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Brief/Technical Note

Physicochemical Properties of Solid Dispersions of Gliclazide in Polyvinylpyrrolidone K90

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KEY WORDS: dissolution; gliclazide; polyvinylpyrrolidone K90; solid dispersion.

INTRODUCTION

Gliclazide is a second generation hypoglycemic sulfonylurea which is useful in the treatment of type 2 diabetes mellitus (1). Following oral administration, however, gliclazide exhibits slow rate of absorption and interindividual variation in bioavailability. Stated problems of gliclazide might be due to its poor water solubility and slow dissolution rate (2–4). But gliclazide exhibits good tolerability, low incidence of hypoglycemic effect, low rate of secondary failure, and low rate of progression of diabetic retinopathy (2,5). Hence, gliclazide appears to be a drug of choice in long-term sulfonylurea therapy for treatment of type 2 diabetes mellitus. Few attempts have been made for improvement of solubility and bioavailability of gliclazide including complexation with cyclodextrin (6,7) or cyclodextrin–hydroxypropylmethylcellulose (8) and using PEG 400 (9) as per present literature. The authors investigated the physicochemical characteristics and dissolution behaviors of gliclazide in physical mixtures as well as solid dispersions with polyethylene glycol 6000 in a previous study (10).

The main objective of this work was to investigate the physicochemical characteristics of gliclazide in physical mixtures (PMs) and solid dispersions (SDs) prepared by using polyvinylpyrrolidone K90 (PVP K90). The possible interactions between gliclazide and PVP K90 in both solid and liquid states were investigated. Interaction in solid state was investigated by Fourier-transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD) analysis, 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). PVP K90 was received from BASF (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 with PVP K90 containing three different weight ratios (1:1, 1:2, 1:5; gliclazide/PVP K90) and denoted as SD 1/1, SD 1/2, and SD 1/5, respectively, were prepared by solvent evaporation method. In the solvent evaporation method, to a solution of gliclazide in chloroform, an appropriate amount of PVP K90 in solution was added. The solvent was evaporated under reduced pressure at 40°C by using a rotary evaporator and the resulting residue was 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 (11,12).

The PMs having the same weight ratio as SDs were prepared by thoroughly mixing the required amount of gliclazide and PVP K90 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.

Phase Solubility of Gliclazide

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors (13). 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 PVP K90 was added. Then, the samples were shaken at 37±0.5°C for 72 h in a water bath (Remi Pvt Ltd, Mumbai). 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 1700, Pharm Spec, Japan).

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Dissolution Studies

Dissolution studies of gliclazide in powder form, SDs, and PMs in triplicate were performed by using the US Pharmacopoeia (USP) model digital tablet dissolution test apparatus-2 (Lab India Ltd, Mumbai) at the paddle rotation speed of 50 rpm in 900 ml 0.1 N HCl containing 0.25% (*w*/*v*) of sodium lauryl sulfate as a dissolution medium at 37±0.5°C (14). The SDs or PMs equivalent to 30 mg of gliclazide were weighed using a digital balance and added into the dissolution medium. At the specified times (every 10 min for 1 h), 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 the UV–Visible spectrophotometer (Shimadzu UV-1700, Pharm Spec). Fresh medium (10 ml), which was prewarmed at 37°C, was added to the dissolution medium after each sampling to maintain a constant volume throughout the test.

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 1.541 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°C to 250°C. An empty aluminum pan was used as a reference.

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 monochromator, 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) and scan step time of 0.5 s.

Fourier-Transform Infrared Spectroscopy

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 disks 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}.

Dissolution Data Analysis

Phase Solubility Studies

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

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

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

$$\Delta G_{tr} = -2.303\,RT \log \frac{S_o}{S_s} \quad (2)$$

where $\frac{S_o}{S_s}$ is the ratio of molar solubility of gliclazide in aqueous solution of PVP K90 to that of the same medium without PVP K90.

In Vitro Dissolution Data

In the present investigation, model-independent and model-dependent approaches are used for comparison of dissolution profiles. Model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency) or on mean dissolution time (15,16). 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 time t (10 and 30 min), 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. PCP Disso v3 software (Pune, India) was used to find best fit model.

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

$$\log UR = \frac{k_2 t}{2.303} \quad (5)$$

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

$$\log R = \log k_4 + n \log t \quad (7)$$

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

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 Hixon–Crowell models, respectively.

Table I. Effect of PVP K90 Concentration and Gibbs-Free Energy on Solubility of Gliclazide in 0.1 N HCl

	Concentration of PVP K90 (% *w/v*)	Concentration of gliclazide (mg ml^{-1}) at 37°C	ΔG_{tr}° (J/mol)
1	0	0.81	
2	2	0.81	0
3	4	1.21	−1,143.55
4	6	1.53	−1,749.30
5	8	1.87	−2,266.5
6	10	2.28	−2,672.73
7	12	2.61	−3,020.83
8	14	2.96	−3,345.22
9	16	3.33	−3,651.21
10	18	3.7	−3,920.44

PVP K90 polyvinylpyrrolidone K90

RESULTS

Phase Solubility Studies

The phase solubility diagram investigated in 0.1 N HCl (pH 1.2) was linear in a wide range of PVP K90 concentrations and correspond to A_L-type profiles (13). The stability constant was found to be 1.20 ml^{-1} mg. At 18% (*w/v*) concentration of PVP K90, the solubility of gliclazide increased by 4.6-fold (Table I). Table I presents the values of Gibbs-free energy associated with the aqueous solubility of gliclazide in the presence of PVP K90.

Dissolution Studies

Q_{10}, Q_{20}, and Q_{30} values (percent drug dissolved within 30 min) are reported in Table II (coefficient of variation is less than 10% in each case). The onset of dissolution of pure gliclazide is very low, about 18.46% of drug being dissolved within 10 min (Q_{10}). SDs of gliclazide with PVP K90 considerably enhanced dissolution rates within 10 min compared to pure gliclazide such as SD at 1:1 (gliclazide/PVP K90) ratio up to 76.29%, SD at 1:2 ratio up to 77.12%, and SD at 1:5 ratio up to 77.73%, respectively. In case of PMs of gliclazide, Q_{10} values increased up to 25.36% at 1:1, up to 33.1% at 1:2, and up to 43.88% at 1:5 (gliclazide/PVP K90) ratio, respectively. From Table II, Q_{20} as well as Q_{30} values indicate, in general, PVP K90-based formulations (SDs and PMs) at high carrier levels exhibited higher dissolution rates than those at low polymer levels (PM 1:1 and SD 1:1 with PM 1:5 and SD 1:5, respectively).

The %DE values were computed at two times, showing the early and late phase of dissolution study for comparative analysis of all the formulations. The %DE values in the initial time period of dissolution study, *i.e.*, $\%DE_{10\ min}$, provide comparative information for very fast releasing formulations, whereas $\%DE_{30\ min}$ provides relative information about both fast and slow releasing formulations. The value of $\%DE_{10\ min}$ for pure gliclazide (9.16%) was enhanced in PMs (21.94%) as well as in SDs (49.87%). The value of $\%DE_{30\ min}$ for the pure drug increased to 45.11% in PMs and up to 73.20% in SDs (Table II).

The obtained values of mean dissolution time (MDT) for pure gliclazide, PMs, and SDs are presented in Table II. The MDT of gliclazide was 12.5 min and it decreased to 7.09 min in SD with PVP K90 at 1:5 (gliclazide/PVP K90) ratio, whereas in case of PMs, MDT decreased to 9.43 min.

Table III shows the regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data. *In vitro* release data of the drug are best fitted to Korsemeyer–Peppas model with *n* value of 0.7249, hence exhibits non-Fickian diffusion. For all PMs (PM 1:2 and PM 1:1), the Higuchi matrix is best fitted except PM 1:5 which exhibits Korsemeyer–Peppas model. All the SDs best fitted to Korsemeyer–Peppas model with *n* values less than 0.4500 tended to exhibit Fickian diffusion characteristics except SD 1:5 which exhibits first-order release kinetics (17,18).

Differential Scanning Calorimetry

The DSC curve of pure gliclazide exhibited a single endothermic response corresponding to the melting of the drug. Onset of melting was observed at 170.8°C, the corresponding heat of fusion (ΔH_F) was 171.2 J/g (Fig. 1 A) (10). During scanning of PVP K90, a broad endotherm ranging from 80°C to 120°C was observed, due to the presence of water. DSC thermograms of PMs and SDs of gliclazide and PVP K90 always exhibited complete absence of melting peak of the drug at 170.8°C and the broad endotherm due to the presence of water ranging from 60°C to 120°C (Fig. 1 D). Repeated scanning of PVP K90-based formula-

Table II. *In Vitro* Dissolution Profile of drug, Physical Mixtures, and Solid Dispersions of Gliclazide in pH 1.2 (0.1 N HCl)

		Dissolution parameters					
Sr. no.	Formulation	$Q_{10\ min}$	$Q_{20\ min}$	$Q_{30\ min}$	$\%DE_{10\ min}$	$\%DE_{30\ min}$	MDT (min)
1	Drug	18.46	32.67	40.82	9.16	23.67	12.5
2	PM 1:1	25.36	38.93	56.68	12.68	30.88	13.66
3	PM 1:2	33.1	48.8	59.5	16.55	37.21	11.24
4	PM 1:5	43.88	58.54	65.77	21.94	45.11	9.43
5	SD 1:1	76.29	80.36	88.24	38.15	66.92	7.25
6	SD 1:2	77.12	87.12	92.45	45.56	70.16	7.24
7	SD 1:5	77.73	93.95	95.84	49.87	73.20	7.09

PM physical mixture, *SD* solid dispersion of gliclazide prepared by the solvent evaporation method, *%DE* percent dissolution efficiency, *MDT* mead dissolution time

Table III. Statistical Parameters of Various Formulations After Fitting Drug Release Data to Various Release Kinetic 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, n	R	K_5
Drug	0.9813	1.4736	0.9939	−0.0184	0.9943	7.1358	0.9952	3.4734, 0.7249	0.9905	−0.0057
PM 1:1	0.8256	1.2789	0.8975	−0.0190	0.9764	8.6575	0.9560	8.5742, 0.5041	0.8774	−0.0055
PM 1:2	0.7319	1.3776	0.8582	−0.0213	0.9695	9.4130	0.9608	15.1667, 0.3712	0.8214	−0.0061
PM 1:5	0.5379	1.5087	0.7312	−0.0247	0.9265	10.4269	0.9421	26.6687, 0.2439	0.6742	−0.0069
SD 1:1	0.1647	2.0615	0.7982	−0.0533	0.8589	14.3741	0.9812	57.9627, 0.1171	0.6450	−0.0123
SD 1:2	0.2008	2.1641	0.8956	−0.0685	0.8646	15.0883	0.9809	58.4002, 0.1287	0.7345	−0.0143
SD 1:5	0.1099	2.2337	0.9362	−0.0903	0.8560	15.5967	0.9166	60.4486, 0.1284	0.7612	−0.0165

H–M Higuchi matrix, *P–K* Peppas–Korsmeyer, *H–C* Hixon–Crowell, *R* correlation coefficient, k_1–k_5 constants of release kinetics, *PM* physical mixture, *SD* solid dispersion of gliclazide prepared by the solvent evaporation method

tions led to disappearance of the endotherm, which is due to evaporation of water during the first run. The presence of broad endothermic peak of PVP K90 and formulations on DSC thermogram was reported by several researchers (19–21).

X-ray Diffractions

Figure 2 shows the X-ray diffraction pattern of pure gliclazide, PVP K90, its physical mixture, and solid dispersion. In the X-ray diffraction pattern of gliclazide, sharp peaks are present at 2θ of 10.59, 14.98, 17.2, 17.85, 18.15, 22.07, 25.42, 26.25, 26.75, and 29.5 (Fig. 2 A), and it suggests that gliclazide is a crystalline material. Pure PVP K90 shows absence of peaks in diffraction spectrum (Fig. 2 B). Peaks characteristic of the drug were observed in the X-ray diffractogram of physical mixture and solid dispersion.

FT-IR Spectroscopy

The IR spectra of SDs and PMs were compared with the standard spectrum of gliclazide (Fig. 3 A). The IR spectrum of gliclazide is characterized by the absorption of carbonyl (C=O) sulfonyl urea group at 1,706 cm^{-1} (6). In the spectra of SDs and PMs, this band was shifted towards higher wave number at 1,711 and 1,709 cm^{-1}, respectively (6). Also, the NH group which is located at 3,265 cm^{-1} from the IR spectrum of gliclazide was shifted to 3,630 cm^{-1} in SDs. The sulfonyl group bands are located at 1,349 and 1,162 cm^{-1} in pure gliclazide. In SDs, the asymmetrical vibration peak of S=0 band was shifted from 1,349 to 1,342 cm^{-1} with decreased frequencies. In SDs, the symmetrical stretching vibration band of S=0 was shifted from 1,162 to 1,113 cm^{-1} with decreased frequencies. The spectrum of PVP K90 exhibited important bands at 2,953 cm^{-1} (C–H stretch) and 1,652 cm^{-1} (C=O). A very broad band was also visible at 3,446 cm^{-1} which was attributed to the presence of water, confirming the appearance of broad endotherm in DSC run due to the presence of water (20).

DISCUSSION

The results of phase solubility are in accordance with the well-established formation of soluble complexes between

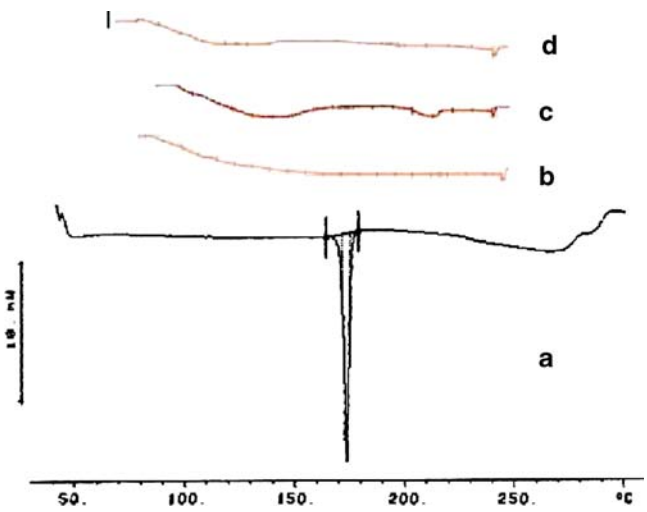

Fig. 1. DSC thermograms of pure gliclazide *a*, pure PVP K90 *b*, gliclazide–PVP K90 PMs at 1:2 ratio *c*, and gliclazide–PVP K90 SDs at 1:2 ratio *d*

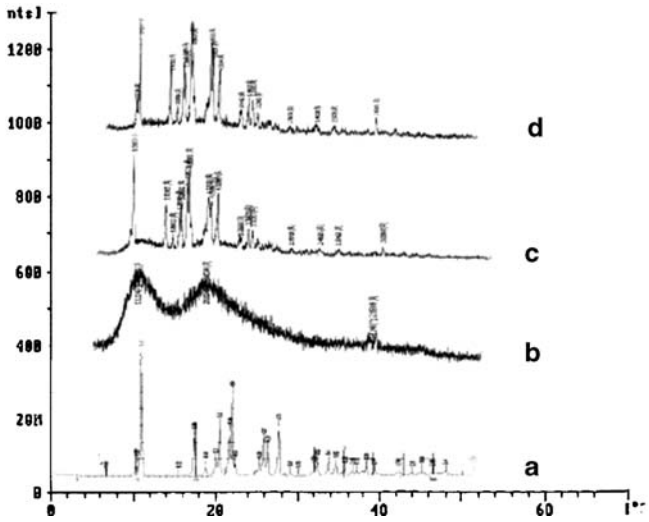

Fig. 2. X-ray diffractograms of pure gliclazide *a*, pure PVP K90 *b*, gliclazide–PVP K90 PMs at 1:2 ratio *c*, and gliclazide–PVP K90 SDs at 1:2 ratio *d*

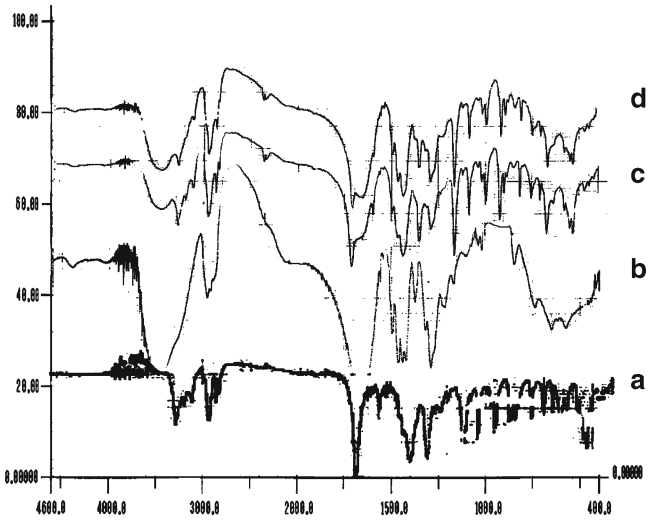

Fig. 3. FT-IR spectrograms of pure gliclazide *a*, pure PVP K90 *b*, gliclazide–PVP K90 PMs at 1:2 ratio *c*, and gliclazide–PVP K90 SDs at 1:2 ratio *d*

water-soluble polymeric carriers and poorly water-soluble drugs (17). ΔG_{tr}° values were all negative for PVP K90 at various concentrations indicating the spontaneous nature of the drug solubilization. The values decreased by increasing PVP K90 concentration, demonstrating that the reaction became more favorable as the concentration of PVP K90 increased.

The results of the dissolution study indicate an improvement of dissolution rate of gliclazide in solid dispersion. The rate of dissolution increases as the concentration of PVP K90 increases in SDs. The improvement of dissolution rate is possibly caused by several factors. Such factors are: (a) the strong hydrophilic character of PVP K90, which improves the water penetration and the wettability of the hydrophobic gliclazide; (b) the optimal dispersion of gliclazide to PVP K90; (c) the absence of crystals (amorphous dispersions) corresponds to lower energy required for dissolution; and (d) the intermolecular hydrogen bonds and the molecular dispersion of gliclazide on PVP leads to partial miscibility, improving the hydrophilic characteristics of the drug substance *via* interactions within the polymer (22). The improvement of dissolution rate of gliclazide in PMs is due to increased wettability of the drug powder (23).

Thermograms of SD (Fig. 1 D) and PM showed the absence of a gliclazide melting endothermic peak. The absence of drug melting endothermic peak in PM and SD indicate that gliclazide is present in amorphous form within PMs and SDs. The inhibition of crystallization of drug in dispersions results in the amorphous form of gliclazide. Crystallization inhibition is attributed to two effects: interactions such as hydrogen bonding between the drug and the polymer and the entrapment of the drug molecules in the polymer matrix during solvent evaporation or a combination of both (24). Numerous studies have shown that polymers like povidone used in solid dispersions can inhibit the crystallization of drugs resulting in an amorphous form of the drug in the solid dispersions (25,26). The formation of an amorphous form of gliclazide in SDs is due to the combination of the two stated effects (22,24). In order to verify the DSC results and to exclude the possibility of existence of crystalline material in solid dispersion, these systems were again evaluated by using X-ray diffraction analysis.

The prominent peaks from pure gliclazide such as at 2θ of 10.59, 14.98, 17.2, *etc*. were observed clearly at the same position in the PMs and in SDs, and their intensities were decreased by 55–60% and by more than 80%, respectively. The X-ray diffraction findings suggested that some portion of gliclazide still existed in the same crystal structures of the pure drug, but the relative reduction of diffraction intensity of gliclazide in SDs at these angles suggests that the crystal size was reduced to microcrystal form (27). The finding of the XRD such as existence of some portion of gliclazide in the same crystal structures of the pure drug is not in agreement with the DSC finding (complete conversion of drug to amorphous form) (28). The XRD findings again suggest that the melting peak of gliclazide in SDs and PMs containing some portion of crystalline gliclazide was also absent. This is due to the interaction between gliclazide and polymer in solid state (28). This further confirms that DSC is not useful for examining the solid state of drug within the PMs and SDs (28). The existence of some portion of gliclazide in the same crystal structures of pure drug was confirmed by the XRD study but not by the DSC study. The absence of an endothermic peak of gliclazide in SDs and PMs suggests an amorphous form of the drug, but again the presence of a sharp peak of the drug with lesser intensity indicates some portion of crystalline drug. DSC and XRD results are in agreement when the crystalline form of the drug is converted into amorphous form completely. Absence of endothermic and diffraction peak of the drug in dispersion indicate an amorphous form, where DSC and XRD results are in agreement with each other. Absence of an endothermic peak of the drug in dispersion and presence of a diffraction peak in XRD with less intensity indicate that the drug is partially converted into amorphous form, and the DSC and XRD results, which are not in agreement with each other, could be due to the presence of some portion of the crystalline drug and the presence of polymer. Microcrystals are formed as a consequence of evaporation of solvent during the preparation of solid dispersions by the solvent evaporation technique. Evaporation of solvent increases the viscosity very rapidly leading to a decrease in drug mobility preventing recrystallization. When the solvent is evaporated completely, drug molecules are frozen in the polymer. A crystal lattice is not formed, but the drug molecules are of randomly "dispersed" order over only a few molecular dimensions (20). The existence of interaction between the drug and polymer is again suggested by FT-IR study.

The shift in the peaks associated with C=O, S=O, and NH groups of gliclazide indicates some sort of solid-state interactions between the drug and the polymer in SD and PM. The interactions are due to intermolecular hydrogen bonding between the drug and polymer. An intermolecular hydrogen bond was expected to occur between the hydrogen atom of the NH group of gliclazide and one of the lone pair electrons of C=O group of polymer and/or C=O group of gliclazide and one of the hydrogen atoms of PVP K90 (20). The shift in the peaks associated with the S=O group of gliclazide could be due to involvement of complexation with PVP K90 (29,30). The FT-IR data suggest the formation of

intermolecular hydrogen bonding between gliclazide and PVP K90. The absence of the endothermic peak of the drug in SDs or PMs is due to intermolecular hydrogen bonding and partial conversion drug into amorphous form.

Conclusions

The solubility and dissolution rate of gliclazide can be enhanced by formulating SDs of gliclazide with PVP K90. The solubilization effect of PVP K90, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility, and development of intermolecular hydrogen bonding are responsible for the enhanced solubility and dissolution rate of gliclazide from its SDs and to some extent in PMs. The results of infrared spectroscopy, X-ray diffractometry, and DSC indicate that some sort of interactions such as intermolecular hydrogen bonding or complexation between the functional groups of gliclazide and PVP K90 have occurred in the molecular level and show microcrystallinity of gliclazide in the solid dispersion, which increased the solubility and the dissolution of gliclazide from the solid dispersion.

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