International Journal of Drug Delivery 2 (2010) 49-57
http://www.arjournals.org/ijdd.html
Research article
ISSN: 0975-0215

Enhanced dissolution and bioavailability of gliclazide using solid dispersion techniques

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Abstract:

Gliclazide is practically insoluble in water and its bioavailability is limited by dissolution rate. To enhance the dissolution rate and bioavailability the present study was aimed to formulate solid dispersions using different water soluble polymers such as polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000) using fusion method and polyvinyl pyrrolidone K-30 (PVP K 30) by solvent evaporation method. The interaction of gliclazide with the hydrophilic polymers was studied by Differential Scanning Calorimetry (DSC), Fourier Transformation-Infrared Spectroscopy (FTIR) and X-Ray diffraction analysis. Solid dispersions were characterized for physicochemical properties like drug content, surface morphology and dissolution studies. Various factors like type of polymer and ratio of the drug to polymer on the solubility and dissolution rate of the drug were also evaluated. Pharmacokinetic studies of optimized formulation were compared with pure drug and marketed formulation in wistar rats. The dissolution of the pure drug and solid dispersion prepared with PVP K 30 (1:1) showed 38.3 $\pm$ 4.5 % and 95 $\pm$ 5.2 % release respectively within 30 min. Peak plasma concentration of pure drug, solid dispersion (PVP K 30) and marketed formulation was found to be 8.76 $\pm$ 2.5, 16.04 $\pm$ 5.5 and 9.24 $\pm$ 3.6 µg/ml respectively, from these results it was observed that there is two fold increase in peak plasma concentration compared to pure drug. Solid dispersion is an effective technique in increasing solubility, dissolution rate and bioavailability of the poorly soluble drugs.

Keywords: Gliclazide; solubility; solid dispersion; pharmacokinetics; peak plasma concentration; half life

Introduction

Gliclazide (1-(3-azabicyclo-[3, 3, 0]-Oct-3-yl)-3-(*p*-tolyl sulfonyl) urea) is an oral potent hypoglycemic second generation sulfonyl urea drug which is used for a long-term treatment of non-insulin dependent diabetes mellitus (NIDDM). It causes hypoglycemia by stimulating release of insulin from pancreatic β cells and by increasing the sensitivity of peripheral tissue to insulin. Previous studies showed that gliclazide possesses good general tolerability, low incidence of hypoglycemia and low rate of secondary failure.

doi:10.5138/ijdd.2010.0975.0215.02011

Gliclazide is insoluble in water and has low dissolution rate [1]. For an oral hypoglycemic drug to be effective, rapid absorption from the gastrointestinal tract is required. However, the absorption rate of gliclazide from the gastrointestinal tract is slow and varied among the subjects.

Gliclazide is insoluble in water which leads to poor dissolution rate and subsequent decrease in its gastrointestinal (GI) absorption [2]. Results of several investigations revealed that the absorption of gliclazide was limited by its dissolution rate. The formation of amorphous forms to increase drug solubility and the reduction of particle size to expand surface area for dissolution and decrease the interfacial tension with the aid of a water-soluble carrier are among the possible mechanisms for increasing dissolution rates there by improving bioavailability of poor water-soluble drugs. Various techniques for the improvement of the dissolution rate of poorly water-soluble drugs include micronization, inclusion complexes with cyclodextrin, amorphous drug, and solid ***dispersions*** with hydrophilic carriers [3]. Hence the present study was aimed to improve the solubility and/or dissolution rate of poorly water-soluble drug through the solid dispersion approach.

The most commonly used hydrophilic carriers for solid dispersions include PEG, PVP, colloidal silicon dioxide, and lipids, such as polyglycolized glycerides (Gelucire) [4]. The solvent evaporation, melt adsorption, fusion, spray drying, spray freezing, spray congealing, melt extrusion, and supercritical fluid precipitation are the techniques reported for the preparation of solid dispersions. There is report on improvement of solubility of gliclazide using cyclodextrin inclusion complex approach [5]. In the present work, fusion and solvent evaporation techniques were used to prepare gliclazide solid dispersions. Hydrophilic carriers like PEG 4000, PEG 6000 and PVP K 30 are used to prepare solid dispersions of gliclazide with different ratios of drug to carrier. The pure drug (PD) and Solid Dispersion (SD) were subjected to DSC, IR and X- Ray Diffraction (XRD) spectroscopic studies to elucidate possible crystal changes in gliclazide and drug-carrier interactions. The optimized solid dispersion was selected for the further assessment of its pharmacokinetic evaluation.

Materials and Methods

Materials

Gliclazide was obtained as gift sample from Lupin Research Park, Pune, India. Polyethylene Glycol (PEG) 4000, PEG 6000 and Polyvinyl Pyrrolidone (PVP) K 30 were purchased from BASF Corporation, Germany. All other materials and solvents used in this study were either pharmaceutical or analytical grade.

Methods

Preparation of the Solid Dispersions (SD)

Solid dispersions (SD) containing gliclazide were prepared in different weight ratios, such as 1:1, 1: 1.5 and 1:2 w/w for PEG 4000 (SD-1, SD-2 and SD-3) and PEG 6000 (SD-4, SD-5 and SD-6) respectively by using fusion method. The SD of PVP K30 were prepared in the weight ratios of 1:0.5, 1:0.75, 1:1 w/w for (SD-7, SD-8 and SD-9) by solvent evaporation method as described below, and the resulting samples were stored in tightly closed containers until use.

Fusion Method

Solid dispersions (SD) were prepared by melting the accurately weighed amounts of PEG (PEG 4000 or PEG 6000) in a water bath and the drug was dispersed in the molten solution [6, 7]. The mixtures were stirred repeatedly, after 10 min cooled either at room temperature or by placing the closed container for 15 min in an ice bath. Solid mass obtained was passed through the # 80 and stored in vacuum desiccator until use.

Solvent Evaporation Method

The solid dispersions were prepared by dissolving the mixture of gliclazide and the PVP K 30 at the weight ratios of 1:0.5, 1:0.75 and 1:1 w/w, with the aid of a minimal volume of mixture of methanol and acetone solvent system (1:1 v/v) [8]. The solvent was removed by evaporation under reduced pressure at 37^{o}C (Osworld Vacuum oven, JRIC-8, Mumbai, India). Solid mass obtained was passed through the # 80 and stored in vacuum desiccator until use.

Physicochemical Characterization

Solubility Measurements

The saturation solubility of drug and SD with PEG 4000, PEG 6000 (1:1, 1: 1.5 and 1:2 w/w) and PVP K

30 (1:0.5, 1:0.75 and 1:1w/w) in distilled water and phosphate buffer saline (PBS pH 7.4) was determined by adding an excess of drug and SD to 10 ml distilled water or PBS in glass stoppered tubes. The stoppered tubes were rotated for 24 h in water bath shaker at 37^{o}C. The saturated solutions were filtered through a 0.45 µm membrane filter, suitably diluted with water and analyzed by UV spectrophotometer, UV-1601PC, Shimadzu, Japan, [9].

Drug Content

Drug content was determined by dissolving 50 mg of solid dispersion in solvent mixture of methanol and acetone (1:1 v/v), suitably diluted with pH 7.4 phosphate buffer, filtered through 0.45 µm membrane filters and analyzed by UV spectrophotometer at 226 nm.

Solid State Characterization

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60) and operating software (TA 60). The samples (drug alone and SD-9) were heated in sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 5°C/min from 25 to 250°C. Empty aluminum pan was used as a reference [10]. The heat flow as a function of temperature was measured for the samples.

FTIR spectroscopy study was conducted using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone and SD-9) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

X-ray diffraction patterns of the samples (drug and SD-9) were obtained using D8 X-ray powder diffractometer (Bruker AXS, Germany) equipped with D8 TOOLS software, a theta compensating slit and a silicon detector [11]. The scans were recorded from 2 to 50^{o}, with a step size of 0.03^{o}, 2θ and a count time of 0.5 sec at 25^{o}C using copper radiation.

Shape and Surface Morphology

The shape and surface morphology of the solid dispersion was studied by scanning electron microscopy (SEM), JEOL, JSM 50A, Tokyo, Japan. The samples were mounted on double-sided adhesive tape that has previously been secured on copper stubs and then analyzed. The accelerating voltage was 5 kV.

Dissolution Studies

The dissolution rate of pure gliclazide and solid dispersion systems were studied using the basket method (USP Type-II) at 37°C in 900 ml of 0.1N HCL (pH 1.2) at 100 rpm [12]. Samples equivalent to 10 mg of gliclazide were subjected to the testing. Five milliliter samples of dissolution medium were withdrawn and filtered at different time intervals for analysis of the drug content at 226 nm using UV Spectrophotometer. At each time of withdrawal, 5 ml of fresh PBS (pH 7.4) was added in the dissolution flask.

Stability Study

After determining the drug content and release studies, the optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40 ± 2ºC and 75 ± 5% RH) for a period of 3 months in a stability chamber (Thermolab, Mumbai, India). The optimized formulations were placed in USP type-I flint vials and hermetically closed with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at 15, 30, 60 and 90 days and evaluated for the drug content and *in vitro* drug release.

Pharmacokinetic Study

The preclinical studies were carried out in healthy Wistar rats (weighing about 200-250g), obtained from central house, Manipal University, Manipal. They were housed in elevated wire cages with free access to food (Lipton feed, Mumbai, India) and water. The preclinical study protocol was approved by Institutional Animal Ethical Committee, Kasturba Medical College, Manipal. The overnight fasted male wistar rats were divided into three different groups (n=6); group I was administered with pure gliclazide and group II with solid dispersion (SD-9) and group III with marketed formulation (Reclide® Tablets, Dr.Reddy's Laboratories, Baddi, India). All three groups were administered through oral route (0.5% sodium CMC suspension) at the dose of 8.3 mg/kg.

Then blood samples were collected at predetermined intervals of 0.5, 1, 2, 4, 6, 8, and 12 h of post-dose into

heparinized tubes from orbital sinus. The plasma was separated immediately using cold centrifugation (Remi Equipments Ltd., Mumbai, India) at 10000 rpm for 5 min and the plasma was stored at -30 ^{o}C until analysis.

Bio Analysis of Gliclazide in Rat Plasma

Chromatographic Condition

Water alliance 2695-separation module with waters 2487 dual UV detector was used. Millennium software version 4.0 s used for data acquisition. Inertsil ODS (25 cm × 4.6 mm, 5 µ) column was used as a stationary phase. Mobile phase comprised of acetonitrile and 0.02 M ammonium acetate buffer, pH 4.5 (60:40 v/v) at the flow rate of 1 ml/min. Injection volume was 50 µl and run time is 12 min, column was maintained at ambient temperature and the eluent was detected at 228 nm.

Extraction Procedure

The extraction of gliclazide in rat plasma was carried out by simple protein precipitation method, using methanol as an extracting solvent. Briefly 100 µL of rat plasma sample was taken in the 1.5 ml eppendorff tubes and mixed with 10 µL of Glimepiride (Internal Standard) working stock solution (100 µg/ml) and vortexed for 1 min. Then 250 µL of methanol was added and vortexed for 4 min and centrifuged at 10000 rpm for 5 min. The clear supernatant 50 µL was subjected for HPLC analysis.

Statistical Analysis

The data were analysed for statistical significance using SPSS 11.5 for windows software by One-Way ANOVA followed by Post-hoc (Dunnett's) test at $p<0.05$. The results were considered as significant if p less than 0.05.

Results

Solubility Studies and Drug Content

The results of saturation solubility studies are given in Table 1. The solubility of pure drug in water and in PBS (pH 7.4) was found to be 27.04 ± 0.56 and 57.06 ± 0.67 µg/ml. The solubility of SD using PEG 4000 (1:2), PEG 6000 (1:2) and PVP K30 (1:1) in water was found to be 57.79 ± 1.35, 58.92 ± 1.46, 60.24 ± 1.75 µg/ml and in PBS (pH 7.4) 81.89 ± 1.35, 83.42 ± 1.76 and 86.24 ± 1.63 µg/ml respectively. The drug content of solid dispersion with PEG 4000, PEG 6000 and PVP K 30 was found to be in the range of 95 ± 1.45 to 98 ± 2.36%.

Table 1: Solubility studies of drug and solid dispersions

Samples	Solubility (µg/ml)	
	Water	PBS
Pure drug	27.04 ± 0.56	57.06 ± 0.67
SD-1	35.59 ± 1.12	63.78 ± 1.19
SD-2	46.87 ± 1.24	72.76 ± 1.21
SD-3	57.79 ± 1.35	81.89 ± 2.35
SD-4	36.22 ± 1.05	65.12 ± 1.13
SD-5	48.86 ± 1.87	73.52 ± 1.15
SD-6	58.92 ± 1.46	83.42 ± 1.76
SD-7	38.23 ± 1.45	56.24 ± 1.43
SD-8	52.24 ± 1.52	71.24 ± 1.25
SD-9	60.24 ± 1.75	86.24 ± 1.63

Solid State Characterization

The solid state characterization of drug and SD were investigated using IR, DSC to study the compatibility with carriers and XRD to find out crystallinity nature of gliclazide and SD [13]. The DSC thermograms of gliclazide, PVP K30 and SD are shown in Figure 1. The sharp melting endotherm of pure gliclazide appeared at 168.9^{o}C, whereas small endotherm was observed in solid dispersions at 160.0^{o}C prepared with PVP K30, indicated the decreased intensity of crystalline nature [14]. It may be due to that the drug molecules were dispersed in the PVP. Thermal property of solid dispersion (SD9) was changed compared to other solid dispersions. Solid dispersions of polyethylene glycol showed slight decrease in melting point of the gliclazide compared to that of pure drug. This may be speculated that gliclazide was dissolving in PEG 4000 and 6000.

The IR spectrum of the solid dispersion was compared with that of the pure drug as given in Figure 3. It can be

clearly seen from the spectra, gliclazide was characterized by the absorption of carbonyl (C=O) sulphonyl urea group at 1708.99 cm^{-1}, NH group at 3275.24 cm^{-1} and sulphonyl group at 1348.29 and 1166.04 cm^{-1}. All peaks were observed in solid dispersion with less intensity.

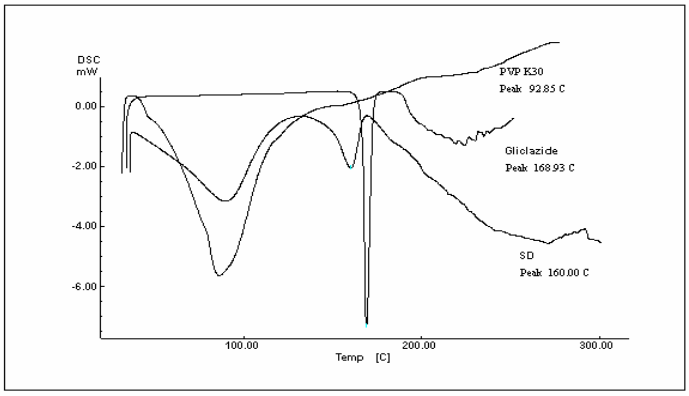

Figure 1. DSC thermograms of pure Gliclazide, PVP K30 and solid dispersion (SD-9)

The crystallinity of pure gliclazide and SD-9 were examined using X-ray diffraction and profiles are depicted in Figure 3.

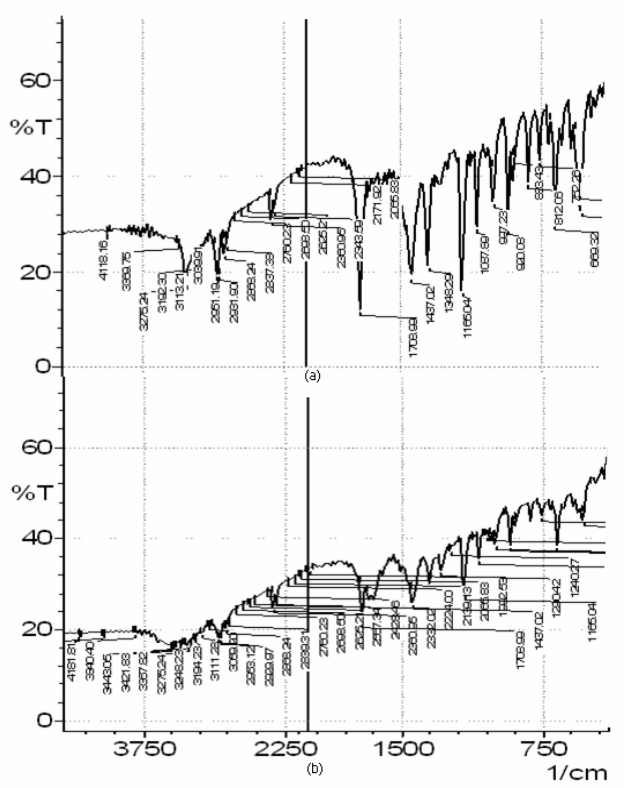

Figure 2. Infra red spectrum of (a) Pure Gliclazide (b) Solid dispersion (SD-9)

The diffraction spectra of gliclazide showed numerous distinct peaks indicating presence of high crystalline state. From the X-Ray diffraction profile, the characteristic gliclazide peaks with high intensity were found to be at 8.45, 8.95 (doublet), 7.30, 7.45 and 6.53, 6.25 at two theta degrees. The XRD pattern of solid dispersion of sample SD-9 exhibited all the characteristic diffraction peaks of gliclazide, with lower intensity. This study revealed that the crystallinity was reduced to a certain extent in the solid dispersion form. The reduction in crystallinity appears in solid dispersions was independent of the method used. XRD profiles of the SD-9 also lacked some of the diffraction peaks associated with gliclazide implying the amorphous nature of gliclazide.

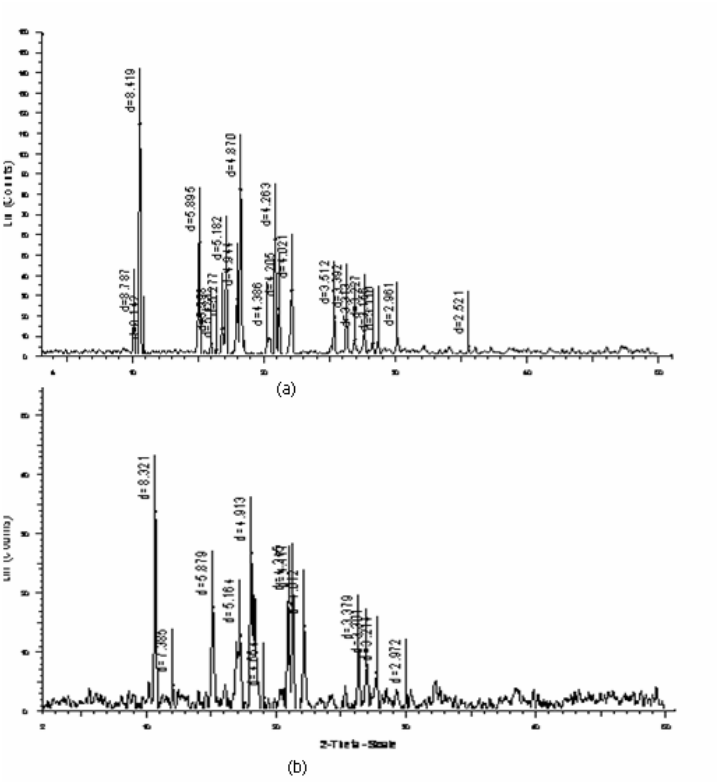

Figure 3. X-ray diffraction patterns of (a) Pure Gliclazide (b) Solid dispersion (SD-9)

Shape and Surface Morphology

The SEM results are shown in Figure 4. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form. Gliclazide existed in lamellar-like crystals, consisted of large crystalline particles of rather irregular size. On the contrary, the solid dispersions appeared in the form

of spherical particles and the original morphology of components disappeared, which supported DSC and XRD data. These results demonstrated that gliclazide in solid dispersion was homogeneously dispersed into PVP K30 at the molecular level.

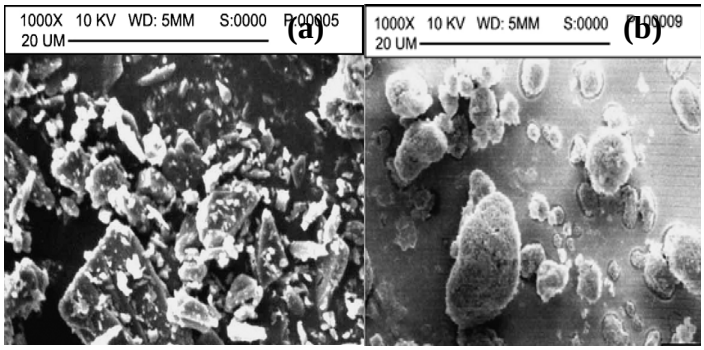

Figure 4. SEM images of (a) Pure Gliclazide (b) Solid dispersion (SD-9)

Dissolution Studies

The dissolution profiles of pure gliclazide and SD with PVP (1:1) were as shown in Table 2 and Figure 5. The dissolution profile of the pure gliclazide and marketed tablet showed 38.3 ± 5.5% and 43.7 ± 4.6 % in 30 min respectively [15]. Drug release of SD with different ratios prepared with PEG 4000 (1:2) showed 81.6 ± 4.6 %, PEG 6000 (1:2) showed 87.4 ± 3.7 % whereas PVP K 30 (1:1) showed 95 ± 3.8 % release in 30 min indicating better release when compared to pure drug and other formulations prepared with PEG 4000 and 6000 [16].

Stability Study

The optimized formulation did not show any significant change in the drug content during stability study. The values for drug content (%) under accelerated stability conditions were: 0 day: 99.98 ± 0.16; 15 days: 99.80 ± 0.32; 30 days: 98.71 ± 0.21; 60 days: 98.30 ± 0.45; 90 days: 98.1 ± 0.27.

Bio Analysis of Gliclazide

The HPLC method was linear over the range of concentration from 0.05-20 µg/mL of rat plasma with the correlation coefficient (r^2 =0.9976). The method was validated as per the US FDA guidelines. The gliclazide peak was well separated from the endogenous interferences and sharp symmetric peak was observed in the chromatograms.

Pharmacokinetic Study

The results of pharmacokinetic study were showed in Table 3. The rat plasma concentration- time profiles curve was shown in the Figure 6. The solid dispersion (SD-9) of gliclazide formulation had increased the systemic exposure ($AUC_{(0-\infty)}$) significantly ($P< 0.05$) compared to the free drug and marketed formulation. The peak plasma concentration (C_{max}) of free drug, SD-9 and marketed formulation was found to be 8.76 $\pm$ 2.5, 16.04 $\pm$ 5.5 and 9.24 $\pm$ 3.6 respectively. There was no significant difference in biological half life ($t_{1/2}$) of SD-9 to that of free drug and marketed formulation [17]. Solid dispersion (SD-9) had a detectable amount of drug in plasma up to 12 h indicating drug retained for longer time in the body when administered in the form of solid dispersion [18].

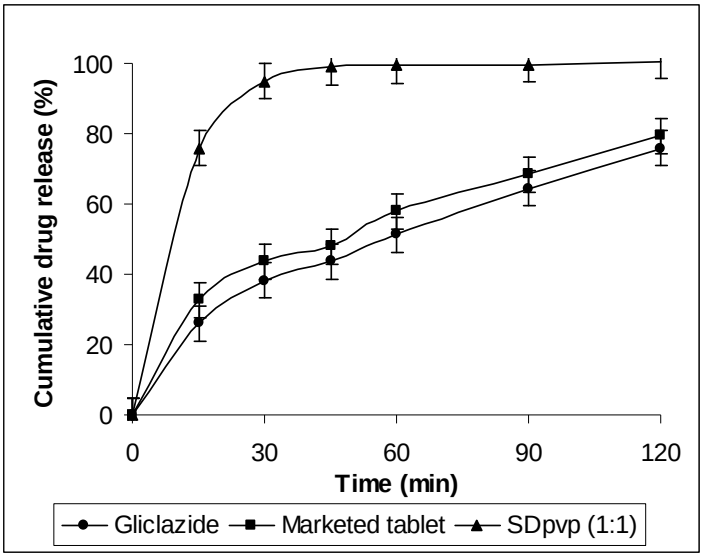

Figure 5. Dissolution profile of Pure Gliclazide, Marketed tablet and Solid dispersion of Gliclazide, SD-9

Discussion

The increase in solubility of gliclazide was observed using hydrophilic polymers. Between the three polymers used, solid dispersion of PVP K30 showed better effect on solubility of gliclazide compared to other polymers. The increase in solubility of gliclazide by PVP K30 probably may be due to the formation of soluble complexes between water-soluble polymeric carrier and poorly soluble drug.

Table 2: *In vitro* dissolution data for pure drug, marketed tablet and solid dispersions.

Time (min)	Cumulative drug release (%) ± Standard deviation										
	Pure Drug	Marketed Tablet	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9
15	26.1 ±2.6	32.8 ±3.5	35.6 ±5.4	42.1 ±4.9	57.5 ±3.1	35.2 ±3.5	41.7 ±2.8	53.3 ±4.3	55.5 ±4.6	65.3 ±3.1	75.9 ±4.6
30	38.3 ±5.5	43.7 ±4.6	75.5 ±1.5	78.4 ±4.3	81.6 ±4.6	78.1 ±3.4	84.1 ±5.9	87.4 ±3.7	85.5 ±3.3	92 ±4.6	95 ±3.8
45	43.6 ±2.5	47.9 ±2.8	83.1 ±4.9	85.8 ±3.4	87.1 ±1.9	83.8 ±2.8	86.7 ±2.5	88.6 ±2.6	93.7 ±6.8	96.3 ±2.7	98.9 ±1.4
60	51.3 ±3.8	57.9 ±5.5	88.8 ±2.8	89.1 ±4.1	90.7 ±4.3	90.6 ±4.7	92.6 ±3.4	94.2 ±4.1	99.8 ±4.2	100.6 ±1.2	99.4 ±2.3
90	64.5 ±1.9	68.4 ±2.9	91.5 ±4.8	93.6 ±2.6	93.9 ±5.4	92.4 ±3.7	94.5 ±4.5	96.4 ±3.8	99.6 ±3.8	100.2 ±0.8	99.7 ±1.4
120	75.8 ±2.6	79.4 ±5.8	93.4 ±2.4	95.1 ±3.7	96.4 ±3.3	96.5 ±2.4	96.5 ±3.7	99.4 ±2.9	100.5 ±3.8	99.5 ±3.2	100.5 ±0.92

The solid state characteristics indicated decreased crystallinity of drug in the form of solid dispersion. The peak position (angle of diffraction) was an indication of crystal structure which peak height was the measure of crystallinity [19]. The diffractograms of pure gliclazide exhibited a series of intense peaks, which were indicative of its crystallinity. Intensity of peak sharpness was reduced in solid dispersion compared to pure drug. Various studies have shown that PVP K30 inhibits crystillanity of drugs and resulting in amorphous nature of drug in the solid dispersions. Crystallization inhibition was 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. The solvent was removed during the preparation of solid dispersions, viscosity of the system increased very rapidly leading to a decrease in drug mobility. When the solvent was evaporated completely, drug molecules were frozen in the polymer matrix. A crystal lattice was not formed, but the drug molecules were randomly "ordered" comparable to the liquid state and exhibited short-range order over only a few molecular dimensions. An increase in the dissolution rate of gliclazide has been attributed to the hydrophilic nature of the polymer, which increased the wettability of the drug and also due to decrease in its crystallinity when prepared as a solid dispersion, which was confirmed by DSC and XRD results. In presence of PVP K-30, drug had better wettability, hence the dissolution of drug was greater in the form of solid dispersion. No considerable changes in the drug release profile of the solid dispersions were observed during the accelerated stability studies for a period of 3 months. The gliclazide solid dispersion formulation had significantly increased systemic availability compared to that of free drug and marketed formulation. It might be due to effect of hydrophilic polymers which would have improved the aqueous solubility and dissolution rate and hence there was improved systemic exposure in pharmacokinetic studies.

Table 3: Pharmacokinetic Parameters of Gliclazide

PK Parameters	Free Drug	Solid Dispersion (SD-9)	Marketed Tablet
C_{max} (µg/mL)	8.76 ± 2.5	16.04 ± 5.5	9.24 ± 3.6
T_{max} (1/hr)	2.1 ± 0.6	2.32 ± 0.4	2.25 ± 0.8
$AUC_{(0-\infty)}$ (µg-hr/mL)	73.90 ± 10.2	130.12 ± 15.2*	76.86 ± 9.2
$T_{1/2}$ (hr)	3.42 ± 1.2	2.79 ± 2.1	3.21 ± 0.8

*P< 0.05 ,95% CI

Conclusion

Pilot study showed that when gliclazide was dispersed in a suitable water-soluble carrier such as PEG 6000 or PVP K 30, its dissolution was enhanced compared with pure drug. The water soluble carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particles in the early stage of dissolution, since the carrier completely dissolves in short time, enhancing the solubility and dissolution of drug. The study clearly showed that addition of PVP K30 to gliclazide improved its dissolution rate. Mechanisms involved are solubilization and improved wetting of the drug in the PVP K30 rich microenvironment formed at the surface of drug crystals after dissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. PVP K30. Finally it could be concluded that solid dispersion of glicalzide using hydrophilic polymers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

Acknowledgements

Authors are thankful to the DST, DBT, AICTE, New Delhi, India for the financial support and infrastructural facilities for the study.

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