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Research Article

PEG BASED SOLID DISPERSIONS OF GLICLAZIDE: A COMPARATIVE STUDY

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ABSTRACT

In the present work, gliclazide loaded polyethylene glycol (PEG) based solid dispersions were prepared using fusion method in order to improve the solubility and dissolution rate of gliclazide. The compatibility of the drug with various formulation components was established. Solid dispersions (SDs) of gliclazide and polyethylene glycol (PEG 4000, 6000 and 8000) at three mass ratios (1:1, 1:3, 1:5 and 1:7) were prepared. Prepared solid dispersion were characterised using different methods i.e. Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry and x-ray diffraction revealed that enhanced solubility and dissolution rate of drug from solid dispersion is due to decrease in crystallinity of drug and additives. In conclusion prepared solid dispersion of the gliclazide with polyethylene glycol (PEG) improved the solubility and dissolution rate of the drug.

Keywords: *Gliclazide, polyethylene glycol, Solid dispersion, Differential scanning calorimetry, X-ray diffraction*

INTRODUCTION

In recent years, diabetes mellitus has become a common disease affecting human health seriously. About 90% of diabetic patients suffer from type II (or non-insulin-dependent) diabetes mellitus (Talari et al., 2011). Sulfonylureas (SUs) are among the oldest class of oral antihyperglycemic agents available for the treatment of type 2 diabetes (McCulloch, 2005).

Gliclazide (GLZ) (N-(4-methylbenzenesulfonyl)-N- (3-azabicyclo-[3.3.0] oct-3-yl) urea, is a second-generation sulfonylurea commonly used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) (Palmer and Brogden, 1993). It stimulates insulin secretion from pancreatic β cells by inhibiting ATP-dependent potassium channels (Nichols and Lederer 1992).Gliclazide also protects the vasculature through improvements in plasma lipids and platelet function (Palmer and Brogden 1993). Mechanisms include the ability of the drug to increase tissue plasminogen activator, fibrinolysis (Harrower, 1994) and its properties as a free radical scavenger (Scott et al. 1991, Jennings et al. 1992, Desfaits et al. 1997, O'Brien et al. 2000).

The major drawback in the therapeutic application and efficacy of Gliclazide (GLD) as oral dosage form is its very low aqueous solubility because of its hydrophobic nature. Poor aqueous solubility and slow dissolution rate of the drug lead to low oral bioavailability consequently irreproducible clinical response or therapeutic failure (Sakpal et al., 2007).

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelia (Nokhodchi et al., 2007). More than 40% of the drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1mg/ml (Agggarwal et al.,2010;Mohanchandran et al.,2010).Thus the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industries (Kumar et al.,2009).

Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug (Arora et al., 2010; Ahire et al., 2010). The solid dispersion of poorly water-soluble drugs in water-soluble polymers enhances drug dissolution and bioavailability (Ford, 1986). Complexation of gliclazide with β-cyclodextrin hydroxypropyl methylcellulose, which enhanced its hypoglycemic activity, has been reported (Aggarwal, 2002). Solid dispersions of gliclazide in PEG 6000 have been developed to increase drug dissolution rate (Biswal, 2008).

The present study was designed to develop and characterize Gliclazide solid dispersions using PEG 4000, 6000 and 8000.

MATERIALS

Gliclazide was received as gift from Arion Health Care Baddi (Himachal Pradesh, India). Polyethylene glycol (PEG) 4000, 6000 and 8000 were purchased form Sigma Aldrich, Germany. Double distilled water was used throughout the study and all the other chemicals used were of analytical grade.

METHODS

Preparation of solid dispersions

Solid dispersions (SDs) of gliclazide at three mass ratios (1:1, 1:3, 1:5 and 1:7) were prepared by the fusion method. PEG (4000, 6000 and 8000) were placed in a porcelain dish and allowed to melt by heating up to 70°C. To the molten mass, an appropriate amount of gliclazide was added and stirred constantly until homogenous dispersion was obtained. The mixture was cooled rapidly by placing the beaker in an ice bath for 5 min to solidify, followed by powdering in a mortar. The powder was sieved through a 100-mesh screen, and stored in screw-cap vial at room temperature until further use.

Determination of Gliclazide solubility

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors (Higuchi and Connors, 1965). 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 (3-18 %w/v) of PEG 4000, 6000 and 8000 was added. The samples were shaken at 25.0±0.5oC for 72 h in a water bath (Rolex, Ambala, India) and filtered through a 0.45µm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 227 nm using a UV-VIS spectrophotometer (Shimadzu UV-1700 Pharmaspec).

Drug content Estimation

The drug content in each solid dispersion was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion equivalent to 10 mg of gliclazide was transferred to a 100 ml volumetric flask containing 20 ml of methanol and dissolved. The solution was filtered through 0.45µm membrane filter paper. One ml of this solution was diluted 100 times with same solvent methanol: distilled water (20:80) and the absorbance was measured at 227 nm

using a UV-VIS spectrophotometer (Shimadzu UV-1700 Pharmaspec).

Dissolution studies

Dissolution studies on Gliclazide powder as well as the SDs were performed using the USP tablet dissolution test apparatus II (Lab India, Mumbai) with the paddle rotating at 50 rpm in 900 ml 0.1N HCl at 37±0.5°C. SDs equivalent to 30 mg of Gliclazide were taken for the dissolution test. At 10 min intervals, 5 ml samples were withdrawn, filtered through a 0.45µm membrane filter and assayed for gliclazide content by measuring the absorbance at 227 nm using UV-Visible spectrophotometer (Shimadzu UV-1700). Fresh medium (5 ml), pre-warmed to 37°C, was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. All the dissolution studies were performed in triplicate (n=3).

Fourier-transform infrared (FTIR) spectroscopy

Fourier-transform infrared **(**FT-IR) spectra FT-IR spectra were recorded using an FT-IR spectrophotometer (Shimadzu). The samples (gliclazide, PEG 4000,6000 and 8000 and the SDs) 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 4000 to 400 cm^{-1}.

Differential scanning calorimetry

DSC measurements were performed on a DSC-6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. Samples (about 1.675 mg of gliclazide SDs containing an equivalent amount of the drug) were placed in sealed aluminium pans and heated under nitrogen flow (20 ml/min) at a scanning rate of 10°C min-1 from 25 to 250 °C. An empty aluminium pan was used as a reference.

X-ray diffraction

The crystalline state of different samples was evaluated with X-ray powder diffraction. Diffraction patterns were obtained at IIC, IIT Roorkee using an XPERT-PRO diffractometer with a radius of 240 mm. The Cu Ka radiation (Ka 1.54060Å) was Ni filtered. Diffractograms specification were Step: 0.009°, Step time – 2 Th/Th locked – Start : 5.000° End : 119.998° – 19.25 – Tem 25°C – Time started 13s -2- Theta 5000° – Theta : 2.500° –Chi 0.00° operation smooth 0.150/ Y scale Mul 0.75°.yj

RESULTS

Drug Content

Results depicted in Table 1 show that the drug concentration in solid dispersions ranged between 97.8 and 99.2 %.

Table 1: Percent drug content in solid dispersion of PEG 4000, PEG 6000, and PEG 8000

Solid dispersion (drug to PEG mass ratio)	Formulation code Solid dispersion (drug to PEG mass ratio)	Drug content (%)
PEG 4000 (1:1)	SD G411	98.16 ± 1.65
PEG 4000(1:3)	SD G413	98.6 3± 2.23
PEG 4000(1:5)	SD G415	97.85± 1.86
PEG 4000(1:7)	SD G417	99.22 ± 1.58
PEG 6000(1:1)	SD G611	98.28 ± 2.35
PEG 6000(1:3)	SD G613	98.73 ± 2.05
PEG 6000(1:5)	SD G615	99.12 ± 1.96
PEG 6000(1:7)	SD G617	98.45 ± 1.75
PEG 8000(1:1)	SD G811	98.67 ± 2.08
PEG 8000(1:3)	SD G813	98.63 ± 1.92
PEG 8000(1:5)	SD G815	98.74 ± 1.72
PEG 8000(1:7)	SD G817	98.55 ± 2.36

Solubility and dissolution data analysis

Solubility studies

Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors (Higuchi and Connors, 1965). Pure Gliclazide (50 mg) and a quantity of physical mixture equivalent to 50 mg of Gliclazide were stirred vigorously in a water bath shaker at 25 ± 0.5°C in sealed vials with 0.1 mol L^{-1} hydrochloric acid (25 ml, pH 1.2) for 24 h. The sample was then centrifuged and filtered through 0.45µm membrane filter. After suitable dilution, the absorbance was measured at 227 nm. For the saturation solubility study, the same treatment was applied to solid dispersions and the concentration of Gliclazide was determined.

Phase-solubility

The value of apparent stability constant Ks, between drug–carrier combinations were computed from the phase-solubility profiles, as shown in Eqn1.

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

Gibbs free energy of transfer of gliclazide from pure water to the aqueous solutions of carrier was calculated as in Eqn2:

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

where So/Ss is the ratio of molar solubility of gliclazide in aqueous solution of PEG 4000,6000 and 8000 to that of the same medium without PEG 4000,6000 and 8000. In solid dispersion of Gliclazide with 18% w/v PEG 4000, 6000 and PEG 8000 increased the solubility by 3.61, 4.29 and 4.77 folds respectively as shown in Table 2.

Dissolution studies

Q10, Q30 and Q60 values (percent drug dissolved within 60 min) are reported in Table 3 and Figure 1. From the table, it is evident that the onset of dissolution of pure gliclazide was very slow (39.82% of drug was dissolved within 60 min). The dissolution rate of gliclazide SDs was considerably enhanced by PEG 4000, 6000 and 8000 within 60 min as compared to pure gliclazide. Dissolution was enhanced with SDs as the molecular weight of PEG increased from 4000 to 8000 at Q_{60min} 75.5 to 90.7 % in ratio 1:1, 82.5 to 94.7 % in ratio 1:3, 90.17 to 97.38% in ratio 1:5 and 89.12 to 96.28% in ratio 1:7. Increase in dissolution of gliclazide was approximately similar in the ratios 1:5 and 1:7.

Fourier-transform infrared (FTIR) spectroscopy

FTIR spectroscopy was used to characterize the possible interactions between drug and carrier in the solid state. The IR

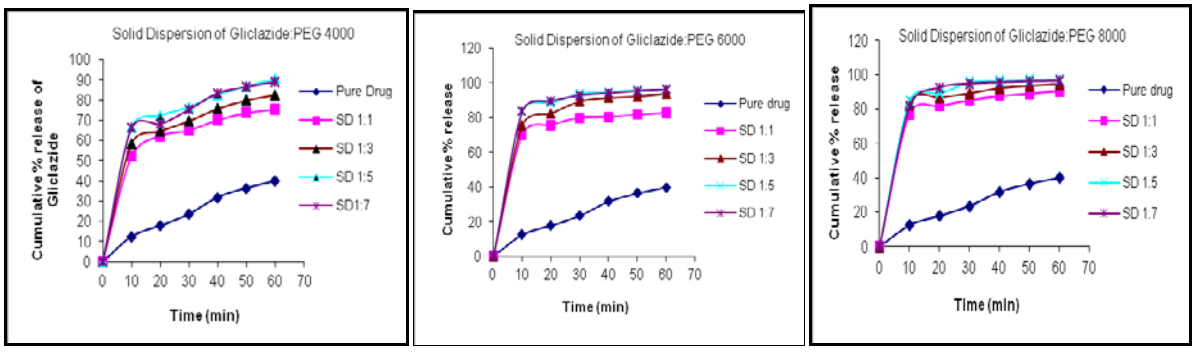
spectra of SDs were compared with the standard spectrum of gliclazide and PEG alone (Fig.2). NH group which is located at 3188 cm $^{-1}$ from the IR spectra of gliclazide shifted to 3191 cm $^{-1}$ in SDs (Table 4). The shift in the peaks associated with the gliclazide indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PEG. This may be attributed to the intermolecular hydrogen bonding between gliclazide and PEG in the solid state.

Table 2: Effect of PEG 4000, 6000 and 8000 concentration and Gibbs free energy on the solubility of Gliclazide

PEG 4000			PEG 6000			PEG 8000		
Concentration PEG 4000 (%w/v)	Gliclazide (mg/ml) at 25^{0}C	G_{tr}^0 (J/Mol)	Concentration PEG 6000 (%w/v)	Gliclazide (mg/ml) at 25^{0}C	G_{tr}^0 (J/Mol)	Concentration PEG 8000 (%w/v)	Gliclazide (mg/ml) at 25^{0}C	G_{tr}^0 (J/Mol)
0	0.75±0.03	0	0	0.75±0.03	0	0	0.75±0.03	0
3	0.86±0.02	-337	3	0.98±0.01	-661	3	1.08±0.01	-841
6	1.23±0.04	-1225	6	1.42±0.02	-1589	6	1.58±0.02	-1845
9	1.65±0.01	-1953	9	1.91±0.05	-2315	9	2.15±0.02	-2609
12	1.98±0.03	-2405	12	2.34±0.01	-2820	12	2.65±0.01	-3128
15	2.32±0.01	-2795	15	2.79±0.02	-3255	15	3.15±0.04	-3556
18	2.71±0.05	-3183	18	3.22±0.03	-3610	18	3.58±0.05	-3874

Table 3: In vitro dissolution of GLZ and solid dispersions of Gliclazide in 0.1 N HCl pH 1.2.

Formulation	Dissolution Parameters (n=3)								
	Q_{10min}			Q_{30min}			Q_{60min}		
	GLZ: PEG 4000	GLZ: PEG 6000	GLZ: PEG 8000	GLZ: PEG 4000	GLZ: PEG 6000	GLZ: PEG 8000	GLZ: PEG 4000	GLZ: PEG 6000	GLZ: PEG 8000
Drug	12.42±0.01	12.42±0.03	12.42±0.06	23.5±0.02	23.5±0.03	23.5±0.02	39.82±0.05	39.82±0.01	39.82±0.03
$SD_{1/1}$	52.12±0.01	70.23±0.04	77.37±0.02	65.14±0.03	79.72±0.02	85.43±0.01	75.5±0.02	82.62±0.03	90.7±0.08
$SD_{1/3}$	58.4±0.03	75.4±0.05	83.25±0.01	69.7±0.03	89.26±0.07	89.2±0.01	82.5±0.02	93.7±0.06	94.7±0.02
$SD_{1/5}$	66.32±0.02	83.4±0.01	84.95±0.04	76.37±0.02	93.62±0.09	95.82±0.04	90.17±0.04	96.27±0.03	97.38±0.03
$SD_{1/7}$	66.32±0.03	83.52±0.02	81.35±0.02	75.35±0.04	92.68±0.03	94.78±0.03	89.12±0.01	96.15±0.02	96.28±0.05

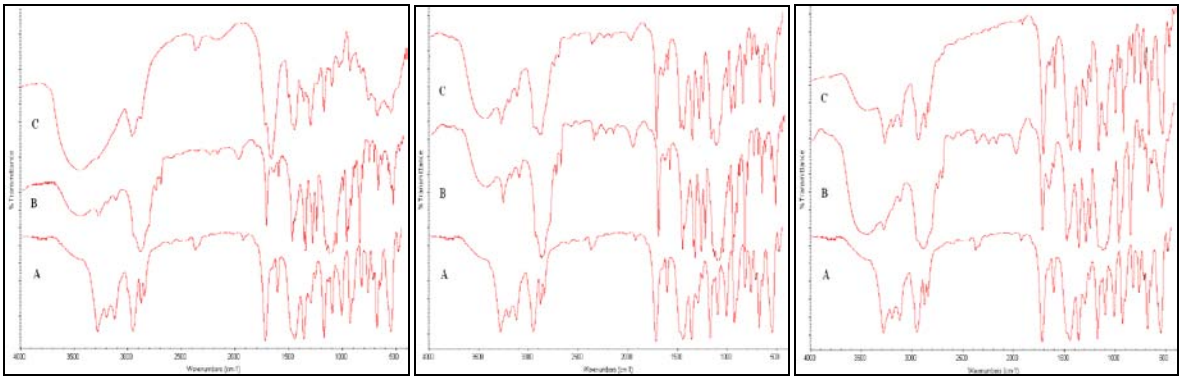


(a) **(b)** **(c)**

Fig. 1: Percent drug released in 0.1 N HCl (pH 1.2) from solid dispersion of Gliclazide with PEG 4000 (a), 6000(b), and 8000(c).

Table 4: Stretching vibrations of Gliclazide and Solid Dispersion (SDs) of Gliclazide with PEG 4000, 6000, and 8000

Stretching	Pure Gliclazide	SDs with PEG 4000	SDs with PEG 6000	SDs with PEG 8000
N-H	3188 cm $^{-1}$	3191 cm $^{-1}$	3191 cm $^{-1}$	3191 cm $^{-1}$
C=O	1709 cm $^{-1}$	1710 cm $^{-1}$	1709 cm $^{-1}$	1709 cm $^{-1}$
S=O	1349 cm $^{-1}$	1349 cm $^{-1}$	1349 cm $^{-1}$	1349 cm $^{-1}$
C-H	2943 cm $^{-1}$	2886 cm $^{-1}$	2887 cm $^{-1}$	2887 cm $^{-1}$
C=C	1644 cm $^{-1}$	1643 cm $^{-1}$	1652 cm $^{-1}$	1646 cm $^{-1}$



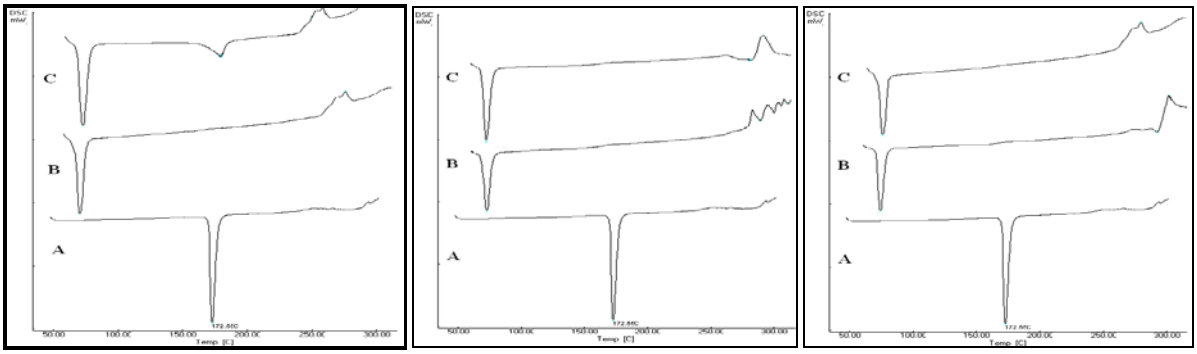
(a) **(b)** **(c)**

Fig. 2: FTIR spectrograms of (a) A – Gliclazide, B-PEG 4000, C-Gliclazide-PEG 4000 SDS, (b) A – Gliclazide, B-PEG 6000, C-Gliclazide-PEG 6000 SDS and (c) A – Gliclazide, B-PEG 8000, C-Gliclazide-PEG 8000 SDS

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 172.6 °C, and the corresponding heat of fusion (H) is 173.8 J/g whereas pure PEG 4000 showed a melting endotherm at 60.2 °C and a corresponding H 235.0 J/g. Similarly PEG 6000 endotherm at 60.5 °C with a H of 242.5 J/g and PEG 8000 showed melting endotherm at 60.7 °C with a H of 254.5 J/g. Thermograms of SDs (Fig. 3) showed the absence of a gliclazide melting peak and one exothermic peak at 253.9 °C; the corresponding H is 741.6 J/g F, 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, Tg.



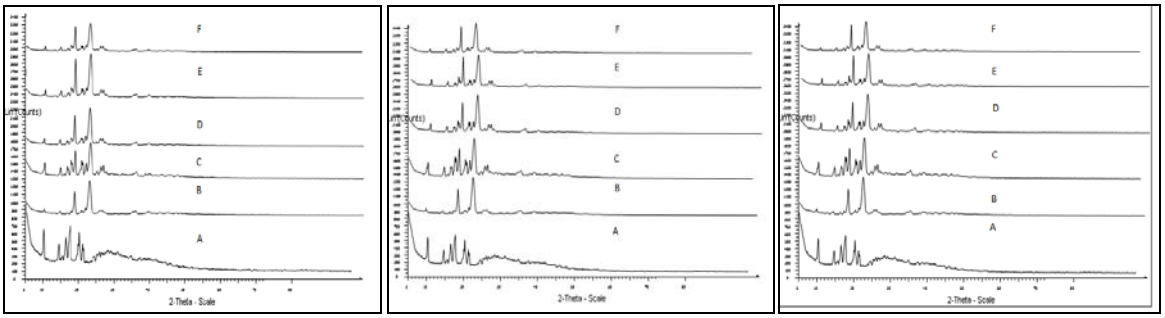
(a) **(b)** **(c)**

Fig. 3: DSC Thermograms of (a) A – Pure gliclazide, B-PEG 4000, C-Gliclazide-PEG 4000 SDS, (b) A – Pure gliclazide, B-PEG 6000, C-Gliclazide-PEG 6000 SDS and (c) A – Pure gliclazide, B-PEG 8000, C-Gliclazide-PEG 8000 SDS.

X-Ray Diffraction

The diffraction spectrum of pure gliclazide showed that the drug is of crystalline nature as demonstrated by numerous peaks observed at 2θ of 10.37, 14.85, 17.87, 17.85, 18.07, 21.06, 22.01, and 25.89 etc in finger print region (Fig.4). Pure PEG 4000 showed two peaks with the highest intensity at 2θ and d-spacings of 19.04 and 4.65 Å; 23.18 and 3.83 Å. Similarly PEG 6000 showed peaks with the highest intensity at 2θ and d-spacings of 19.41 and 4.65 Å ; 23.34 and 3.78 Å and PEG 8000 showed peaks with the highest intensity at 2θ and d-spacings of 19.10 ; 22.89 and 3.98 Å. Some changes in gliclazide peak position were observed in SDs. The prominent peaks from pure gliclazide were clearly seen at the same positions in the SDs, but with decreased intensities. As the amount of PEG increased (Fig.4) in the solid dispersion, relative reduction in diffraction intensity of gliclazide in PEG preparations at these angles was observed which suggests that the size of the crystals was reduced to a microcrystalline form.

The positions of PEG 4000, 6000 and 8000 peak patterns in the 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 microcrystalline form in the SDs.



(a) **(b)** **(c)**

Fig. 4: X-ray diffractograms of (a) A-Pure gliclazide, B- Pure PEG 4000,C-SDG411,D-SDG413,E-SDG415 and F-SDG417 (b) A-Pure gliclazide, B- PEG 6000,C- SDG611,D-SDG613,E-SDG615 and F-SDG617 (c) A- Pure gliclazide, B-Pure PEG 8000, C-SDG811,D-SDG813,E-SDG815 and F-SDG817

DISCUSSION

The poor aqueous solubility of the drug gives rise to difficulties in the pharmaceutical formulation of dosage forms and may lead to variable bio availability. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently improve the bio availability of poorly soluble drugs (Walke et al., 2011). The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. drug–polymer miscibility and stability) and pharmacokinetic (e.g. rate of absorption) constraints (Kalia and Poddar, 2011).

Solubility

The phase-solubility results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs. Increased solubility may be due to improved dissolution of gliclazide particles in aqueous solution by PEG 4000, 6000 and 8000. An indication of the process of transfer of gliclazide from pure water to the aqueous solution of PEG may be obtained from the values of Gibbs free energy change. Gtr values were found to be negative for PEG 4000, 6000 and 8000 at various concentrations indicating the spontaneous nature of drug solubilization.

Dissolution

The increase in the dissolution kinetics of gliclazide from polyethylene glycol soluble dispersion may be due to the reduction of crystal size, absence of aggregation of drug crystals and conversion of the drug from crystalline to amorphous/microcrystalline state. Improvement in the wettability of the gliclazide might have resulted from the formation of a film of polyethylene glycol around it, thus reducing the hydrophobicity of their surfaces. This explains the improvement in the dissolution of solid dispersions.

FTIR spectroscopy

The shift of the peaks of gliclazide in SDs was as a result of physical interaction between gliclazide and PEG 4000, 6000 and 8000. However, the minor shift of NH peak of gliclazide in SDs could be due to hydrogen bonding between the hydrogen atom of the NH group of gliclazide and one of the ion pairs of oxygen atom in the PEG.

X-ray diffraction

The relative reduction of diffraction intensity of gliclazide in SD preparations at these angles suggests that the size of the crystals was reduced to that of microcrystals. The positions of PEG 4000, 6000 and 8000 peak patterns in the SDs were the same and superimposable, which again rules out the possibility of well defined chemical interaction and new compound formation between these two components. The results of this study imply that gliclazide is present in partially crystalline or microcrystalline form in the SDs. The present finding, i.e., the presence of microcrystal or a partially crystalline state of gliclazide in SDs is in agreement with results for other drugs.

Differential scanning calorimetry

The absence of a gliclazide melting peak in 6000 and 8000 and the presence of one exothermic peak in 4000 SD suggested that gliclazide is completely soluble in the liquid phase of the polymer or the absence of a crystalline form of gliclazide. The exothermic peak might be due to crystallisation above Tg (glass transition temperature). The molecular motion of amorphous solid depends on temperature. The kinetic energy of amorphous solids increases significantly as the temperature gets close to Tg. Due to the thermodynamic instability of amorphous solids, compared to the crystalline state, spontaneous crystallisation is always possible as soon as molecular mobility is above the threshold of nucleation. However, the melting peaks of PEG 4000, 6000 and 8000 in SDs were observed at the same temperature (63.9 °C) as the pure PEG 4000, 6000 and 8000. It is speculated that gliclazide dissolved in molten PEG 4000, 6000 and 8000 during the DSC measurement, and that only one endothermic peak at 63.4 °C, corresponding to melting of PEG 4000, 6000 and 8000, was observed.

CONCLUSION

The solubility and dissolution rate of gliclazide can be enhanced by the use of gliclazide - PEG 8000 SDs. The solubilisation effect of PEG 8000 results in the reduction of aggregation of the drug particles, elimination of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles, and this is probably responsible for the enhanced solubility and dissolution rate of gliclazide in the SDs. DSC of gliclazide SDs did not indicate the presence of crystalline gliclazide because the drug dissolved completely below its melting point. However, XRD studies indicated the presence of 20% crystalline gliclazide in SDs. There was no well defined chemical interaction between gliclazide and PEG 8000. Gliclazide - PEG 8000 SDs provide a promising approach to enhance the solubility and dissolution rate of the drug.

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