J. Pharm. Pharmac., 1976, **28**, 758–761 *Received December* 15, 1975

Polymorphism of disopyramide

S. R. GUNNING, M. FREEMAN AND J. A. STEAD*

Roussel Laboratories, Kingfisher Drive, Covingham, Swindon, Wilts., U.K.

Two crystal forms of disopyramide have been characterized using X-ray diffraction, differential scanning calorimetry and infrared spectroscopy. The kinetics of the solid state transformation of Form I to Form II has been analysed using the Prout-Tompkins theory. An activation energy of 144 kJ mol^{-1} is calculated for the system. Dissolution and plasma concentrations show no significant differences in bioavailability between the two polymorphs.

Polymorphism, as defined by Verma & Krishna (1966), includes every possible difference in the crystalline structure of a substance of constant chemical composition except homogeneous deformations. The pharmaceutical implications of polymorphism have been reviewed by Haleblian & McCrone (1969), and the effects on physical stability, drug bioavailability and tableting are now recognized.

Disopyramide (4-diisopropylamino-2-phenyl-2-[2-pyridyl]-butyramide) is an anti-arrhythmic agent which has been the subject of an International Symposium (Symposium on Disopyramide, 1976).

This work includes the characterization of two distinct polymorphic forms of disopyramide, their dissolution rate characteristics, their relative bioavailabilities when administered to man, and the kinetics of the solid-state transformation of Form I to Form II.

MATERIALS AND METHODS

Materials

Form I was prepared by crystallization from cyclohexane. Disopyramide (400 g) was dissolved in cyclohexane (1000 ml) by heating to 45°. The solution was rapidly cooled to 10°, and the crystals were collected after standing for 12 h. After washing the crystals with cyclohexane at 10°, they were dried under vacuum and had a specific surface area of 0·95 m^2g^{-1}, as determined by nitrogen adsorption in a Ströhlein Area Meter. Form II was prepared from Form I by heating at 76° for 10 days and had a specific surface area of 0·29 m^2g^{-1}. Purity tests for the two samples are given in Table 1.

Characterization of the polymorphs

The existence of the two polymorphic forms has been confirmed by infrared spectroscopy, X-ray diffractometry and differential scanning calorimetry.

* Correspondence.

Infrared spectra were obtained with a Pye Unicam double beam grating infrared spectrophotometer model 1000 using the pressed potassium bromide disc technique. The sample preparation caused no detectable phase conversion.

X-ray powder diffraction patterns were taken with a Phillips generator with nickel filtered CuKα radiation (40Kv 15 mA) and a Debye Scherrer 11·5 cm diameter powder diffraction camera.

Differential scanning calorimetry was carried out using a Dupont 900 differential thermal analyser fitted with a Dupont modular calorimeter cell.

Four samples of each form were weighed into aluminium sample holder liners and thermograms were run using a heating rate of 10° min^{-1} at an x axis sensitivity of 20° in^{-1} and y axis sensitivity of 0·2° in^{-1}, and the areas under the endotherms were determined.

Table 1. *Elemental analysis and purity tests for disopyramide polymorphs.*

Preparation	Theory %	Found %	m.p. °C	Form assigned
Cyclohexane crystallization	C 74·34	74·44	86–88°	I
	H 8·55	8·66		
	N 12·39	12·45		
Heating at 76°	C 74·34	74·53	97	II
	H 8·55	8·68		
	N 12·39	12·43		

Purity tests: t.l.c. faint trace of impurity at R_F 0·4 for both polymorphs (R_F 0·6). Water content < 0·3 % for both polymorphs. Solvent none for both polymorphs. Titrimety %: 99·7 ± 0·4 for form I. 100·0 ± 0·4 for form II

Determination of intrinsic dissolution rate

Approximately 500 mg of drug was compressed into a flat disc (12·7 mm in diameter) using a F3 single punch tablet machine (Manesty Machines Ltd), which had been instrumented with strain gauges (Data Acquisitions Ltd). A compression pressure of about 96 MN m^{-2} was employed, the tablet press being operated manually. No phase conversion

could be detected by DSC or X-ray diffraction due to compression.

The discs were placed in a Teflon holder such that only one planar suface was exposed to the dissolution medium (900 ml) in which the holder was immersed to a depth of 2 cm and at a distance of 2 cm from the wall of a 1 litre beaker.

The dissolution rate was determined in 0·1 and 0·001 N hydrochloric acid and water at 37°. With the latter two solvents, the ionic strength was adjusted to 0·1 using Analar sodium chloride. The stirrer (Quickfit No. ST1/2) (100 rev min^{-1}) was located 2 cm from the bottom of the vessel.

The dissolution medium was pumped via polythene tubing to continuous flow microcells (Zeiss, MR1D) and the absorbance measured using a Zeiss PMQ II spectrophotometer. The absorbance at appropriate time periods was printed out and related to concentration using previously constructed calibration graphs for each dissolution medium.

In vivo *studies*

Capsules of polymorphs I and II (100 mg) were prepared using automatic encapsulation equipment and identical formulations which on assay gave a mean over both batches of 99 mg per capsule, with a uniformity of dosage (10 capsules per batch) within ± 8 % over both capsule lots.

Three healthy volunteers (2 male and 1 female) were given the preparations at weekly intervals after an overnight fast in a double blind complete cross-over study. No food was taken during the first 4 h after administration. Blood samples (10 ml), taken at appropriate times, were analysed for disopyramide according to Hutsell & Stachelski (1975).

Solid state transformation

Form I was stored at 37, 50, 65, 70 and 76° in well closed glass jars and sampled at appropriate time intervals.

The samples (about 6 mg) were subjected to differential scanning calorimetry as described previously. The % conversion to Form II was determined from the ratio of the areas of the melting endotherms of Forms I and II. The instrument was calibrated using pure samples of the polymorphs and the composition of mixtures could be determined to a precision of ± 5 % or better. This method of analysis is appropriate for disopyramide since there is no detectable transition of Form I to Form II below the melting point of the material during the time course of the thermoscan.

RESULTS AND DISCUSSION

The representative X-ray diffraction photographs, infrared spectra and differential calorimetric scans are shown in Figs 1, 2 and 3 respectively for the two polymorphs. In each case, distinct differences are evident and offer rapid methods of polymorph identification.

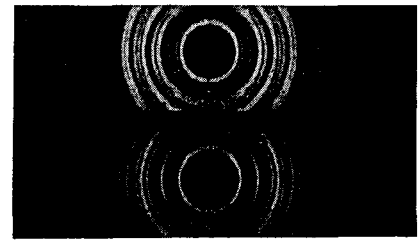

FIG. 1. X-ray powder diffraction patterns of disopyramide. a Form I, b Form II.

Intrinsic dissolution rates for the two forms obtained under conditions of constant agitation and constant surface at 37° showed no significant difference (Table 2). This suggests that 37° is close to the transition temperature, at which the free energies of the two forms are equal. Preliminary results of solubility studies at various temperatures support this statement.

The plasma concentrations between 1·5 and 6 h showed no significant differences when *t*-tests were made on the mean results for each polymorph at each sampling time.

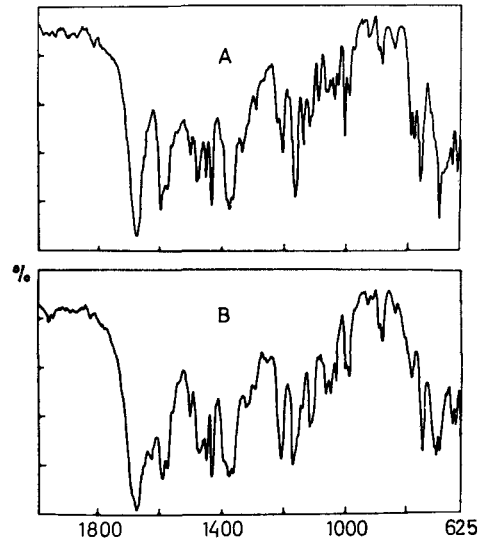

FIG. 2. Infrared absorption spectra of disopyramide. A Form I, B Form II.

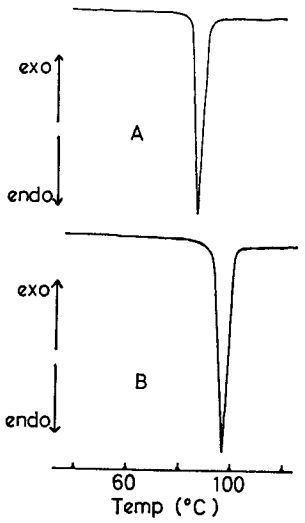

FIG. 3. Differential calorimetric scan of disopyramide. A Form I, B Form II.

Few studies have been made on the velocity of polymorphic transitions of pharmaceuticals in the solid-state. Shami, Bernardo & others (1972) have investigated the kinetics of transformation of sulphathiazole from Form I to II. The quantity of Form I unconverted at various times was estimated using the method of Moustafa & Carless (1969), which involved measurement of the area of the transition endotherm obtained by differential scanning calorimetry. Disopyramide shows no transition under such circumstances and the method is consequently not applicable. Moustafa, Khalil & others (1972) have used the infrared absorbance ratio method to follow the solid-state interconversion of sulphamethoxydiazine polymorphs. With disopyramide Forms I and II, the characteristic absorption bands did not give sufficiently constant absorbance ratios for quantitiative use. The composition of mixtures of Forms I and II were therefore obtained from the areas of the melting point endotherms.

Table 2. *Dissolution rates of disopyramide polymorphs as a function of pH of the dissolution medium at 37°.*

Dissolution fluid	Dissolution rate ±95% C.I. of rate, mg cm^{-2} min^{-1} Form I	Form II
0·1N HCl	12·1 ± 2·5	12·0 ± 2·0
0·001 N HCl*	0·40 ± 0·038	0·38 ± 0·041
Water*	0·30 ± 0·032	0·27 ± 0·029

A *t*-test on the slopes of the regression lines for each polymorph in each dissolution medium showed that the dissolution rates of the two polymorphs were not significantly different.

* Ionic strength adjusted to 0·1 using sodium chloride.

C.I. = confidence interval, i.e. the limits of error for the mean.

The curves obtained in the kinetic study at 50, 65, 70 and 76° were sigmoidal and typical of many solid-state decompositions (Carstenson 1974; Pope & Lach, 1975). No transformation was observed over two years at 37°.

The data from the kinetic study were linearized in Fig. 4 by the use of equations suggested by Prout & Tompkins (1944) for *decomposition* in the solid phase with no prior melting or liquefaction.

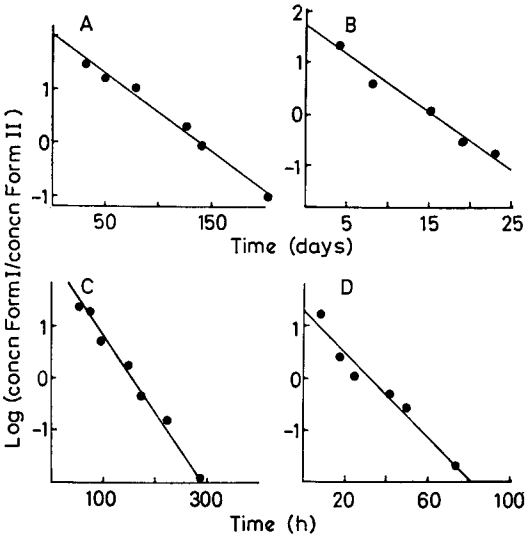

FIG. 4. Linearized plot using Prout Tompkins kinetics of the transformation of disopyramide Form I to Form II in the solid state after storage at various temperatures. A 50°, B 65°, C 70°, D 76°.

Their final derived equation has the form

$$\ln\left[\frac{x}{1-x}\right] = Kt + C$$

where x is the mole fraction of Form I, K is the rate constant for tranformation, and t is the time.

A consideration of the mechanism postulated by Prout & Tompkins (1944) shows that it is also appropriate for solid-state polymorphic transformations. Thus, the assumption is made that the phase change is governed by the formation and growth of active nuclei. Initiation occurs at certain nuclei which are associated with crystalline defects, and the conversion of these energetically favoured molecules leads to the formation of product molecules having a unit cell geometry differing from the

original polymorph. These set up strains in the crystal leading to further crystalline defects, and hence an increase in the velocity of transformation. Therefore, a branching mechanism develops which eventually becomes subject to interference since, when a plane of molecules which have already undergone a phase change is encountered, the branch is broken.

Reaction rates were determined for the rates of conversion and an Arrhenius-type treatment of the data resulted in the following linear regression equation (coefficient of correlation: 0·994):

$$\ln K = -7{\cdot}469 \times 10^3 T^{-1} + 21{\cdot}6$$

The apparent heat of activation was determined to be 144 $kJmol^{-1}$.

The term transition temperature appears to have been used somewhat loosely in the pharmaceutical literature. It is important to differentiate between the instantaneous transition temperature of a polymorph as determined, for example, by differential scanning calorimetry and the thermodynamic transition temperature as determined, for example, by solubility. With disopyramide, the two temperatures differ substantially, the thermodynamic transition temperature being about 37°, and the temperature of instantaneous conversion being above the melting point of the material. At 37°, the velocity of transition is imperceptible due to the large energy barrier opposing transition in the solid-state. As the temperature is increased, passage over the energy barrier is facilitated by thermal agitation, although melting occurs before a high enough temperature is achieved to permit instantaneous conversion.

A similar large difference in the two transition temperatures is seen for sulphathiazole, which has a thermodynamic transition temperature of 94·5° (Milosovich, 1964), and undergoes instantaneous transition at 140–148° (Moustafa & Carless, 1969).

The decrease in surface area on phase conversion is interesting. On the basis of the Prout-Tompkins theory, an increase in surface area would have appeared the most likely result, since the strains developed in the crystals due to the formation of product molecules may be expected to lead to the development of cracks in the crystals. A possible explanation is that the polymorphic transformation may be associated with the development of a liquid phase, although this is not readily discernible. The formation and subsequent solidification of such melting regions may lead to a decrease in surface area due to crystal growth or by the filling of minute pores or crevices in the original crystals.

Some cases of reactions in melting solids show sigmoid curves and have been treated using the Prout-Tompkins theory (Debenham & Owen, 1966), although if a reaction occurs only in liquid regions in equilibrium with solid, application of a solid-state kinetic treatment may be only superficially useful (Pincock & Kiovsky, 1966). Therefore, it is difficult to resolve whether the polymorphic transformation of disopyramide is a true solid-state reaction or whether it is facilitated by regions of liquefaction. In either case, the kinetics of transformation of disopyramide from Form I to Form II differ from that of sulphamethoxydiazine, which follows apparent first order kinetics (Moustafa & others, 1972), and from that of sulphathiazole, which exhibits kinetics analagous to crystal growth from solution (Shami & others, 1972).

Acknowledgements

We thank Dr S. I. Ankier of these Laboratories for co-ordinating the plasma concentration study, Dr R. Bird of the Royal Military College of Science, Shrivenham, for access to their Differential Thermal Analyser, and Mr E. Minshall of the University of Bath for carrying out the X-ray diffraction studies.

REFERENCES

Carstenson, J. T. (1974). *J. pharm. Sci.*, **63**, 1–14.
Debenham. D. F. & Owen, A. J. (1966). *J. chem. Soc.* (B), 675–678.
Haleblian, J. & McCrone, W. (1969). *J. pharm. Sci.*, **58**, 911–929.
Hutsell, T. C. & Stachelski, S. L. (1975). *J. Chromat.*, **106**, 151–158.
Milosovich, G. (1964), *J. pharm. Sci.*, **53**, 484–487.
Moustafa, M. A. & Carless, J. E. (1969). *J. Pharm. Pharmac.*, **21**, 359–365.
Moustafa, M. A., Khalil, S. A., Ebian, A. R. & Motawi, M. M. (1972). *J. pharm. Sci.*, **24**, 921–926.
Pincock, R. E. & Kiovsky, T. E. (1966). *Chem. Commun.*, **23**, 864–866.
Pope, D. G. & Lach, J. L. (1975). *Pharm. acta Helv.*, **50**, 165–177.
Prout, E. G. & Tompkins, F. C. (1944). *Trans. Faraday Soc.*, **40**, 488–498.
Shami, E. G., Bernardo. P. D., Rattie, E. S. & Ravin, L. J. (1972). *J. pharm. Sci.*, **61**, 1318–1320.
Symposium on Disopyramide (1976). *J. int med. Res.*, **4**, *Suppl.* **1**.
Verma, A. R. & Krishna, P. (1966). *Polymorphism and Polytypism in Crystals.* New York: Wiley.