ELSEVIER

International Journal of Pharmaceutics 195 (2000) 239–246

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Preparation and characterisation of a new insoluble polymorphic form of glibenclamide

A. Panagopoulou-Kaplani, S. Malamataris *

Department of Pharmaceutical Technology, School of Pharmacy, University of Thessaloniki, Thessaloniki 54006, Greece

Received 3 August 1999; received in revised form 10 November 1999; accepted 10 November 1999

Abstract

A crystalline form of glibenclamide, with higher melting point (218°C) and lower solubility in simulated gastric and intestinal fluids, was arisen during an attempt to elucidate transitional phases by melting, cooling and reheating. The new form was obtained from the glassy state, by applying sublimation at 130–160°C and was characterised by differential scanning calorimetry (DSC), infrared (IR) spectroscopy, scanning electron microscopy (SEM), hot-stage microscopy (HSM), X-ray powder diffraction (XRD) and solubility studies. Formation of the new crystal form is considered as reason of reduction in dissolution and bioavailability of tablets.

Keywords: Glibenclamide; New crystal form; Equilibrium solubility; Sublimation

1. Introduction

Glibenclamide is an oral hypoglycemic agent of the sulphonylurea group used in the treatment of non-insulin dependent diabetes and has a history of low bioavailability, which is attributed to poor dissolution (Borchert et al., 1976; Arnqvist et al., 1983; Chalk et al., 1986). Also, marked differences were observed, in respect to in vitro dissolution behaviour of tablets, during a recent multinational postmarket comparative study (Blume et al., 1993).

Several factors influencing dissolution and bioavailability of glibenclamide have been examined, such as micronisation (Rupp et al., 1984), molecular dispersion (Ganley et al., 1984), incorporation of surfactants (Singh, 1986), inclusion complexation with cyclodextrin (Mitrevej et al., 1996), crystal modification (Suleiman and Najib, 1989; Hassan et al., 1997) and glass formation (Hassan et al., 1991; Salem et al., 1997). Nevertheless, the investigations on the crystal forms of tableted glibenclamide are limited, although the sulphonylurea derivatives of similar molecular structure have been shown to exhibit polymorphism (Borka, 1977; Girgis-Takla and Dakas, 1989). Only recently, it has been reported that crystallisation of glibenclamide from different sol-

* Corresponding author. Tel.: +30-31-997-651; fax: +30-31-997-652.

E-mail address: smalam@pharm.auth.gr (S. Malamataris)

0378-5173/00/$ - see front matter
PII: S0378-5173(99)00401-9

vents gave two polymorphic forms and pseudo-polymorphs (solvates), which were significantly different with regard to solubility and melting properties (Suleiman and Najib, 1989; Hassan et al., 1997). Also, glassy form of glibenclamide was obtained by quick cooling of melt, showing changes in solubility with storage at different temperatures attributed to transformation from glassy to crystalline form (Hassan et al., 1991; Salem et al., 1997).

Since solid state properties are very important for the solubility and crystal transformation is a complex process, it was thought of interest to elucidate the transitional phases of glibenclamide. During this attempt a new crystal form was arisen, whose preparation and characterisation is presented in this paper.

2. Materials and methods

2.1. Materials

Pharmaceutical grade of crystalline glibenclamide, in micronized powder form, was kindly supplied by Hoechst Marion Rousel, Frankfurt, Germany. KBr used for the IR spectroscopy and all the reagents used for solubility assessment were of analytical grade. Distilled water was obtained from an all glass still.

2.2. Elucidation of transitional phases

Samples of glibenclamide were transferred into 20 ml glass test tubes, which were immersed in a paraffin oil-bath maintained at 185°C by using a digital programmable temperature controller (PolyScience, model 9510, refrigerated circulator, USA). The samples were kept at this temperature for 5 min to ensure a complete melt and subsequently cooled in two different ways, at a slow rate (10°C h^{-1}) and at a quick rate (immediate transfer to 25°C). Three samples were used for each thermal treatment and differential scanning calorimetry (DSC) analysis, hot-stage microscopy (HSM) examination and determination of equilibrium solubility in simulated gastric and intestinal fluid was carried out with them.

2.3. Preparation of new crystal form (sublimation)

Sublimation was applied by spreading a portion of quickly cooled melt (glassy glibenclamide) on a petri dish covered with a watch glass operating as condenser and by heating at gradually increased temperature, from 130 to 160°C for over 6 h. A hotplate with digital indication of temperature (type SH1D, Stuart Scientific, England) was used for heating and the crystals formed on the inner surface of watch glass were collected. They were characterised by using DSC, infrared (IR) spectroscopy, X-ray diffraction (XRD), HSM and scanning electron microscopy (SEM), as well as by assessing the solubility in simulated gastric and intestinal fluid (pH 1.2 and 7.4).

2.4. Differential scanning calorimetry (DSC)

A Shimadzu DSC-50 equipped with a TA-50 WSI analysis program was used to obtain scans under nitrogen purge of 70 ml min^{-1}, at a heating rate of 10°C min^{-1}. Samples (3.0 ± 0.1 mg) were scanned between 30 and 250°C, in crimped aluminium pans (Shimadzu P/N 201-53090) and a similar empty pan was used as reference. Points of extrapolated melting onset were determined automatically and mean values for three samples were calculated for each case of thermal treatment.

2.5. Hot-stage microscopy (HSM)

A CCD camera head (Sanyo model VC-2512) connected to a Quantimet 500 image processing and analysis system (Leica, Cambridge, England) was mounted on a Carl Zeiss microscope equipped with a hot stage (Reichert, Austria). Samples kept between slip-covers were heated at a rate of 5°C min^{-1} and their changes were monitored and printed through the image analysis system on a laser printer.

2.6. Infrared (IR) spectroscopy

Potassium bromide disks of samples (1% w/w) were prepared using a manual hydraulic press (Graseby Specac, England) and spectra were obtained on a Perkin-Elmer FT-IR1605 spectrophotometer.

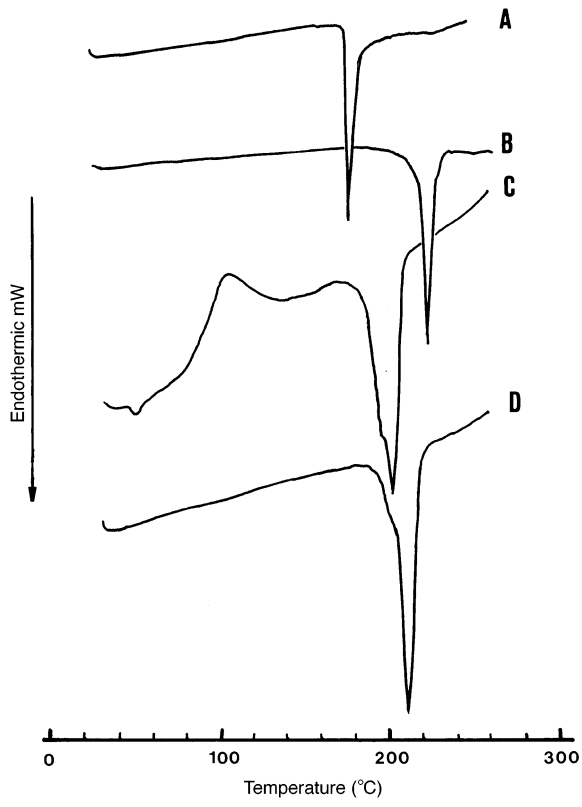

Fig. 1. Representative DSC scans of thermally treated glibenclamide. (A) raw material; (B) new crystal form; (C) melted at 185°C and quickly cooled (glass) and (D) melted at 185°C and slowly cooled.

2.7. X-ray powder diffraction (XRD)

The X-ray powder diffraction patterns were recorded on a Philips PW 1730/10 Diffractometer (Ni filtered Cu Kα, voltage 35 kV, current 25 mA, 2000 cps, 1.2° min^{-1}).

2.8. Scanning electron microscopy (SEM)

Samples were examined in a JEOL JSM 840A scanning electron microscope.

2.9. Solubility assessment

Solubility was determined at 25°C in simulated gastric (pH 1.2) and intestinal (pH 7.4) fluid without enzyme [simulated gastric fluid (SGF) and simulated intestinal fluid (SIF)]. Excess powder of raw material, glassy state and new crystal form of glibenclamide was dispersed in 10 ml fluid and shaken for 72 h. Aliquot of the supernatant solution was filtered from the suspension by positive pressure at 25°C and the filtrate assayed spectrophotometrically. Each calculated value of solubility is the average of three determinations.

3. Results and discussion

Representative DSC scans obtained during the attempt to elucidate the transitional phases and for the characterisation of the new crystal form are shown in Fig. 1. The temperature ranges, where exo- and endotherms appeared are listed in Table 1 together with the solubility values.

The DSC scans of the raw material (untreated glibenclamide, Fig. 1A) show one endothermic peak with extrapolated onset at 175°C, while those of the new crystal form (Fig. 1B) also show one endothermic peak, but at higher extrapolated onset (218°C). The quickly cooled melts show one endotherm at 40–56°C, one exotherm at 90–135°C and another endotherm at 198°C (Fig. 1C),

Table 1
Endo- and exotherms on DSC scans and equilibrium solubility in SGF and SIF of thermally treated glibenclamide

Thermal treatment	Endotherm[a] (°C)	Exotherm[a] (°C)	Endotherm[a] (°C)	Solubility (mg/l) ± S.D.	
				SGF	SIF
None (raw material)	–	–	175	1.0 ± 0.1	2.9 ± 0.2
Sublimation	–	–	218	<0.1	1.1 ± 0.1
Quick cooling	42–56	90–135	198	17.5 ± 0.7	53.5 ± 1.5
Slow cooling	–	–	210	6.9 ± 0.3	8.5 ± 0.4

[a] S.D. < 1°C.

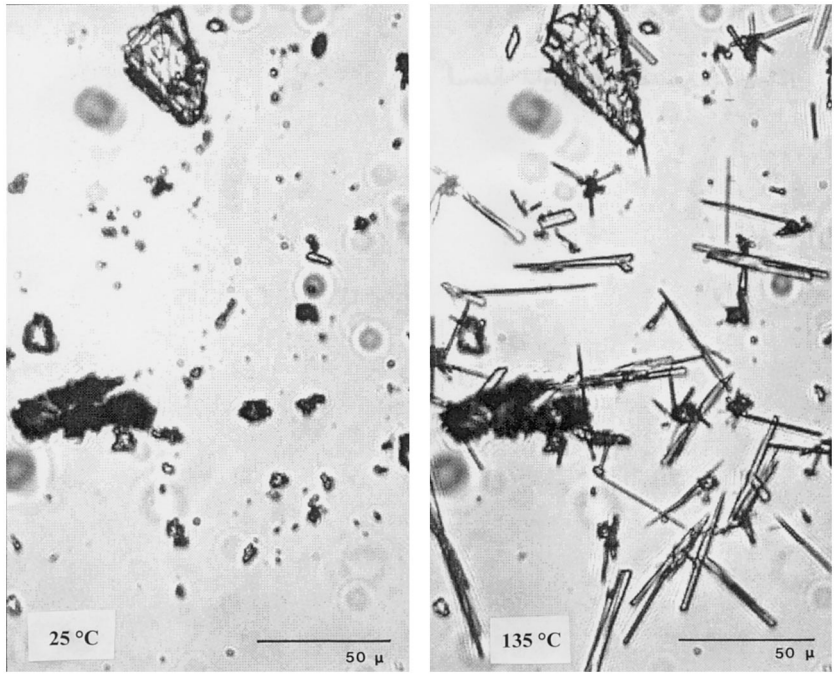

Fig. 2. Recrystallisation of quickly cooled melt (glass) at 130–160°C.

while the slowly cooled melts show one endotherm at 210°C (Fig. 1D).

Upon quick cooling the melts should solidify to a less stable glassy form. Therefore, the first endotherm, at 40–56°C, can be a melting one, corresponding to the less stable or glassy form and the following exotherm (Fig. 1C) to it's recrystallisation in a more stable crystal form with higher final extrapolated melting onset (198°C). In contrast, the slowly cooled melts do not show exotherm at all. Probably, because the recrystallisation is completed during the cooling, since the sample stayed for longer time at the region of recrystallisation temperature (90–135°C) or because the formation of less stable glassy form is avoided or diminished as a consequence of diminished overcooling of melts. Recrystallisation of glassy glibenclamide at the above temperature range was confirmed by HSM examination (Fig. 2).

Fig. 3 shows SEM photographs of raw material, new crystal form obtained by sublimation and of quickly and slowly cooled melts. They show great differences in crystal habit and agree with the findings of HSM (Fig. 2).

The X-ray diffraction patterns of the raw material, the new crystalline form and the quickly and slowly cooled melts, are given in Fig. 4. It can be seen that there are extensive differences in the intensity and position of the peaks between the raw material and the new crystal form. The pattern of the quickly cooled melt (glass) is typical of an amorphous nature, as it was expected, and that of the slowly cooled melt shows the co-existence of amorphous and new crystalline form.

The IR spectra of KBr disks are shown in Fig. 5. The spectrum of the raw material (Fig. 5A) is similar to that published by Takla (1981), while this of new crystal form (Fig. 5B) exhibits significant differences in the intensities, as well as in the positions of most absorption peaks, especially in the peaks of urea C=O stretching, of urea N–H bending and of SO_2 asymmetrical and symmetrical stretching, as given in Table 2.

The possibility of more than one kind of intermolecular hydrogen bonding, together with the partial transformation of keto- to enol- form (Girgis-Takla and Dakas, 1989), could explain the glass formation during quick cooling of

glibenclamide as well as the formation of the new crystal form.

Molecular decomposition of glibenclamide during sublimation is not expected since it does not occur during melting (Hassan et al., 1991) and was checked by IR spectroscopy of ethanolic solutions. The IR spectra for solutions of raw material and new crystal form in absolute ethanol, shown in Fig. 6, were identical.

Regarding the solubility results (Table 1), it can be seen that the new crystal form has the lowest solubility and the quickly cooled melt (glass) the highest, as it was expected from the corresponding melting points. The slowly cooled melt and the raw material have an intermediate solubility and the first of them shows higher solubility, although it has higher melting point than the raw material. This controversy may be attributed to co-existence of glass and new crystal form in the sample obtained by slow cooling, as it is evidenced by the DSC scans of cooled melts (Fig. 1C and D) and confirmed by the SEM photograph of slowly cooled melts (Fig. 3D).

The observed crystal state changes of glibenclamide may be responsible for the variation in dissolution testing and in bioavailability of tablets reported (Blume et al., 1993). During the tabletting process increases in temperature of the tablet mass between 5–30°C above the ambient value may occur due to the generation of friction heat (Hanus and King, 1968). Still higher temperature will be developed at the minute contact points between the particles. This together with the anisotropic application of pressure and lowering of melting point can cause the liquefaction of the glibenclamide asperities during the tablet compression (Rankel and Higuchi, 1968; Malamataris and Pilpel, 1981) and consequently change the

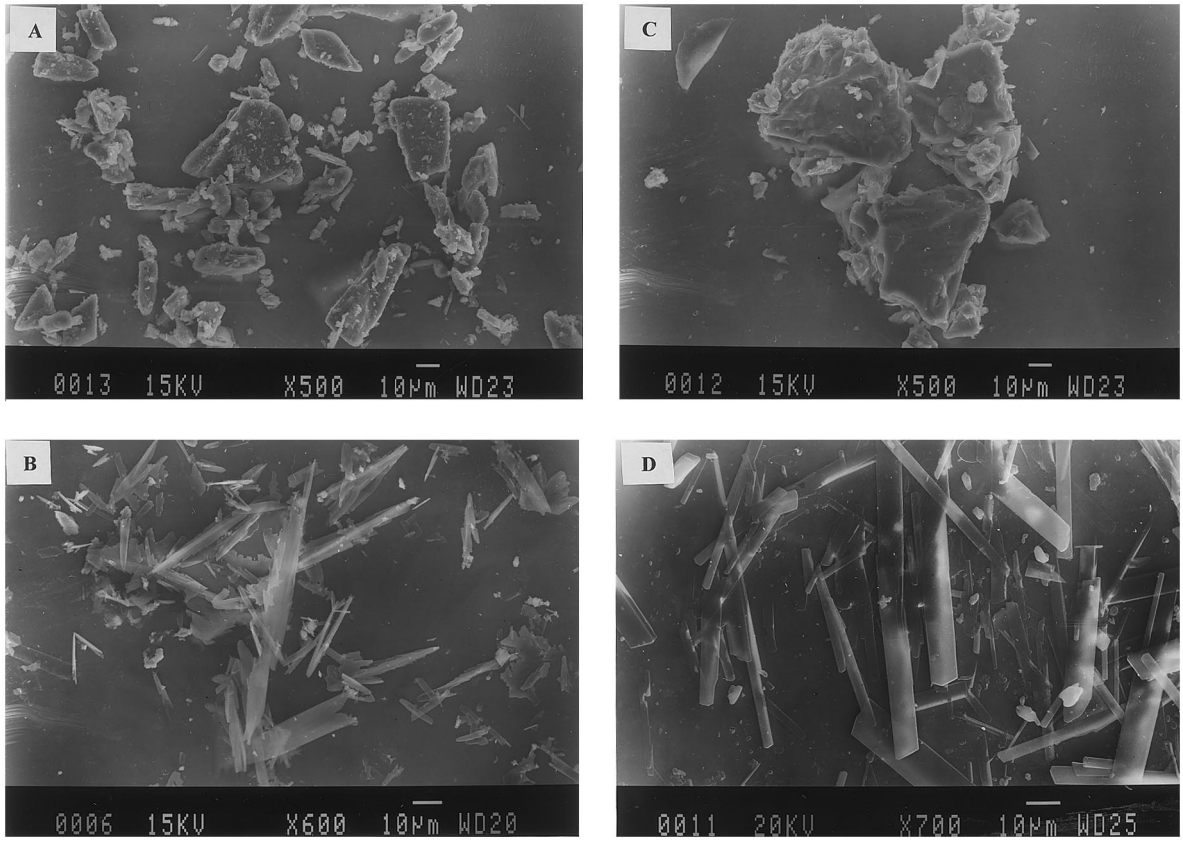

Fig. 3. SEM photographs of thermally treated glibenclamide (legend as in Fig. 1).

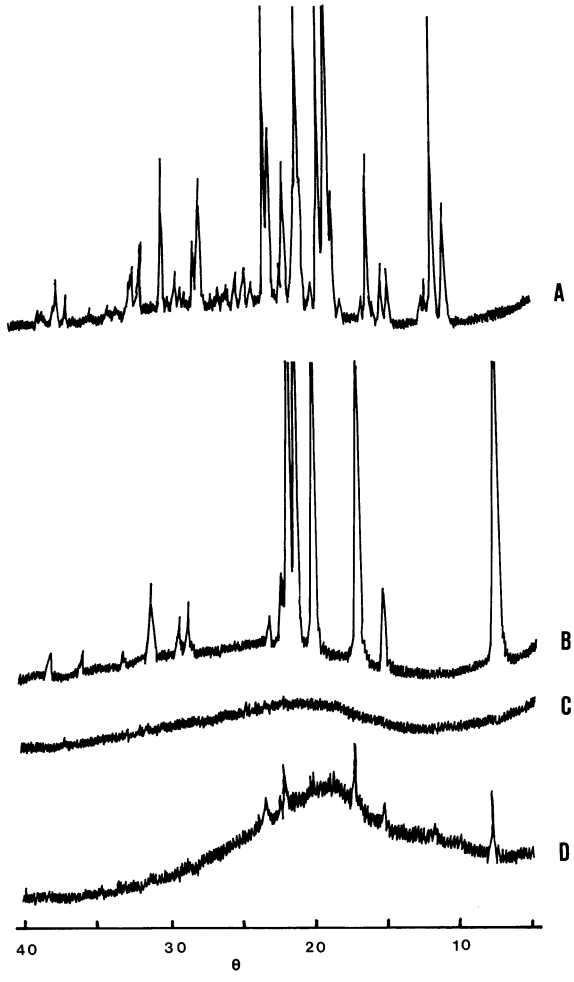

Fig. 4. XRD spectra of thermally treated glibenclamide (legend as in Fig. 1).

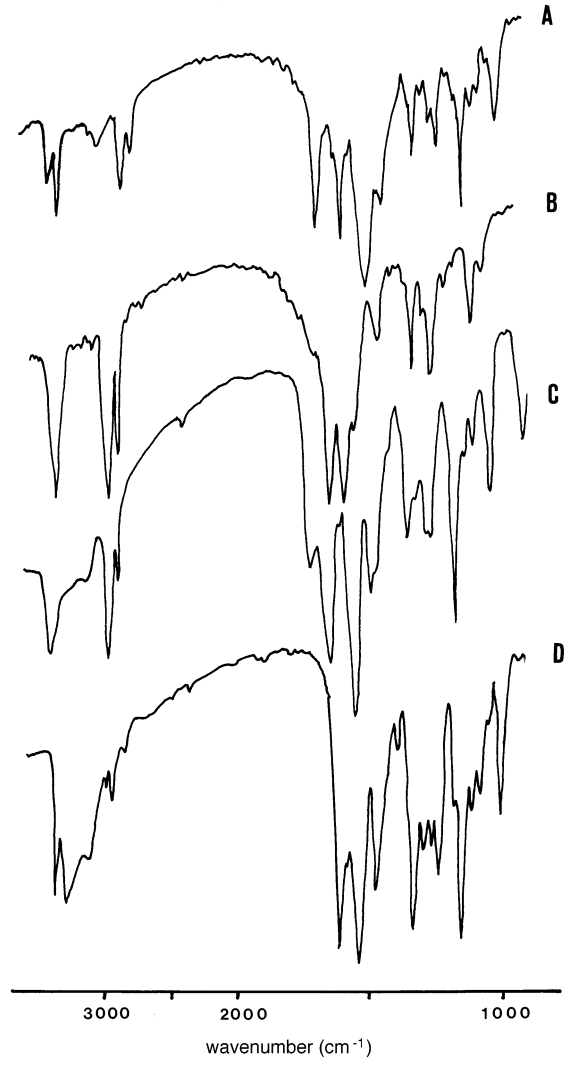

Fig. 5. IR spectra of thermally treated glibenclamide (legend as in Fig. 1).

Table 2
IR data of thermally treated glibenclamide

Material	Urea NH stretching	Urea C=O stretching	Amide C=O stretching	Urea NH bending	SO_2 asymm.	SO_2 symm.
Raw material	3310 3360	1717	1619	1520	1340	1157
New crystals	3330		1623	1574	1312	1086
Quickly cooled	3359	1702	1629	1536	1339	1158
Slowly cooled	3357		1615	1541	1339	1157

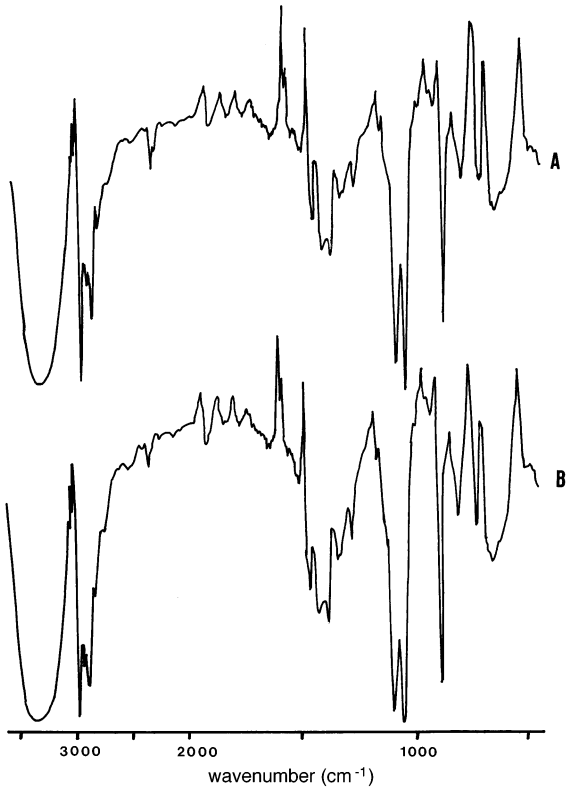

Fig. 6. IR spectra of ethanolic solutions for raw material (A), and new crystal form (B).

glibenclamide solid state. Therefore, dissolution and bioavailability may be affected in a manner depending on the temperature reduction (cooling) of the tableted mass immediately after compression, on the storage conditions of the tablets and on the testing time after the compression, besides the excipients involved.

From the above discussion it can be concluded that cooling of melted glibenclamide and subsequent storage conditions are very important factors for the development of the new crystal form and reduction of solubility. Therefore, elucidation of possible relation between changes in the solid state and dissolution rate of glibenclamide under usual variability of production and storage conditions of tablets are thought to be of interest and is in progress in our laboratory on experimental and commercial formulations.

Acknowledgements

The authors would like to thank Professor S. Sklavounos, for the powder X-ray diffraction analyses and scanning electron microphotographs.

References

Arnqvist, H.J., Karlberg, B.E., Melander, A., 1983. Pharmacokinetics and effects of glibenclamide in two formulations, HB 419 and HB 420, in type 2 diabetes. Ann. Clin. Res. 37, 21–25.

Blume, H., Ali, S.L., Siewert, M., 1993. Pharmaceutical quality of glibenclamide products. A multinational postmarket comparative study. Drug Dev. Ind. Pharm. 19, 2713–2741.

Borchert, H., Muller, H., Pfeifer, S., 1976. Zur biologischen Verfugbarkeit von Glibenclamide in Abhangigkeit von der Teilchengrosse. Pharmazie 31, 307–309.

Borka, L., 1977. The polymorphism of bumetanide, of glibornuride and of chlorpromazine picrate. Acta Pharm. Suec. 14, 205–209.

Chalk, J.B., Patterson, M., Smith, M.T., Eadie, M.J., 1986. Correlation between in vitro dissolution, in vivo bioavailability and hypoglycaemic effect of oral glibenclamide. Eur. J. Clin. Pharmacol. 31, 177–182.

Ganley, J.A., McEven, J., Calvert, R.T., Barker, C.J., 1984. The effect of in vivo dispension and gastric emptying on glibenclamide absorption from a novel, rapidly dissolving capsule formulation. J. Pharm. Pharmacol. 36, 734–739.

Girgis-Takla, P., Dakas, C.J., 1989. An infrared study of tautomerism in acetohexamide polymorphs. J. Pharm. Pharmacol. 41, 227–230.

Hanus, E.J., King, L.D., 1968. Thermodynamic effects in the compression of solids. J. Pharm. Sci. 57, 677–684.

Hassan, M.A., Najib, N.M., Suleiman, M.S., 1991. Characterization of glibenclamide glassy state. Int. J. Pharm. 67, 131–137.

Hassan, M.A., Salem, M.S., Sallam, E., Al-Hindawi, M.K., 1997. Preparation and characterization of a new polymorphic form and a solvate of glibenclamide. Acta Pharm. Hung. 67, 81–88.

Malamataris, S., Pilpel, N., 1981. Effect of temperature on the tensile strength of lactose coated with fatty acids. Powder Technol. 28, 35–42.

Mitrevej, A., Sinchaipanid, N., Junyaprasert, V., Warintornuwat, L., 1996. Effect of grinding of β-cyclodextrin and glibenclamide on tablet properties. Drug Dev. Ind. Pharm. 22, 1237–1241.

Rankel, A.S., Higuchi, T., 1968. Physics of tablet compression XV. Thermodynamic and kinetic aspects of adhesion under pressure. J. Pharm. Sci. 57, 574–577.

Rupp, W., Badian, M., Heptner, W., Malerczyk, V., 1984. Bioavailability and in vitro liberation of glibenclamide from a new dosage form. Biopharm. Pharmacokinet. Eur. Congr. 2nd 1, 413–420.

Salem, M.S., Najib, N.M., Hassan, M.A., Suleiman, M.S., 1997. Dissolution kinetics of glibenclamide glass. Acta Pharm. Hung. 67, 13–17.

Singh, J., 1986. Effect of sodium lauryl sulfate and Tween® 80 on the therapeutic efficacy of glibenclamide tablet formulations in terms of BSL lowering in rabbits and diabetic human volunteers. Drug Dev. Ind. Pharm. 12, 851–866.

Suleiman, M.S., Najib, N.M., 1989. Isolation and physicochemical characterization of solid forms of glibenclamide. Int. J. Pharm. 50, 103–109.

Takla, P.G., 1981. Glibenclamide. Analytical Profiles of Drug Substances 10, 337–355.