

An Approach for Improvement of the Dissolution Rate of Gliclazide

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ABSTRACT

Gliclazide is an anti-diabetic drug that is poorly soluble in water. This paper describes an approach to improve the dissolution rate of gliclazide by using solid dispersions (SDs) in polyethylene glycol 4000 (PEG 4000). The phase-solubility behavior of gliclazide in the presence of various concentrations of PEG 4000 in 0.1 N HCl at 37 °C was obtained. The solubility of gliclazide increased with increasing amounts of PEG 4000 in water. The Gibbs free energy (ΔG_{tr}°) values were all negative. The solid dispersions were prepared with a solvent-melting method using different concentrations of PEG 4000. X-ray diffraction, infrared spectroscopy, and DSC were used to examine the physicochemical characteristics of solid dispersions of gliclazide and PEG. The dissolution rate of gliclazide in SDs with PEG 4000 was enhanced. The FTIR spectroscopic studies showed the presence of intermolecular hydrogen bonding between gliclazide and PEG 4000 in the solid state. The DSC and XRD studies indicate the amorphous and microcrystalline states of gliclazide in SDs with PEG 4000.

INTRODUCTION

Gliclazide is a second-generation hypoglycemic sulfonylurea that is useful in the treatment of Type 2 diabetes mellitus (1). Gliclazide shows good tolerability and a low incidence of hypoglycemia; a low rate of secondary failure inhibits platelet aggregation and increases fibrinolysis (2, 3). Thus gliclazide appears to be a drug of choice in long-term sulfonylurea therapy for the control of Type 2 diabetes mellitus (4). It shows low aqueous solubility and dissolution rate and often shows low and irregular bioavailability after oral administration. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of formulation development. The solid dispersion of poorly water-soluble drugs in water-soluble polymers enhances drug dissolution and bioavailability (5).

The preparation and characterization of complexes of gliclazide with β -cyclodextrin have been reported (6–8). Complexation of gliclazide with β -cyclodextrin-hydroxypropyl methylcellulose, which enhanced its hypoglycemic activity, has been reported (9). In addition, accelerated absorption of gliclazide using PEG 400 was studied earlier (10). Solid dispersions of gliclazide in PEG 6000 have been developed to increase drug dissolution rate (11). Enhancement of the solubility of gliclazide using polyvinylpyrrolidone K90 has been reported (12). The molecular weight of the polymer may play a role in the performance of a solid dispersion. The rationale of the present study was to investigate the use of lower molecular weight PEG 4000 for the preparation of solid dispersions with the objectives of improving dissolution

rate of gliclazide and obtaining different behavior as compared with PEG 6000.

MATERIALS AND METHODS

Materials

A gift sample of gliclazide was received from Aristo Pharmaceuticals Ltd. (Mumbai, India). PEG 4000 was received from Clariant (Germany). Double-distilled water was used throughout the study, and all other chemicals were of analytical grade.

Preparation of SDs

The SDs of gliclazide with PEG 4000 contained three different weight ratios of gliclazide/PEG 4000 (1:1, 1:2, 1:5), which are denoted as SD 1/1, SD 1/2, and SD 1/5, respectively. The solid dispersions were prepared by a solvent-melting method using different concentrations of PEG 4000. In the solvent-melting method, the required amount of PEG 4000 was melted in a glass container on a water bath maintained at a temperature of about 50–65 °C. The required amount of gliclazide solution in chloroform was added to the molten PEG 4000 and mixed thoroughly with a glass rod for 5 min. The glass container was placed in an ice bath for about 5 min; the mixture cooled rapidly and solidified. The hardened mixture was then powdered in a mortar, sieved through a 100-mesh screen, and stored in a screw-cap vial at room temperature until use.

Physical mixtures (PMs) having the same weight ratios as the SDs were prepared by thoroughly mixing the required amounts of gliclazide and PEG 4000 for 10 min in a mortar. The resulting mixtures were sieved through a 100-mesh sieve and denoted as PM 1/1, PM 1/2, and PM 1/5. The mixtures were stored in screw-cap vials at room temperature until use.

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Solubility Determinations of Gliclazide

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors (13). An excess amount of gliclazide was placed in a screw-cap glass vial to which 20 mL of an aqueous solution containing various concentrations of PEG 4000 was added. The samples were shaken at 37 ± 0.5 °C for 72 h in a water bath (Remi Pvt Ltd, Mumbai). After 72 h, the samples were filtered through a 0.45- μ m membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at 227 nm using a UV-vis spectrophotometer (Shimadzu UV-1700, Pharm Spec).

Dissolution Studies

Dissolution studies of gliclazide in powder form, SDs, and PMs were performed using USP Apparatus 2 (Lab India, Mumbai) at a paddle rotation speed of 50 rpm in 900 mL 0.1 N HCl containing 0.25% (w/v) SLS at 37 ± 0.5 °C. SDs or PMs equivalent to 30 mg of gliclazide were weighed using a digital balance (Sartorius) and added to the dissolution medium. At specified times (every 10 min for 1 h), 10-mL samples were withdrawn using a 0.45- μ m syringe filter (Sepyrane, Mumbai) and then assayed for the gliclazide content by measuring the absorbance at 227 nm using a UV-vis spectrophotometer (Shimadzu UV-1700, PharmSpec). Fresh medium (10 mL) that was prewarmed at 37 °C was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. Dissolution studies were performed in triplicate ($n = 3$), and calculated mean values of cumulative drug release were used to plot the release curves.

Fourier Transform Infrared Spectroscopy

Infrared spectra were obtained using an FTIR-430 spectrometer (Jasco, Japan). Samples of gliclazide, SDs, and PMs were ground and mixed thoroughly with potassium bromide at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 T for 5 min in a hydraulic press. Forty scans from 4000 to 400 cm^{-1} were obtained at a resolution of 4 cm^{-1} .

Differential Scanning Calorimetry

The DSC measurements were performed on a DSC-6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 1.675 mg of gliclazide or equivalent) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 °C/min from 25 to 250 °C. An empty aluminum pan was used as reference.

X-Ray Diffraction

X-ray powder diffraction patterns were obtained at room temperature using a PW1710 X-ray diffractometer (Philips, Holland) with a Cu anode and a graphite

monochromator, operated at a voltage of 35 kV and a current of 20 mA. The samples were analyzed in the 2θ angle range of 5–70°, and the process parameters were set as scan-step size of 0.02° (2θ) and scan-step time of 0.5 s.

Dissolution Data Analysis

Phase-Solubility Studies

The value of the apparent stability constant, K_s , for drug-carrier combinations was computed from the phase-solubility profiles, as described by

$$K_s = \frac{\text{Slope}}{\text{Intercept} (1 - \text{Slope})} \quad (1)$$

The value of K_s for drug-carrier combinations can also be computed from the phase-solubility profiles by

$$K_s = \frac{S_t - S_0}{S_0 (L_t - S_t + S_0)} \quad (2)$$

where S_t is the total concentration of dissolved drug, S_0 is the equilibrium solubility of drug in the presence of polymer, and L_t is the total concentration of polymer (14).

The Gibbs free energy of transfer (ΔG_{tr}°) of gliclazide from pure water to aqueous solutions of carrier was calculated as

$$\Delta G_{tr} = -2.303 RT \left(\log \frac{S_0}{S_s} \right) \quad (3)$$

where S_0/S_s is the ratio of the molar solubility of gliclazide in aqueous solution of PEG 4000 to that in the same medium without PEG 4000.

RESULTS AND DISCUSSION

Solubility Studies

The phase-solubility diagram investigated in 0.1 N HCl (pH 1.2) is linear over a wide range of PEG 4000 concentrations and corresponds to A_L -type profiles (13). The stability constant is 0.193 mg/mL. The values of the stability constant depend on slope values. The greater the value of the slope, the greater is the capacity of the polymer to solubilize the drug. It has been reported that Gelucire 44/14, which has a larger slope value, shows a greater capacity to solubilize halofantrine than PEG 8000 and PVP K 30 (15). The stability constant values vary slightly with polymer molecular weight. The values of the stability constants increase with increasing polymer molecular weight. Trapani et al. (16) reported that PEG 6000 shows a lower solubilization capacity than PEG 4000 (102 and 92 mg/mL for PEG 6000 and PEG 4000, respectively). These results agree with the well-established formation of soluble complexes between the water-soluble polymeric carriers and poorly water-soluble drugs (17). At an 18% (w/v) concentration of PEG 4000, the solubility of gliclazide increased by a factor of 3.4 (Table 1). Increased solubility may be due to the improved wettability of the gliclazide particles in aqueous solution

Table 1. Effect of PEG 4000 Concentration and Gibbs Free Energy on Gliclazide Solubility

| Concentration of PEG 4000 (% w/v) | Concentration of Gliclazide (mg/mL) at 37 °C | ΔG_{tr}° (J/Mol) |
|-----------------------------------|--|---------------------------------|
| 0 | 0.80 ± 0.02 | 0 |
| 2 | 0.81 ± 0.01 | 0 |
| 4 | 1.06 ± 0.05 | -698 |
| 6 | 1.28 ± 0.01 | -1184 |
| 8 | 1.53 ± 0.05 | -1644 |
| 10 | 1.76 ± 0.08 | -2005 |
| 12 | 1.97 ± 0.09 | -2295 |
| 14 | 2.2 ± 0.01 | -2580 |
| 16 | 2.45 ± 0.02 | -2857 |
| 18 | 2.75 ± 0.08 | -3155 |

from PEG 4000. The values of Gibbs free energy change are an indication of the process of transfer of gliclazide from pure water to aqueous solution of PEG 4000. Table 1 presents the values of the Gibbs free energy associated with the aqueous solubility of gliclazide in the presence of PEG 4000. The ΔG_{tr}° values are all negative for PEG 4000 at various concentrations, indicating the spontaneous nature of the drug solubilization.

Dissolution Studies

The Q_{10} , Q_{20} , and Q_{30} values are reported in Table 2, and dissolution profiles are shown in Figure 1. From the results in Table 2, it is evident that the dissolution onset of pure gliclazide is very low, about 40.82% of the drug being dissolved within 30 min. SDs of gliclazide with PEG 4000 show considerably enhanced dissolution rates within 30 min compared with those for pure gliclazide and PMs. Model-independent approaches are based on the ratio of the area under the dissolution curve (dissolution efficiency) or on mean dissolution time (18, 19). The percent dissolution efficiency (%DE) and mean dissolution time (MDT) were also computed to compare the relative performance of various concentrations of carrier in SDs and PMs. The %DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t , expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time. The %DE can be calculated from

$$\%DE = \frac{\int_0^t Y dt}{Y_{100}t} \times 100\% \quad (4)$$

where Y is the percent drug dissolved at time t .

The value of %DE_{10min} for pure gliclazide (9.16%) was enhanced in PMs (15.45%) as well as in SDs (35.92%). The

Table 2. In Vitro Dissolution Profile of Gliclazide, Physical Mixture of Gliclazide, and Solid Dispersion of Gliclazide in 0.1 N HCl (pH 1.2)

| Formulation | Dissolution Parameters | | | | | MDT (min) |
|-------------|------------------------|----------|----------|------------------------|------------------------|-----------|
| | Q_{10} | Q_{20} | Q_{30} | % DE _{10 min} | % DE _{30 min} | |
| Drug | 18.46 | 32.67 | 40.82 | 9.16 | 23.67 | 12.5 |
| PM1/1 | 22.0 | 34.0 | 51.7 | 11.0 | 27.28 | 15.86 |
| PM1/2 | 22.8 | 38.1 | 54.9 | 11.38 | 29.42 | 15.84 |
| PM1/5 | 30.9 | 42.0 | 57.0 | 15.45 | 33.81 | 14.38 |
| SD1/1 | 54.61 | 63.94 | 67.5 | 27.31 | 50.76 | 12.42 |
| SD1/2 | 59.6 | 65.9 | 69.8 | 29.82 | 53.48 | 11.52 |
| SD1/5 | 71.8 | 78.5 | 82.7 | 35.92 | 63.91 | 9.5 |

value of %DE_{30min} for the pure drug was increased to 33.81% in PMs and up to 63.91% in SDs (Table 2).

To understand the extent of gliclazide dissolution rate enhancement from its SDs and PMs, the dissolution data for pure gliclazide, SDs, and PMs were used to calculate the mean dissolution time (MDT). The mean dissolution time can be calculated by using eq 5 (20).

$$MDT_{in\ vitro} = \frac{\sum_{i=1}^n T_{mid} \Delta M}{\sum_{i=1}^n \Delta M} \quad (5)$$

Here, i is the dissolution sample number, n is the number of dissolution sampling times, T_{mid} is the midpoint between times T_i and T_{i-1} , and ΔM is the amount of gliclazide dissolved (μg) between times T_i and T_{i-1} .

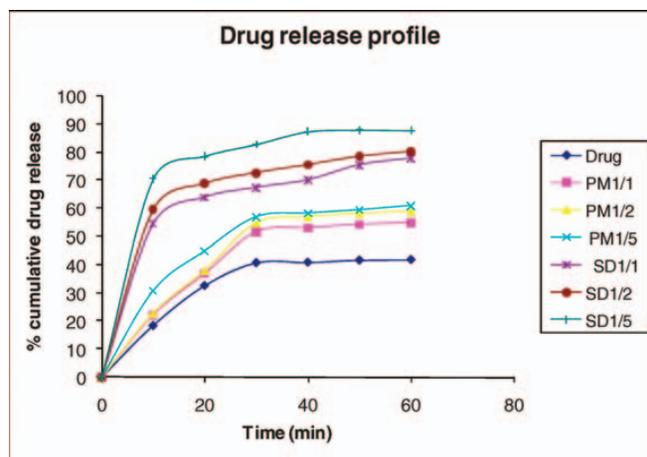


Figure 1. In vitro dissolution profiles of gliclazide, a physical mixture of gliclazide, and a solid dispersion of gliclazide in 0.1 N HCl (pH 1.2).

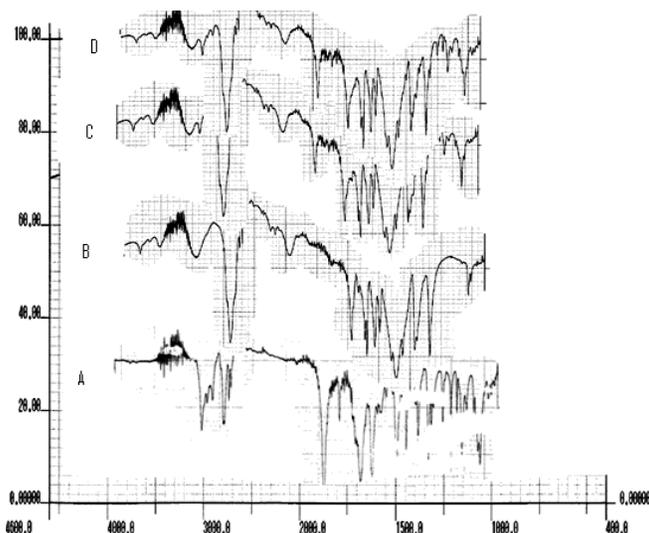


Figure 2. FTIR spectra of (A) pure gliclazide, (B) pure PEG 4000, (C) gliclazide-PEG 4000 PM, and (D) gliclazide-PEG 4000 SD.

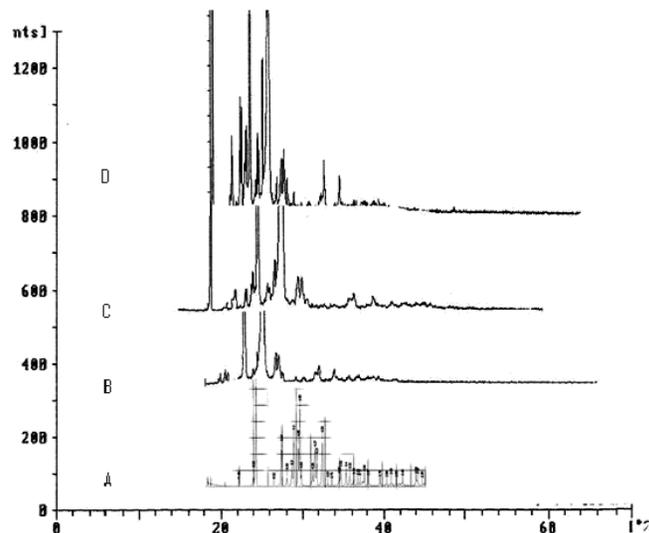


Figure 3. X-Ray diffractograms of (A) pure gliclazide, (B) pure PEG 4000, (C) gliclazide-PEG 4000 PM, and (D) gliclazide-PEG 4000 SD.

The *MDT* values for pure gliclazide, PMs, and SDs are presented in Table 2. The *MDT* for gliclazide is 12.5 min; it decreased to 9.5 min in SDs with PEG 4000 at a 1:5 gliclazide/PEG 4000 ratio.

The magnitude of the mean dissolution time and the percent dissolution efficiency for each formulation were calculated using PCP Disso v3 software (Pune, India).

The increase in dissolution kinetics of gliclazide from PEG SDs may be due to the reduction of crystal size, the absence of aggregation of drug crystals, and the conversion of drug from crystalline to the amorphous or microcrystalline state (5). An increase in gliclazide wettability could result from the formation of a film of polyethylene glycol around it, which modifies the hydrophobicity of the surfaces and explains the mechanism of improved dissolution rate in PMs (21, 22).

FTIR Spectroscopy

FTIR spectroscopy was used to characterize the possible interactions between drug and carrier in the solid state. The IR spectra of SDs and PMs were compared with the standard spectrum of gliclazide (Figure 2A). The IR spectrum of gliclazide is characterized by the absorption of the carbonyl (C=O) sulfonylurea group at 1706 cm^{-1} (6). In the spectra of the SDs and PMs, this band is shifted toward higher frequencies at 1712 cm^{-1} and 1720 cm^{-1} , respectively. Also, the -NH group band at 3265 cm^{-1} in the spectrum of gliclazide is shifted to 3367 cm^{-1} in the SDs. The sulfonyl group bands are located at 1349 cm^{-1} and 1162 cm^{-1} in pure gliclazide. In the SDs, the asymmetric vibration peak of the S=O band is shifted from 1349 cm^{-1} to 1346 cm^{-1} with decreased intensity. In the SDs, the symmetrical stretching vibration band of S=O is shifted from 1162 cm^{-1} to 1112 cm^{-1} with

decreased intensities. Important vibrations in the spectrum of PEG 4000 are the C-H stretch at 2890 cm^{-1} and the C-O stretch at 1113 cm^{-1} . The shift in the peaks associated with the gliclazide sulfonylurea group indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PEG 4000 interacting with the oxygen atoms of the sulfonyl group. This led to the conclusion that the changes seen are a result of intermolecular hydrogen bonding between gliclazide and PEG 4000 in the solid state.

X-Ray Diffraction

The diffraction spectrum of pure gliclazide shows that the drug was of crystalline nature as demonstrated by numerous peaks observed at 2θ of 10.59, 14.98, 17.2, 17.85, 18.15, 22.07, 25.42, 26.25, 26.75, and 29.5 (Figure 3A). Pure PEG 4000 shows two peaks with the highest intensity at 2θ and *d*-spacings of 19.14 and 4.63 Å; 22.95 and 3.87 Å; 23.28 and 3.81 Å; and 23.49 and 3.78 Å. Some changes in gliclazide peak position were observed in PMs as well as SDs. The prominent peaks from pure gliclazide were clearly seen at the same positions in the PMs and SDs, but with decreased intensities. The relative reduction in diffraction intensity of gliclazide in PEG 4000 preparations at these angles suggests that the size of the crystals was reduced to a microcrystal form (23). The positions of PEG 4000 peak patterns in the PMs and SDs are the same and superimposable, which, again, rules out the possibility of a well-defined chemical interaction and new compound formation between these two components. Results of this study imply that gliclazide is present in a partially crystalline or microcrystalline form in the SDs. Valizadeh et al. (24) characterized indomethacin-PEG 6000 SDs prepared by a melting method and concluded

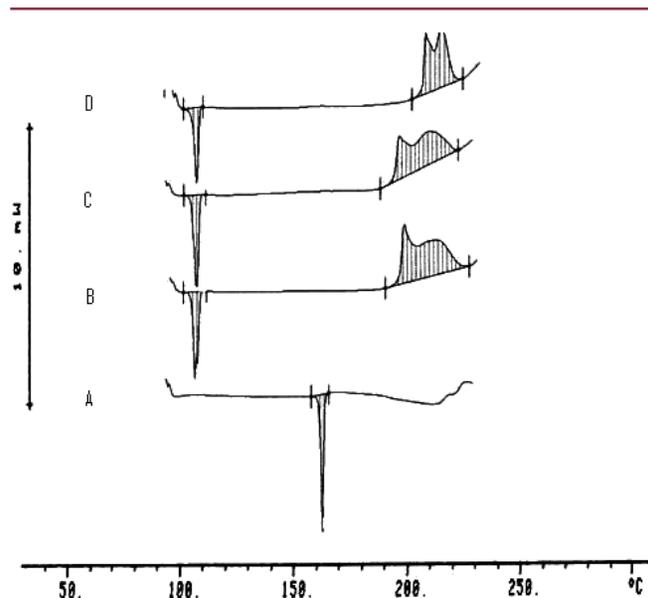


Figure 4. DSC thermograms of (A) pure gliclazide, (B) pure PEG 4000, (C) gliclazide-PEG 4000 PM, and (D) gliclazide-PEG 4000 SD.

that the drug was in a microcrystalline form and that no well-defined chemical interaction took place between indomethacin and PEG 6000, either in solution or in the solid state.

Differential Scanning Calorimetry

The DSC curve of pure gliclazide exhibits a single endotherm corresponding to the melting of the drug. The onset of melting was observed at 170.8 °C, and the corresponding heat of fusion (ΔH_f) is 171.8 J/g (Figure 4A), whereas pure PEG 4000 shows a melting endotherm at 60.2 °C and a corresponding ΔH_f of 235.0 J/g. Thermograms of SDs (Figure 4D) show the absence of a gliclazide melting peak and one exothermic peak at 253.9 °C; the corresponding ΔH_f is 741.6 J/g suggesting that gliclazide is completely soluble in the liquid phase of the polymer or that the crystalline nature of gliclazide is absent. The exothermic peak may be due to crystallization above the glass transition temperature, T_g . The molecular motion of amorphous solids depends on temperature. The kinetic energy of amorphous solids increases significantly as the temperature increases to T_g . Because of the thermodynamic instability of amorphous solids relative to the crystalline state, spontaneous crystallization is always possible as soon as molecular mobility is above the threshold of nucleation. However, the observed melting peak for PEG 4000 in SDs is at the same temperature (59.4 °C) as for pure PEG 4000. The absence of an endothermic peak of drug in SDs has also been reported by other research groups (25, 26). The PM formulations of gliclazide and PEG 4000 also show no melting peak for gliclazide (Figure 4C), even though the peaks derived from gliclazide are observed in XRD

(Figure 3A). It is speculated that gliclazide dissolved in the melted PEG 4000 during the DSC measurement; only one endothermic peak at 63.4 °C corresponding to the melting of PEG 4000 was observed. This result agrees with the report of Yamashita et al. (26); their DSC study reported the absence of an endothermic peak of tacrolimus in the PM formulation of tacrolimus and PEG 4000.

CONCLUSIONS

The solubility and dissolution rate of gliclazide can be enhanced in SDs with PEG 4000. The solubilization effect of PEG 4000, reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of surface properties of the drug particles may be responsible for the enhanced solubility and dissolution rate of gliclazide from its SDs and PMs. DSC of gliclazide SDs in PEG 4000 and corresponding PMs do not indicate the presence of crystalline gliclazide, because gliclazide dissolved completely below its melting point. The absence of an endothermic peak of gliclazide in the DSC thermograms of SDs with PEG 4000 shows the conversion of gliclazide from the crystalline to the microcrystalline state. The FTIR spectroscopic studies show the presence of intermolecular hydrogen bonding between gliclazide and PEG 4000 in the solid state. It can be concluded that gliclazide SDs with PEG 4000 provide a promising way to enhance its solubility and dissolution rate but are less effective than those prepared with PEG 6000.

ACKNOWLEDGMENTS

The authors are grateful to Aristo Pharmaceuticals Pvt. Ltd, Mumbai, India, and Clariant GmbH, Sulzbach, Germany, for their interest and for supplying gliclazide and various grades of polyethylene glycol, respectively. Mr. S. Biswal acknowledges the Principal, Royal College of Pharmacy and Health Sciences, Berhampur, for providing the necessary facilities.

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