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Isolation and physicochemical characterization of solid forms of glibenclamide

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Summary

Two polymorphs and two pseudo-polymorphs of glibenclamide were obtained by crystallization from a number of solvents. They were characterized by thermal microscopy, differential scanning calorimetry, thermogravimetry, X-ray powder diffraction, infrared spectroscopy, and dynamic and equilibrium solubility studies. Substantial differences were detected between the polymorphs and pseudo-polymorphs. Particularly, the pentanol and toluene solvates were significantly different with regard to dissolution rate and equilibrium solubility from each other and from the two polymorphs.

Introduction

Glibenclamide (**1**) is a sulfonylurea derivative that is orally active as a hypoglycemic drug. It exists as a crystalline powder which is sparingly soluble in water.

Sulfonylureas have been shown to exhibit polymorphism. Tolbutamide was reported to exist in 4 polymorphic forms (Simmons et al., 1972; Burger, 1975a; Al-Saieq and Riley, 1981) with form III being the most soluble but much too unstable to be exploited (Al-Saieq and Riley, 1981). Chlorpropamide was also shown to occur in different polymorphic forms (Burger, 1975a) without significant differences in their biological activity (Burger, 1975a and b). However, the in vitro availability of chlorpropamide from tablets was reported to be affected by the type of polymorph used in the tablet preparation (Burger, 1975a and b). Further, acetohexamide was reported to occur in 2 (Takla and Chroneos, 1977) and 3 (Al-Saieq and Riley, 1982) polymorphic forms with form II having the highest dissolution rate and of sufficient stability to be exploited (Al-Saieq and Riley, 1981).

The occurrence of polymorphic forms of **1** has not been reported. As different polymorphs or pseudo-polymorphs of a drug substance may vary in their physical and chemical properties which can affect their physical and chemical stability (Haleblian and McCrone, 1969) and biological activity (Mullins and Macek, 1960; Aguiar et al., 1967; Poole et al., 1968), the potential of **1** to exhibit polymorphism was investigated. This was achieved by crystallization of **1** from different organic solvents under varying conditions. The isolated crystal forms were characterized by thermal techniques, X-ray powder diffraction, infrared spectroscopy, and equilibrium and dynamic solubility methods.

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Materials and Methods

Chemicals

Glibenclamide was of pharmaceutical grade. Dioxane, acetonitrile, pentanol and toluene were analytical grade. Double-distilled water from an all-glass still was used in the equilibrium and dynamic solubility studies.

Methods

Preparation of the crystal forms

Form I: 2 g of **1** were added to 100 ml of dioxane and heated to boiling until solution was effected. The solution was then allowed to cool slowly at room temperature. The resulting crystals were collected by filtration and dried under a current of N_2 before stored in a desiccator over silica for at least 24 h before use.

Form II: 2 g of **1** were dissolved in 100 ml of acetonitrile at 81.6 °C and the solution was rapidly cooled to 5 °C. The resulting crystals were collected as previously outlined.

Pentanol solvate: 1 g of **1** was dissolved in 100 ml pentanol at 135 °C and the solution was allowed to cool slowly at room temperature. The resulting crystals were collected as outlined previously.

Toluene solvate: 1 g of **1** was added to 100 ml of toluene at 110.5 °C and the solution was filtered. The filtrate was allowed to cool slowly at room temperature. The resulting crystals were collected as outlined previously.

Infrared spectroscopy

Potassium bromide disks of the samples (1 : 80) were prepared and the spectra were obtained on a Shimadzu IR spectrometer.

Thermal analysis

The thermograms of the samples were recorded on a simultaneous thermogravimetric (TG)–differential scanning calorimetric (DSC) Stanton RedCroft ST 785 thermal analyzer connected to a data acquisition station and a graphic plotter. Samples (about 9.5 mg) were placed into uncrimped aluminium pans and heated against an inert reference (aluminium oxide) at 10 or 20 $°C \cdot min^{-1}$ under a purge of nitrogen at a flow rate of 50 ml over the temperature range 30–250 °C.

Thermomicroscopy

The melting points and overall behavior during the heating process were studied with a Thermovar thermomicroscope equipped with a Kofler hot-stage and a KAM2 Camera System and connected to a Reichert controller. The samples were placed on the hot-stage at room temperature and heated at a rate of 5 $°C \cdot min^{-1}$. Photomicrographs before and during the heating process were obtained.

X-Ray powder diffraction

The powder X-ray diffraction patterns of the crystal forms were recorded on a Philips PW 1050/81 Goniometer with a PW 1729 Generator, a PW 1710 Diffractometer controllor and a PM 8203 A Recorder, employing Ni-filtered, Cu-K_α radiation with $\lambda = 0.15418$ nm. Samples were mounted on glass slides after being ground.

Equilibrium solubility

Each crystal form (50 mg) was placed in 50 ml of distilled water maintained at various temperatures (27, 35 or 45 °C), and shaken at 90 strokes/min for 8 h. The samples were filtered through a Millipore filter (0.45 μm) and the absorbances were measured at 227 nm with a UV-240 Shimadzu spectrophotometer. The concentrations of **1** were then determined by references to a suitably-prepared calibration curve.

Dynamic solubility

The dissolution of each crystal form was measured at 37 °C as outlined previously except that samples were taken at appropriate intervals for 3 h rather than at the end of the 8 h period.

Results and Discussion

Thermomicroscopy

The first evidence as to the existence of **1** in more than one crystal or pseudo-polymorphic form came from thermomicroscopic observations. The photomicrographs exhibited in Fig. 1 clearly demostrate differences in the crystal habits of **1** obtained from different organic solvents. All crystal forms exhibit birefringence under the polarizing microscope. The crystals obtained from dioxane were lamellar and melt at 170.4°C whereas those obtained from acetonitrile were long

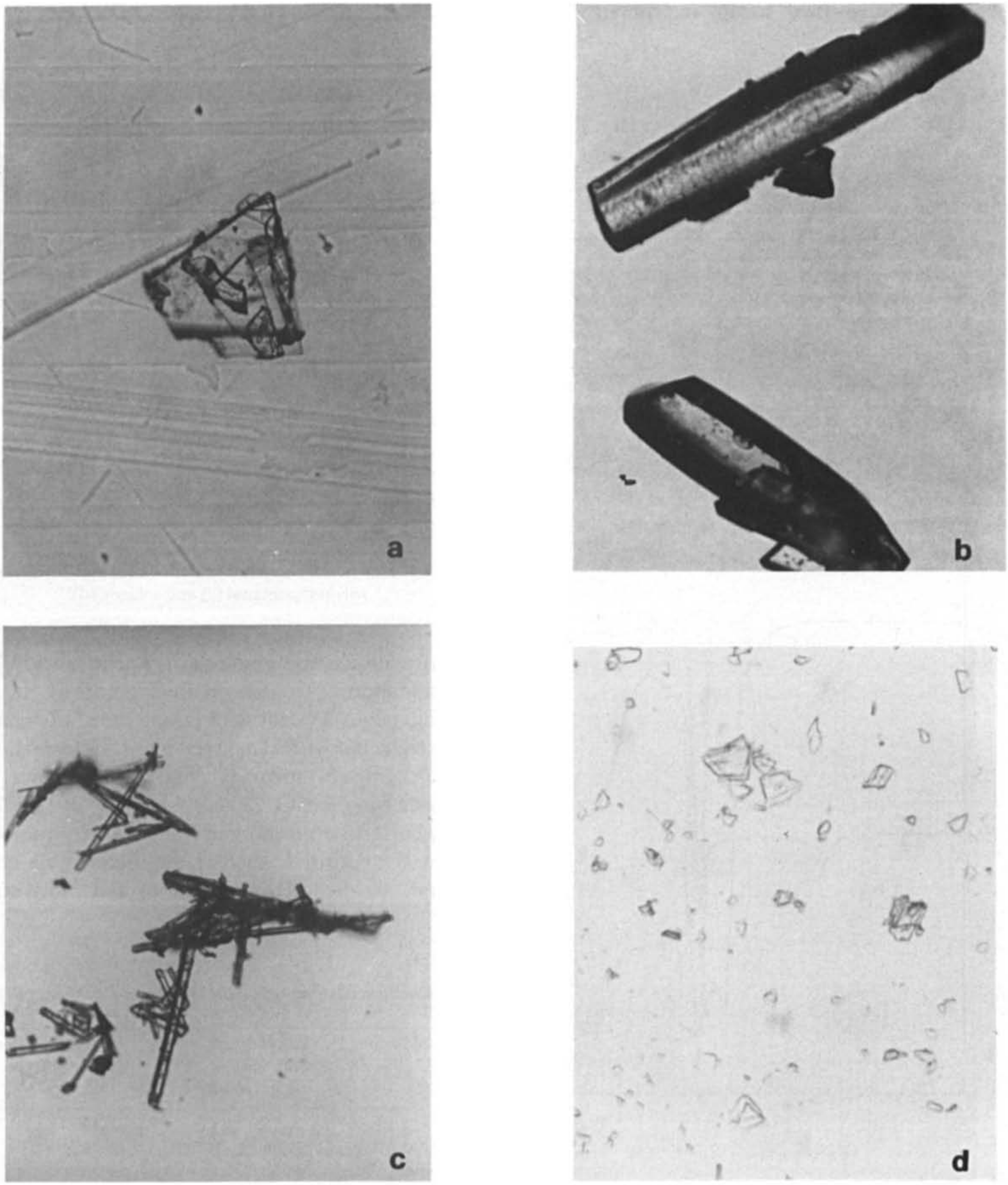

Fig. 1. Photomicrographs of forms I (a) and II (b) and the solvates pentanol (c) and toluene (d) at room temperature (40 ×).

acicular and melt at 170.1° C. The crystals obtained from pentanol were needle-shaped and melt at 166.4° C whereas those obtained from toluene were lamellar but smaller than those obtained from dioxane and melt at 170.5° C. All crystal forms were transformed to an amorphous form upon cooling.

Thermal analysis

The DSC–TG thermograms of the crystal forms are shown in Fig. 2. The DSC curve of form I (Fig 2, a) exhibits one endothermic peak at 173.1° C corresponding to the melting point of **1**. The simultaneous TG curve does not show any change in weight below the melting point of form I. The DSC curve of form II (Fig. 2, b) shows two endothermic peaks. The first peak at 148.7° C may correspond to polymorphic transformation of form II to form I whereas the second one corresponds to the melting point of the most stable

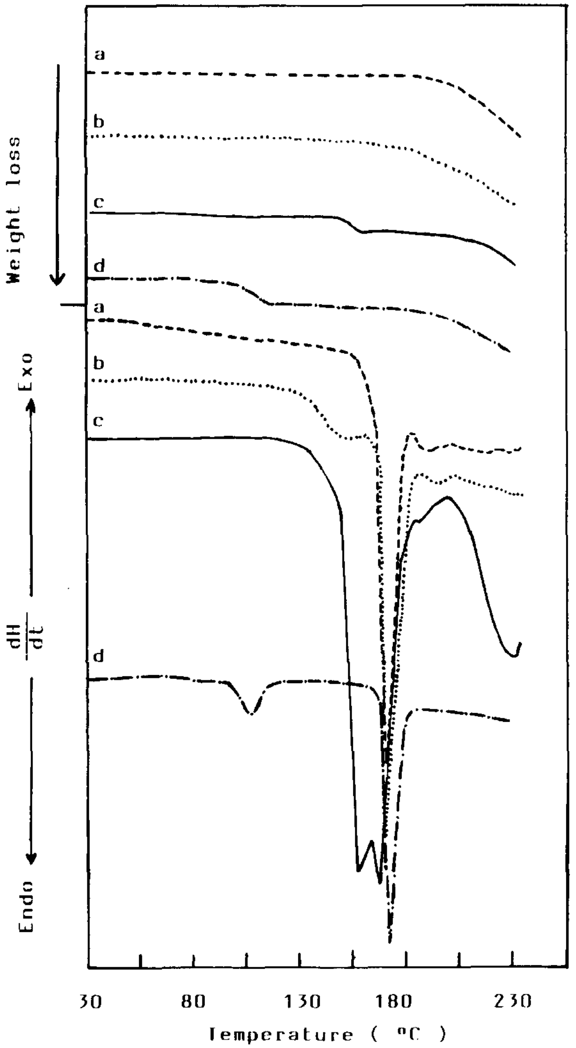

Fig. 2. TG and DSC thermograms of forms I (a) and II (b) and the solvates pentanol (c) and toluene (d).

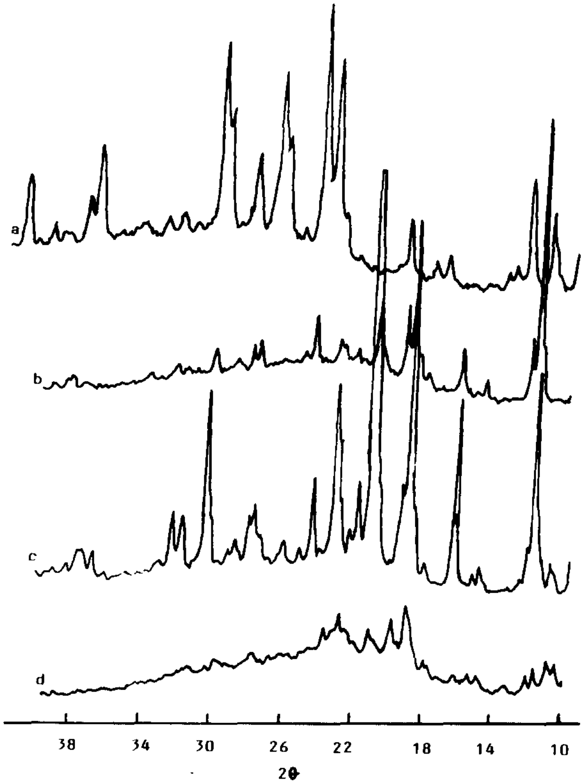

Fig. 3. X-Ray powder diffractograms of I (a) and II (b) and the solvates pentanol (c) and toluene (d).

TABLE 1

Equilibrium solubilities and heats of solution for the crystal forms

Crystal form	Equilibrium/ solubility at 37 ° C (mg/100 ml)	Heat of solution (kcal/mol)
I	0.66	18.15
II	1.06	15.70
Pentanol solvate	33.70	5.25
Toluene solvate	2.51	18.00

form (form I). This was supported by the TG curve which does not show any changes in weight below the melting point, thus excluding the notion that the first endothermic peak may be due to desolvation.

The DSC curve of the pentanol solvate (Fig. 2, c) exhibits one broad double peak. The first peak occurs at 159.4 °C and corresponds to desolvation as evidenced from the TG curve which shows a one-stage loss in weight over the temperature range 142.1–166.1 °C. The amount of solvent pentanol lost corresponds to a 1 : 8 solvate. The second peak corresponds to the melting of form I. The DSC curve of the toluene solvate (Fig. 2, d) exhibits two endothermic peaks. The first peak is broad and occurs at 109.5 °C. It is associated with a one-stage weight loss as indicated from the TG curve which suggests a 1 : 3 (toluene : glibenclamide) solvate. The DSC–TG curves of the commercial powder of 1 were found to be identical to those of form I.

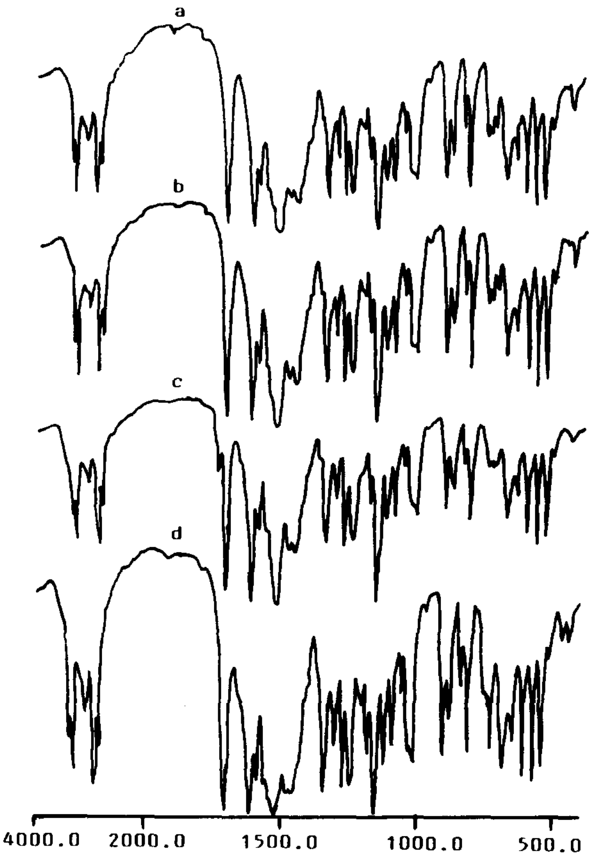

Fig. 4. IR spectra of forms I (a) and II (b) and the solvates pentanol (c) and tolene (d).

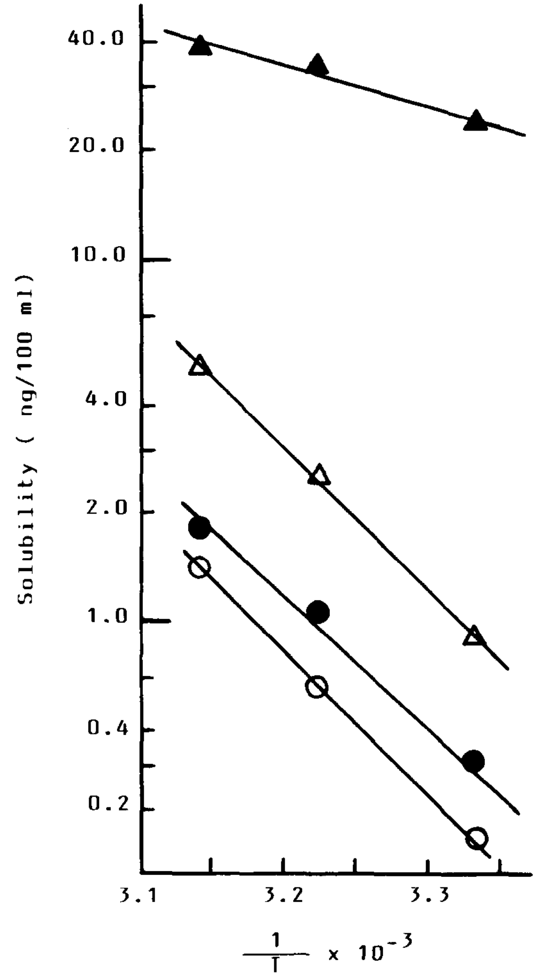

Fig. 5. The van't Hoff-type plot of the forms I (○) and II (●) and the solvates pentanol (▲) and toluene (△).

X-Ray diffraction

The X-ray diffraction patterns (Fig. 3) of the crystal forms show substantial differences in both the intensity and position of the peaks suggesting the existence of different crystal forms. The toluene solvate exhibits fewer and less intense peaks compared to the pentanol solvate. The commercial powder of 1 showed an identical pattern to form I.

Infrared (IR) spectroscopy

The IR spectra of the differenct crystal forms did not show any differences at 4000–2000 cm^{-1} and only slight differences in the fingerprint region (Fig. 4). The IR spectrum of form II did not differ from that of form I. However, the IR spectra of the pentanol and toluene solvates differ from each other and from those of forms I and II. The 3 small peaks exhibited at 728, 748 and 756 cm^{-1} almost disappeared. Further differences include a small sharp peak at 1244 cm^{-1} with the pentanol solvate and a small peak at 468 cm^{-1} with the toluene solvate. It should be mentioned that the IR spectrum of the commercial powder of **1** resembles that of form I. Further, the IR spectra of **1** crystallized from methanol, chloroform, acetone, ethanol/distilled water, and pyridine were also identical to that of form I.

Equilibrium solubility

The solubility of the crystal forms of **1** at 37 ° C is shown in Table 1. The pentanol solvate apparently has the highest solubility followed by the toluene solvate. Form II shows an intermediate solubility whereas form I, the most stable form, shows the lowest solubility.

The equilibrium solubilities obtained over the temperature range 27–45 ° C, when plotted according to the vant't Hoff equation, gave a reasonably good linear relationship for all crystal forms (Fig. 5). It is noted that there is a direct relationship between solubility and temperature. The values of the heat of solution for each of the crystal forms was calculated from the slopes of the van't Hoff-type plot and are shown in Table 1. The highest solubility of the pentanol solvate could be explained on the basis of its lowest heat of solution. The entropy of the system could be high enough to counteract the relatively high heat of solution and to significantly lower the free energy of the system and hence increase the solubility of the toluene solvate over other systems having the same heat of solution (i.e. form I).

Dissolution rate

The dissolution profiles of the crystal forms at 37 ° C are shown in Fig. 6. No attempt was made to use particles of the same size as the particles were used without grinding and sieving. The profiles indicate that the pentanol solvate has the greatest dissolution rate followed by the toluene solvate. The two solvates have higher dissolution rates than the two crystal forms. The latter do not significantly differ from each other. There is no indication of any phase transformation.

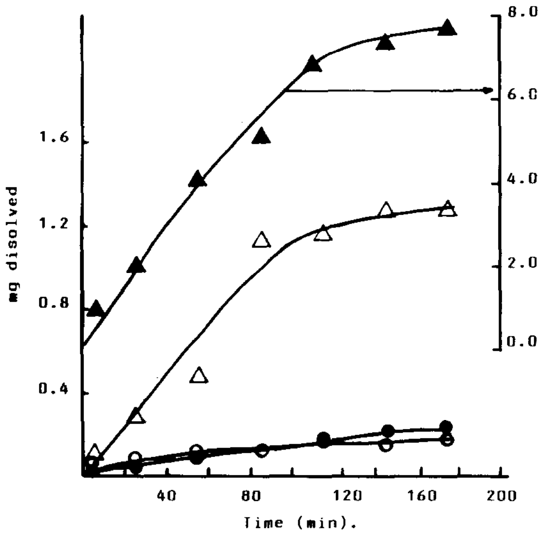

Fig. 6. Dissolution profiles of forms I (○) and II (●) and the solvates pentanol (▲) and toluene (△).

Conclusions

Glibenclamide, crystallized from different organic solvents, was found to exist in two polymorphic forms (I and II) and two pseudo-polymorphic forms (pentanol and toluene solvates). The crystal and solvated forms were characterized by thermomicroscopy, DSC, TG, X-ray, IR spectroscopy, and dynamic and equilibrium solubility studies. Form I was the most stable and least soluble whereas form II was metastable and had an intermediate solubility. The pentanol solvate had the highest solubility (~ 51 times that of form I) followed by the toluene solvate (~ 3.8 times that of form I). The impact of the occurrence of **1** in more than one polymorphic or pseudo-polymorphic form on the bioavailability of **1** is under investigation in our laboratory.

Acknowledgements

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