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Research Article

Enhancement of Dissolution Rate of Gliclazide Using Solid Dispersions with Polyethylene Glycol 6000

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Abstract. The aim of the present study was to enhance the dissolution rate of gliclazide using its solid dispersions (SDs) with polyethylene glycol (PEG) 6000. The phase solubility behavior of gliclazide in presence of various concentrations of PEG 6000 in 0.1 N HCl was obtained at 37 °C. The solubility of gliclazide increased with increasing amount of PEG 6000 in water. Gibbs free energy (ΔG_{tr}^{o}) values were all negative, indicating the spontaneous nature of gliclazide solubilization and they decreased with increase in the PEG 6000 concentration, demonstrating that the reaction conditions became more favorable as the concentration of PEG 6000 increased. The SDs of gliclazide with PEG 6000 were prepared at 1:1, 1:2 and 1:5 (gliclazide/PEG 6000) ratio by melting-solvent method and solvent evaporation method. Evaluation of the properties of the SDs was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. The SDs of gliclazide with PEG 6000 exhibited enhanced dissolution rate of gliclazide, and the rate increased with increasing concentration of PEG 6000 in SDs. Mean dissolution time (MDT) of gliclazide decreased significantly after preparation of SDs and physical mixture with PEG 6000. The FTIR spectroscopic studies showed the stability of gliclazide and absence of well-defined gliclazide–PEG 6000 interaction. The DSC and XRD studies indicated the microcrystalline or amorphous state of gliclazide in SDs of gliclazide with PEG 6000.

KEY WORDS: dissolution; gliclazide; PEG 6000; solid dispersion; solubility.

INTRODUCTION

Polyethylene glycols (PEGs) with molecular weights of 1,500–20,000 are used for the preparation of solid dispersions (SDs). Solubility of PEGs in water is generally good, but decreases with increase in molecular weight. A particular advantage of PEGs for formation SDs is that they also have good solubility in many organic solvents. The melting points of PEGs of interest lies under 65 °C in every case (*e.g.*, the melting ranges of PEG 1000, PEG 4000, PEG 6000, and PEG 20,000 are 30–40, 50–58, 55–63, and 60–63 °C respectively) (1). The relatively low melting points of PEGs are advantageous for manufacturing of SDs by melting method. Further, PEGs have the ability to solubilize some compounds and improve wettability (2). The SDs of drugs with PEG 6000 may be useful to solve various problems such as stability, solubility, dissolution and bioavailability (3–10).

Gliclazide, [1-(3-azabicyclo(3,3,0)oct-3-yl)-3-*p*-tolylsulfonylurea] is a second generation hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM) (Fig. 1) (11). Prior reports reveal that the drug shows good tolerability, low incidence of hypoglycemia, and a low rate secondary failure (12). In addition, it has a potential for slowing the progression of diabetic retinopathy. For the reasons stated gliclazide appears to be a drug of choice in long term sulfonylurea therapy for the control of NIDDM (12,13). Gliclazide is a white crystalline powder, relatively insoluble in water. The pK_a of gliclazide is 5.8. Gliclazide exhibits slow GI absorption rate and inter individual variations of its bioavailability (13). The slow absorption rate of drug usually originates from either poor dissolution of drug from the formulation or poor permeability of drug across GI membrane. The slow dissolution can be attributed, at least in part, to hydrophobicity of gliclazide powder as evidenced by poor wetting of powder surface by water. For poorly water soluble and highly permeable (class-II) drugs, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract (14). Therefore, together with permeability, the solubility and or dissolution rate of a drug are key determinants of its oral bioavailability (15). This observation suggests that the increased GI absorption of gliclazide could be

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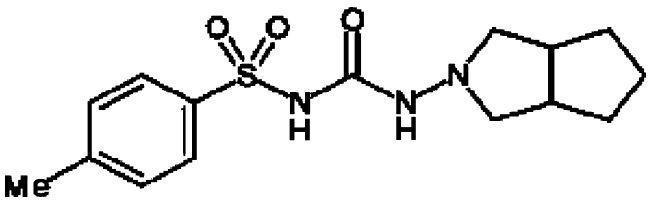

Fig. 1. Structure of gliclazide

achieved by use of solid dispersions which enhance dissolution and solve inter individual variation in bioavailability.

A number of methods have been attempted to improve the solubility and or dissolution rate of poorly soluble drugs, the most promising method for promoting dissolution rate is formation of SDs (16). The primary objective of the present study is to investigate the possibility of improving the release properties of gliclazide via SDs with PEG 6000. The possible interactions between gliclazide and PEG 6000 in both solid and liquid states were investigated. Interaction in the solid state was investigated by Fourier-transform infrared (FT-IR) spectroscopy, X-ray diffraction analysis (XRD) and differential scanning calorimetry (DSC). Interaction in solution was studied by phase solubility analysis and dissolution experiments.

MATERIALS AND METHODS

Materials

A gift sample of gliclazide was received from Aristo Pharmaceuticals Ltd., (Mumbai, India). PEG 6000 was received from Clariant (Germany). Double distilled water was used throughout the study and all the other chemicals used were of analytical grade.

Preparation of SDs

The SDs of gliclazide in PEG 6000 containing three different weight ratios (1:1, 1:2, 1:5) (gliclazide/PEG 6000) and denoted as SD1/1, SD1/2 and SD 1/5 respectively, were prepared by two methods such as melting-solvent method and solvent evaporation method. For solvent evaporation method, to a solution of gliclazide in chloroform, an appropriate amount of PEG 6000 was added. The solvent was evaporated under reduced pressure at 40 °C by using rotary evaporator and the resulting residue dried under vacuum for 3 h. The mixture was stored overnight in a desiccator. The hardened mixture was powdered in a mortar, sieved through a 100-mesh screen, and stored in a screw-cap vial at room temperature until further use (7). For melting-solvent method, a required amount of PEG 6000 was melted in a glass container on a water bath maintained at about 50–60 °C. A required amount of gliclazide solution in chloroform was added to the molten PEG 6000 and mixed thoroughly with a glass rod for 5 min (17). The mixture was cooled rapidly by placing the glass container in an ice bath for about 5 min 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 further use.

The PMs having the same weight ratio as SDs were prepared by thoroughly mixing the required amount of gliclazide and PEG 6000 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 respectively. The mixtures were stored in a screw-cap vial at room temperature until use.

Solubility Determinations of Gliclazide

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors (18). In brief, an excess amount of gliclazide was taken into a screw-capped glass vial to which 20 mL of aqueous solution containing various concentrations of PEG 6000 was added. Then the samples were shaken at 37±0.5 °C for 72 h in a water bath (Remi Pvt Ltd, Mumbai) (This duration was previously tested to be sufficient to reach equilibrium). After 72 h, samples were filtered through a 0.45 μm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 227 nm using a UV–VIS spectrophotometer (Shimadzu 1601PC, Japan).

Dissolution Studies

Dissolution studies of gliclazide in powder form, SDs, and PMs were performed by using the U.S.Pharmacopoeia (USP) model digital tablet dissolution test apparatus-2 (Veego Scientific Co.) at the paddle rotation speed of 50 rpm in 900 mL 0.1 N HCl containing 0.25% (*w/v*) of sodium lauryl sulfate (SLS) as a dissolution medium at 37±0.5 °C (19–21). The SDs or PMs equivalent to 10 mg of gliclazide were weighed using a digital balance (Ohaus Corp) and added into the dissolution medium. At the specified times (every 10 min for 2 hours), 10 mL samples were withdrawn by using syringe filter (0.45 μm) (Sepyrane, Mumbai) and then assayed for gliclazide content by measuring the absorbance at 227 nm using a UV-Visible spectrophotometer (Shimadzu 1601PC, Japan). Fresh medium (10 mL), which was prewarmed at 37 °C, was added to the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), and calculated mean values of cumulative drug release were used while plotting the release curves.

Fourier-transform Infrared Spectroscopy

Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR spectrometer-430 (Jasco, Japan). The samples (gliclazide or SDs or PMs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4,600 to 300 cm^{-1}.

Differential Scanning Calorimetry (DSC)

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 its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 °C min^{-1} from 25 to 250 °C. An empty aluminum pan was used as reference.

Table I. Effect of PEG 6000 Concentration and Gibbs Free Energy on Solubility of Gliclazide

	Concentration of PEG 6000 (% *w/v*)	Concentration of gliclazide(mg/mL) at 37 °C	ΔG_{tr}^{o} (J/Mol)
1	0	0.81±0.02	
2	2	0.81±0.01	0
3	4	1.11±0.05	−789.4
4	6	1.43±0.01	−1,457
5	8	1.74±0.05	−1,937
6	10	2.11±0.08	−2,463
7	12	2.39±0.09	−2,762
8	14	2.64±0.01	−3,030
9	16	2.97±0.02	−3,330
10	18	3.28±0.08	−3,600

X-Ray Diffraction

The X-ray powder diffraction patterns were obtained at room temperature using a PW1710 X-ray diffractometer (Philips, Holland) with Cu as anode material and graphite monochromatic, operated at a voltage of 35 kV, current 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), scan step time of 0.5 s.

Dissolution Data Analysis

Phase-solubility Studies

The value of apparent stability constant, K_s, between drug–carrier combinations were computed from the phase-solubility profiles, as described below

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

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

$$\Delta G_{tr}^{o} = -2.303\, RT \text{Log} \frac{S_o}{S_s} \tag{2}$$

Where $\frac{S_o}{S_s}$ is the ratio of molar solubility of gliclazide in aqueous solution of PEG 6000 to that of the same medium without PEG 6000.

In Vitro Dissolution Data

To compare dissolution profiles, several approaches can be followed such as analysis of variance (ANOVA)-based model-independent and model dependent approaches (22). In the present work, model-independent and model dependent approaches are used for comparison of dissolution profiles. ANOVA based is commonly used to detect significant differences between groups and, there by can be used to

Table II. *In-vitro* Dissolution Profile of Gliclazide, Physical Mixture of Gliclazide and Solid Dispersion of Gliclazide in pH 1.2 Buffers

Sr. No.	Formulation	Dissolution parameters					
		Q_{10} min	Q_{20} min	Q_{30} min	% $DE_{10\ min}$	% $DE_{30\ min}$	MDT (min)
1	Drug	18.46	32.67	40.82	9.16	23.67	12.5
2	PM1/1	24.91	39.84	56.73	22.42	31.04	13.5
3	PM1/2	27.59	45.49	58.98	25.06	34.04	12.4
4	PM1/5	42.53	57.24	62.20	35.58	43.54	8.8
5	$SD_{SE}1/1$	73.52	79.12	86.80	36.54	65.35	7.4
6	$SD_{MS}1/1$	75.20	80.39	88.80	37.55	66.62	7.4
7	$SD_{SE}1/2$	77.93	85.60	91.37	38.97	69.64	6.9
8	$SD_{MS}1/2$	79.56	88.75	92.55	39.75	71.51	6.8
9	$SD_{SE}1/5$	83.75	91.92	95.42	41.88	74.46	6.5
10	$SD_{MS}1/5$	85.95	94.63	96.73	42.98	76.39	6.2

PM Physical mixture, SD_{SE} solid dispersion of gliclazide prepared by solvent evaporation method, SD_{MS} solid dispersion of gliclazide prepared by melting-solvent method.

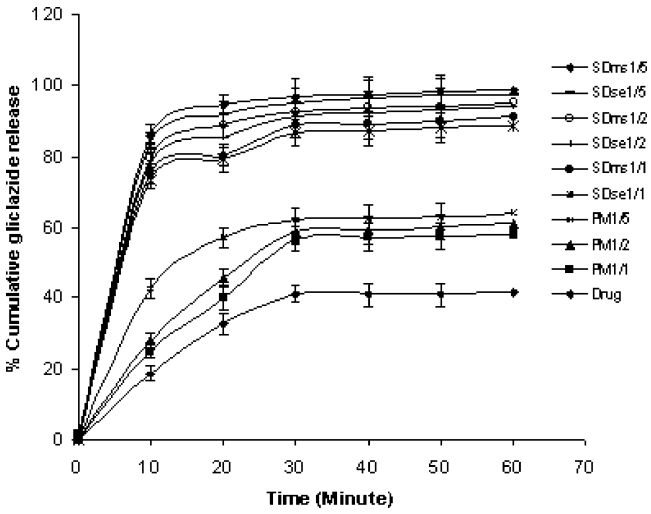

Fig. 2. *In-vitro* dissolution profile of gliclazide, physical mixture and solid dispersion of gliclazide with PEG 6000 in pH 1.2 buffer

detect statistically significant differences between dissolution profiles. Model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency) or on mean dissolution time (19,23). Percent dissolution efficiency (%DE) and mean dissolution time were also computed to compare the relative performance of various concentrations of carrier in SDs and PMs. The magnitude of %DE at 10 min ($\%DE_{10\ min}$) and 30 min ($\%DE_{30\ min}$) for each formulation was computed as the percent ratio of area under the dissolution curve up to the time, t, to that of the area of the rectangle described by 100% dissolution at the same time. The magnitude of mean dissolution time for each formulation was calculated using PCP Disso v3 software (Pune, India).

$$\%DE = \frac{\int_0^t Y dt}{Y_{100} t} \quad (3)$$

In the model-dependent approaches, release data were fitted to five kinetic models including the zero order (Eq. 4), first order (Eq. 5), Higuchi matrix (Eq. 6), Peppas–Korsmeyer (Eq. 7) and Hixson–Crowell (Eq. 8) release equations to find the equation with the best fit using PCP Disso v3 software (Pune, India).

$$R = k_1 t \quad (4)$$

$$\text{LogUR} = \frac{k_2 t}{2.303} \quad (5)$$

$$R = k_3 \sqrt{t} \quad (6)$$

$$\text{Log}R = \text{Log}k_4 + n\text{Log}t \quad (7)$$

$$(\text{UR})^{1/3} = k_5 t \quad (8)$$

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4, and k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, and Hixson–Crowell model, respectively.

RESULTS AND DISCUSSION

Solubility Studies

Solubility experiments showed that the concentration of gliclazide in 0.1 N HCl is notably affected by the presence of PEG 6000 (Table I) (9). The phase-solubility diagram investigated in 0.1 N HCl (pH 1.2) was linear in a wide range of PEG 6000 concentrations and correspond to A_L-type profiles (Fig is not given) (18). The stability constant was found to be 0.186 mL^{-1} mg. The results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs (6, 24, 25). At 18% (*w*/*v*) concentration of PEG 6000, the solubility of gliclazide increased by 4.04 fold (Table I). An indication of the process of transfer of gliclazide from

Table III. Statistical Parameters of Various Formulations After Fitting Drug Release Data to Various Release Kinetics Models

	Zero-order model		First-order model		H-M model		P–K model		H–C model	
Formulations	R	k_1	R	k_2	R	k_3	R	k_4	R	k_5
Drug	0.9813	1.4736	0.9939	−0.0184	0.9943	7.1358	0.9952	3.4734	0.9905	−0.0057
PM1/1	0.9905	1.9630	0.9940	−0.0273	0.9974	9.4625	0.9978	4.4669	0.9934	−0.0081
PM1/2	0.9821	2.1046	0.993	−0.0300	0.9918	10.1965	0.9955	5.6060	0.9963	−0.0088
PM1/5	0.8804	2.4427	0.9328	−0.0366	0.9825	12.1367	0.9832	19.3967	0.9186	−0.0106
$SD_{SE}1/1$	0.7810	3.5156	0.9099	−0.0753	0.9568	17.6967	0.9766	52.1165	0.8658	−0.0189
$SD_{MS}1/1$	0.7815	3.5857	0.9198	−0.0800	0.9568	18.0478	0.9678	53.2082	0.8732	−0.0197
$SD_{SE}1/2$	0.7713	3.7251	0.9205	−0.0896	0.9540	18.7759	0.9998	56.5974	0.8688	−0.0214
$SD_{MS}1/2$	0.7699	3.8190	0.9289	−0.0982	0.9538	19.2543	0.9946	57.7262	0.8743	−0.0227
$SD_{SE}1/5$	0.7557	3.9562	0.9401	−0.1150	0.9481	19.9767	0.9958	63.6354	0.8759	−0.0251
$SD_{MS}1/5$	0.7451	4.0390	0.9343	−0.1288	0.9441	20.4196	0.9718	67.1604	0.8679	−0.0269

H-M Highuchi matrix, *P–K* Peppas–Korsmeyer, *H–C* Hixson–Crowell, R correlation coefficient, k_1–k_5 constants of release kinetics, *PM* physical mixture, SD_{SE} solid dispersion of gliclazide prepared by solvent evaporation method, SD_{MS} solid dispersion of gliclazide prepared by melting-solvent method

pure water to the aqueous solution of PEG 6000 may be obtained from the values of Gibbs free energy change. Table II presents the values of Gibbs free energy associated with the aqueous solubility of gliclazide in presence of PEG 6000. ΔG_{tr}^{o} values were all negative for PEG 6000 at various concentrations indicating the spontaneous nature of the drug solubilization.

Dissolution Studies

The results of the dissolution studies for individual samples (gliclazide alone, PMs and SDs) over the period of 1 h are shown in Fig. 2. Q_{10}, Q_{20} and Q_{30} values (percent drug dissolved within 30 min) are reported in Table II. From Table II it is evident that onset of dissolution of pure gliclazide is very low, about 40.44% of drug being dissolved within 30 min. SDs of gliclazide with PEG 6000 considerably enhanced dissolution rates within 30 min compared to pure gliclazide and PMs. The value of $\%DE_{10\ min}$ for pure gliclazide (9.16%) was enhanced in PMs (35.58%) as well as in SDs (42.98%). The value of $\%DE_{30\ min}$ for the pure drug was increased to 43.54% in PMs and up to 76.39% in SDs (Table III). Also the $\%DE_{30\ min}$ values revealed more dissolution improvement of gliclazide in SD_{MS} than SD_{SE} at same carrier concentrations.

The obtained values of mean dissolution time (MDT) for pure gliclazide, PMs and SDs are presented in Table II. The MDT of gliclazide is 12.5 min; it decreased to 6.2 min for the SDs with PEG 6000 at 1:5 (gliclazide/PEG 6000) ratio.

Table III shows the regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data. The goodness of fit for various models investigated for drug, PMs and SDs ranked in order of Korsemeyer–Peppas > Higuchi > First order > Hixson–Crowell cube root law > Zero order. *In vitro* release data of drug best fitted to Korsemeyer–Peppas model with *n* value 0.7249 hence exhibits non Fickian diffusion. Except for PM 1:2 (gliclazide/PEG 6000) which exhibited Hixson–Crowell cube root law, all the SDs tended to exhibit Fickian diffusion characteristics as corresponding values of n were lower than the standard value for declaring Fickian release behavior *i.e.* 0.4500 (26,27).

Figure 2 also compares dissolution profiles of SDs of identical composition prepared by using different methods.

Table IV. Comparison of FTIR Spectra of Gliclazide and SDs

Gliclazide	SDs	Comments
532	542	
	610	New peak
629	627	
669	664	
	672	New peak
944	919	
	940	
1,080	1,084	Band width change new peak
	1,104	
1,162	1,157	Change in S=0 symmetric stretching
1,349	1,342	Change in S=0 asymmetric stretching
1,706	1,711	Carbonyl stretching
3,265	3,365	NH stretching

The SDs prepared by the melt-solvent method show faster dissolution rate than those prepared by solvent method (28). Possible mechanisms have been proposed to account for the increase in the dissolution kinetics of drugs from polyethylene glycol SDs. The mechanisms include the carrier controlled dissolution (29–31), the continuous drug layer formation (30) and that involving the release of intact particles with dissolution occurring over a large surface area (32). The latter mechanism has been suggested to be important at low drug levels. It is also clear that a modification of the surface properties and hence a reduction of the value of the contact angle which improves the wettability of the powder should lead to an increase of dissolution kinetics. An improvement of wettability of the powder could result from the formation of a film of polyethylene glycol around the drug substance particles which modifies the hydrophobicity of the surfaces (33). Other mechanisms of increased dissolution rates of SDs have been proposed by Ford (16) are reduction of crystal size, absence of aggregation of crystalline drug and conversion of drug from crystalline to amorphous state (16). The dissolution enhancement of gliclazide from PEG 6000 dispersions in the present work was mainly due to formation of microcrystalline or amorphous drug in the solid dispersion.

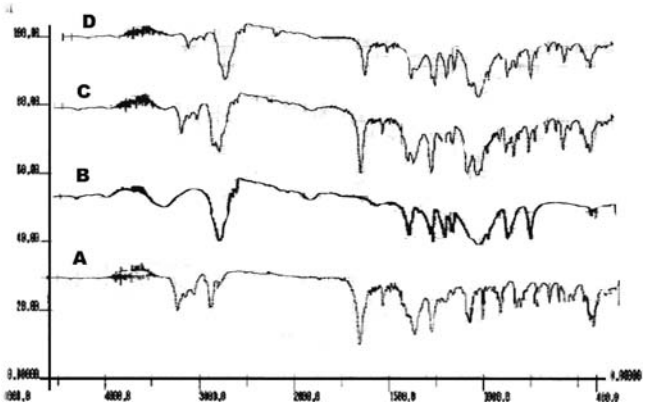

Fig. 3. FTIR spectrograms of pure gliclazide (*A*), pure PEG 6000 (*B*), gliclazide–PEG 6000 PM at 1:2 ratio (*C*), gliclazide–PEG 6000 SD at 1:2 ratio (*D*)

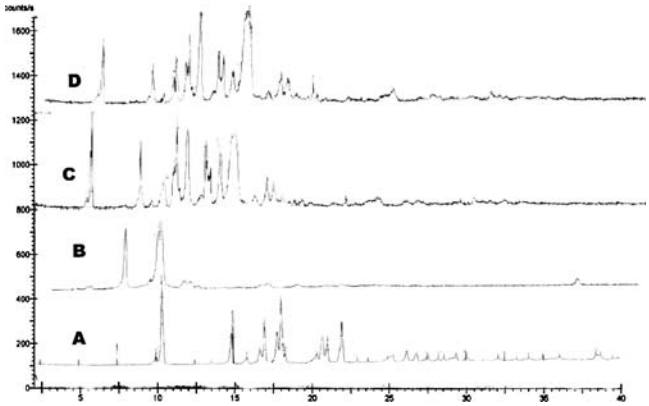

Fig. 4. X-ray diffractograms of pure gliclazide (*A*), pure PEG 6000 (*B*), gliclazide–PEG 6000 PM at 1:2 ratio (*C*), gliclazide–PEG 6000 SD at 1:2 ratio (*D*)

Table V. Intensities at Characteristic Diffraction Angles 2θ (°) and *d*-values (Å) for Gliclazide

2θ	*d*-Value	Intensity	2θ	*d*-Value	Intensity
10.02	8.83	118	25.02	3.55	196
10.59	8.45	1138	25.12	3.52	244
14.98	5.94	558	26.25	3.4	243
15.75	5.58	218	26.75	3.32	205
16.76	5.31	265	27.01	3.23	195
17.21	5.19	681	28.25	3.16	185
17.85	4.96	625	29.51	3.03	197
18.15	4.89	1,068	30.11	2.96	121
18.86	4.83	226	33.25	2.69	102
20.81	4.35	221	34.11	2.62	194
21.11	4.21	405	35.2	2.56	187
22.07	4.03	662	36.5	2.49	182
23.01	3.87	112	39.5	2.28	122
23.65	3.75	105			

FTIR-spectroscopy

The IR spectra of SDs and PMs were compared with the standard spectrum of gliclazide (Fig. 3, Table IV). IR spectrum of gliclazide is characterized by the absorption of carbonyl (C=O) sulphonyl urea group at 1,706 cm^{-1} (34). In spectra of SDs and PMs, this band was shifted towards higher frequencies at 1,725 and 1,711 cm^{-1} respectively (34). Also the NH group which is located at 3,265 cm^{-1} from the IR spectrum of gliclazide shifted to 3,365 cm^{-1} in SDs. The sulphonyl group bands are located at 1,349 and 1,162 cm^{-1} in pure gliclazide. In SDs, the asymmetric vibration peak of S=0 band was shifted from 1,349 to 1,341 cm^{-1} with decreased frequencies. In SDs, the symmetric stretching vibration band of S=0 was shifted from 1,162 to 1,157 cm^{-1} with decreased frequencies. Important vibrations detected in the spectrum of PEG 6000 are the C–H stretching at 2,890 cm^{-1}, C–O stretching at 1,110 cm^{-1} and –OH stretching at 3,350 cm^{-1}. The shift in the peaks associated with sulfonylurea group of the gliclazide indicates an increase in bond strength possibly due to stabilizing effect of the hydrogen atoms of PEG 6000 interacting with the oxygen atoms of the sulphonyl group (35). Mentioned evidences thus lead to the conclusion that changes seen are as a result of physical interaction (hydrogen bonding or complexation) between the gliclazide and PEG 6000 in solid state. It could be expected to have hydrogen bonding between the hydrogen atom of the NH group of gliclazide and one of the ion pairs of oxygen atom in the PEG 6000.

X-ray Diffraction (XRD)

The diffraction spectrum of pure gliclazide showed that the drug was crystalline as demonstrated by numerous peaks observed at 2θ of 10.59°, 14.98°, 17.21°, 17.85°, 18.15°, 22.07°, 25.42°, 26.25°, 26.75° and 29.51° (finger print region) *etc* (Fig. 4A). The characteristic peaks for gliclazide and the intensities are presented in Table V. Pure PEG 6000 showed two peaks with highest intensity at 2θ and *d*-spacings of 19.41 and 4.65 Å, 23.34 and 3.785 Å. The extent of crystallinity influences the dissolution of the drug. An amorphous or metastable form will dissolve at the fastest rate because of its higher internal energy and greater molecular motion, which enhance the thermodynamic properties compared to crystalline materials (36). Some changes in peaks position of gliclazide were observed in PMs as well as SDs. The prominent peaks from pure gliclazide at 2θ of 10.59°, 14.98°, 17.21°, 18.15° and 22.07° *etc* were clearly seen at the same position in the PMs but in SDs the intensities were significantly decreased. More decreased intensity of gliclazide peaks were observed in SDs prepared by melting-solvent method than in SDs prepared by solvent evaporation method. From the aforesaid observations, we can conclude that the crystalline nature of the drug was still maintained, but the relative reduction of diffraction intensity of gliclazide in PEG 6000 preparation suggests that the quality of the crystals was reduced (9). The change in intensities of gliclazide peaks observed in SDs with PEG 6000 relative to the corresponding PMs can be explained as a result of change in crystal size. The positions of PEG 6000 peak patterns in the PMs and SDs were same and super imposable, which again ruled out the possibility of chemical interaction and compound formation between the two components. Results of this study indicate that gliclazide is present in partially crystalline or microcrystalline form in the SDs. Valizaden *et al.*, characterized indomethacin–PEG 6000 SDs prepared by melting method and concluded that the drug was in microcrystalline form and

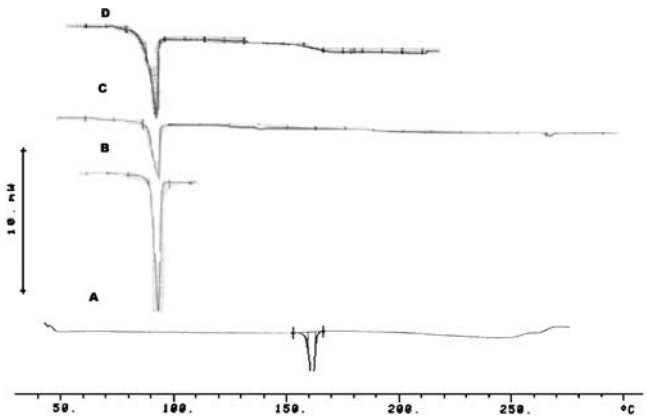

Fig. 5. DSC thermograms of pure gliclazide (*A*), pure PEG 6000 (*B*), gliclazide–PEG 6000 PM at 1:2 ratio (*C*), gliclazide–PEG 6000 SD at 1:2 ratio (*D*)

no chemical interaction took place between indomethacin and PEG 6000 either in solution or in the solid state. The present finding *i.e.* the presence of microcrystalline or partially crystalline state of gliclazide in SDs is in agreement with several studies on other drugs (8).

Differential Scanning Calorimetry

The DSC curve of pure gliclazide exhibited a single endothermic response corresponding to the melting of drug. Onset of melting was observed at 170.8 °C, the corresponding heat of fusion (ΔH_F) was 171.8 J/g (Fig. 5A) where as pure PEG 6000 showed a melting endotherm at 61.9 °C and the corresponding heat of fusion (ΔH_F) was 188.6 J/g (33). Thermograms of SDs (Fig. 5D) showed the absence of a gliclazide peak, suggesting that gliclazide is completely soluble in the liquid phase of polymer or absence of crystalline nature of gliclazide. However, the melting peak of PEG 6000 in SDs was observed at slightly lower temperature (59.2 to 60.1 °C) than that of pure PEG 6000. Absence of an endothermic peak of drug in SDs has also been reported by other researcher groups (20,21,28,37,38). The PMs formulation of gliclazide and PEG 6000 also showed no endothermic peak of gliclazide (Fig. 5C), even though the peaks derived from gliclazide were observed in XRD (Fig. 4A). It is speculated that gliclazide dissolved in melted PEG 6000 during the DSC measurement, only one endothermic peak at 57 °C corresponding to melting of PEG 6000 was observed. This result is in agreement with report of Yamashita *et al.* (39). In a DSC study, absence endothermic peak of tacrolimus in the PMs formulation of tacrolimus and PEG 6000 was reported (39).

CONCLUSION

The solubility and dissolution rate of gliclazide can be enhanced by formulating SDs of gliclazide with PEG 6000. The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of gliclazide from its SD and to some extent in PMs. No endothermic peak of gliclazide was present in the DSC thermograms of SDs with PEG 6000 suggesting the absence of crystalline gliclazide, however, the XRD studies indicated the presence of appreciable proportion of crystalline gliclazide (important peak intensity was decreased in SDs). From FTIR spectroscopy, it was concluded that there was no well defined chemical interaction between gliclazide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed.

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