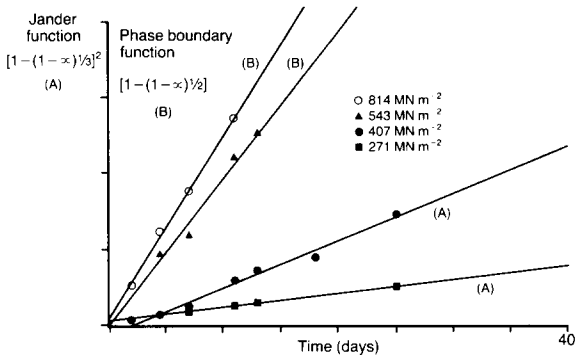

Fig. 8. Solid state kinetics at 20 °C.

It may be expected that the conversion would be autocatalytic, but the process was found to stop if the compacts were ground to a fine powder, thus releasing the internal pressure on the drug particles. It has previously been shown (Chan and Doelker, 1985) that the extent of polymorphic transformation closely follows the pressure and density distributions within a tablet. The pressures reported in this study represent mean values from upper punch measurements and the transformations were averaged over a number of tablets.

Rate constants calculated from the phase boundary plot for tablets compressed to 814 MN · m^{-2} (Table 4) showed typical Arrhenius temperature dependence (Fig. 9) from which the activation energy E was calculated to be 79 kJ/mol. Thus, there is a significant energy barrier to conversion although the enthalpy of transition is negligible. However, it should be noted that the magnitude of the activation energy for solid state reactions does not necessarily relate to the ease by which the

TABLE 3

Summary of kinetic model analysis

Compaction Pressure MN · m^{-2}	m	r	Kinetic equation	m (Theoretical)
271	0.41	0.999	$[1-(1-\alpha)]^2 = kt$	0.54
407	0.57	0.993	$[1-(1-\alpha)]^2 = kt$	0.54
543	1.11	0.989	$1-(1-\alpha) = kt$	1.11
814	1.20	0.998	$1-(1-\alpha) = kt$	1.11

TABLE 4

Summary of rate constants / day

Compaction Pressure MN · m^{-2}	k_{20}	(r)	T °C	k_t @ 814 MN · m^{-2}	(r)
271	0.0002	(0.956)	20	0.060	(0.999)
407	0.0264	(0.989)	30	0.154	(0.993)
543	0.0483	(0.993)	37	0.272	(0.991)
814	0.0602	(0.999)	50	1.272	(0.984)

TABLE 5

Comparison of thermodynamic parameters for polymorphic drugs

Drug	ΔG_T (kJ/mol)	ΔH_T (kJ/mol)
Chloramphenicol	3.24	26.0
Mefenamic acid	1.05	4.3
Piroxicam	0.08	2.5
Paroxetine	1.25	0.0

reaction takes place. Ohnishi et al. (1987), for instance, has reported activation energies as high as 826 kJ/mol for the thermal conversion of bromovaleryl urea polymorphs and as low as 164 kJ/mol for comparable reactions with Benoxaprofen (Yokoyama et al., 1986). In this context the transformation of Form II paroxetine hydrochloride is a facile process. The Arrhenius parameters for heterogeneous reactions are generally quoted by analogy to those relating to gas phase reactions which are derived from the collision theory of reaction rates (Bamford and Tipper, 1980). Clearly the statistical distribution of the energies of free moving molecules on which the Arrhenius equation is based cannot apply to the solid state and the activation energies so determined will not have the same significance. A similar relationship was shown to exist between the rate constants and the compaction pressure at constant temperature (Fig. 10), in spite of the change of kinetics.

Extrapolation of this plot to the pressures that might be encountered in the production of tablets

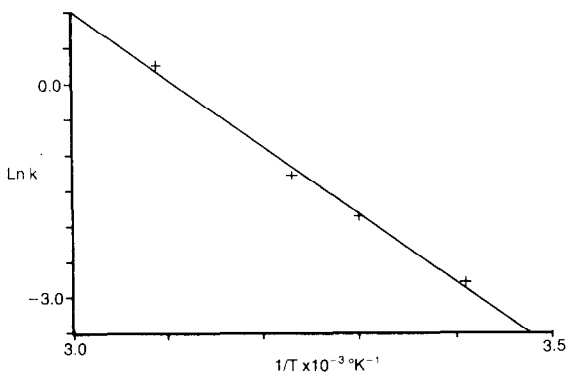

Fig. 9. Effect of temperature on rate constant at 814 MN · m^{-2}

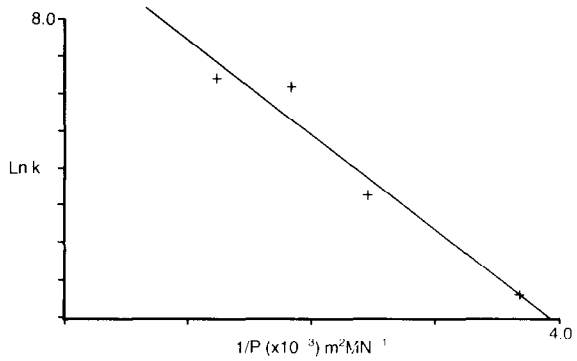

Fig. 10. Effect of compaction pressure on rate constant.

for clinical use suggested that the conversion would be negligible after several years at 20 °C. There are likely to be small differences in conversion rates for tablets, where excipients other than sodium cloride are used, reflecting differences in compression behaviour and mechanisms of particle bonding. However, the margin for error is large and similar conclusions can be drawn.

Conclusions

Infrared spectroscopy provides a useful means of identifying two pseudopolymorphs of paroxetine hydrochloride in drug substance and in mixtures with commonly used excipients. It also enables the transformation of Form II to be monitored and quantified under suitable conditions. Thermal analytical and solubility determinations also distinguish the two crystalline forms. All the evidence suggests that the non-hygroscopic hemihydrate (Form I) is the more energetically stable form. Although the energy barrier to conversion is relatively large the energy differences between the forms are small and transformation can only be effected in the presence of seed crystals in a humid environment or under extreme conditions of pressure. Both forms have been shown to have very good chemical stability and it is unlikely that the solubility and intrinsic dissolution rate differences would affect bioavailability from oral dosage forms particularly as this drug substance has been shown to have a terminal phase elimination half-life in excess of 10 h (Beecham Pharmaceuticals, Internal Communication).

The choice of preferred form appears to be one of physical convenience. In this context the non-hygroscopic nature of Form I may well be advantageous in that complications of moisture uptake during processing or analysis would be avoided.

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