Preparation and characterization of gliclazide-polyethylene glycol 4000 solid dispersions

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The objective of the present investigation was to study the effect of polyethylene glycol 4000 (PEG 4000) on in vitro dissolution of gliclazide from solid dispersions. Initial studies were carried out using physical mixtures of the drug and carrier. Solid dispersions were prepared by the melting or fusion method. Phase and saturation solubility study, in vitro dissolution of pure drug, physical mixtures and solid dispersions were carried out. PEG was found to be effective in increasing the dissolution of gliclazide in solid dispersions when compared to pure drug. FT-IR spectroscopy, differential scanning calorimetry and X-ray diffractometry studies were carried out in order to characterize the drug in the physical mixtures and solid dispersions. Dissolution enhancement was attributed to decreased crystallinity of the drug and to the wetting and solubilizing effect of the carrier from the solid dispersions of gliclazide. In conclusion, dissolution of gliclazide can be enhanced by the use of hydrophilic carrier.

Keywords: gliclazide, solid dispersions, polyethylene glycol

Up to 40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs (1). Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract (2–4). The dissolution characteristics of poorly soluble drugs can be enhanced by several methods (5–7). Solid dispersion is one of the effective and widely used techniques for dissolution enhancement (8). The two basic procedures used to prepare solid dispersions are the melting or fusion (9) and solvent evaporation (10) techniques. The increase in dissolution rate for solid dispersions can be attributed to a number of factors (11), which include reduction in particle size, absence of aggregation or agglomeration of fine crystallites of the drug, possible solu-

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bilitation effect of the polymer, excellent wettability and dispersibility of the drug from solid dispersion and partial conversion of the drug into amorphous form.

Gliclazide [1-(3-azabicyclo (3,3,0)oct-3yl)-3-p-tolyl-sulphonylurea] is a second generation, hypoglycemic sulphonylurea (12) and is used in the treatment of non-insulin dependent diabetes mellitus. Due to short duration of its action, it is considered suitable for diabetic patients with renal impairment and for elderly patients that have reduced renal function and follow a sulphonylurea treatment, which may increase the risk of hypoglycemia (13). Because of its low solubility and low dissolution in gastric fluids, it shows variation in bioavailability (14).

Polyethylene glycol (PEG) is used for the preparation of solid dispersions. A particular advantage of PEGs for the formation of solid dispersions is that they have good solubility in many organic solvents. The melting point of PEGs lies below 65 °C in all cases (15), which is advantageous for the manufacture of solid dispersions. Additional attractive features of PEGs include their ability to solubilize some compounds (16) and also improve compound wettability. Therefore, in the present study, it was chosen as a suitable polymer for the preparation of solid dispersions. Solid dispersions were then evaluated by dissolution, FT-IR spectroscopy, differential scanning calorimetry (DSC) and X-ray diffractometry (XRD).

EXPERIMENTAL

Materials

A gift sample of gliclazide was received from Indi Pharma Pvt. Ltd. (India) and PEG 4000 was purchased from Qualigens Fine Chemicals (India).

Methods

Physical mixtures of gliclazide. – Physical mixtures of gliclazide at three different mass ratios (1:1, 1:3 and 1:5) were prepared in a glass mortar by light trituration for 5 minutes. The mixtures were passed through a sieve. The prepared mixtures were then filled in glass bottles, sealed and stored in a dessicator until further use.

Solid dispersions of gliclazide. – Solid dispersions of gliclazide at three mass ratios (1:1, 1:3 and 1:5) were prepared by the melt or fusion method. PEG 4000 was 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. For rapid solidification, the resultant solution was cooled in an ice bath and stored in dessicator for 24 h. It was then scrapped, pulverized and passed through a sieve. The prepared solid dispersions were then filled in glass bottles, sealed and stored in a dessicator until further use.

Drug content. – The drug content in each solid dispersion and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 60 mg of gliclazide, was transferred to a 100-mL volumetric flask containing 10 mL of methanol and dissolved. The volume was
made up to 100 mL with NaOH (0.1 mol L⁻¹). The solution was filtered through a 0.45-μm membrane filter paper. One mL of this solution was diluted 100 times with NaOH (0.1 mol L⁻¹) to achieve 6 μmol L⁻¹ and the absorbance was measured at 226 nm.

**Phase and saturation solubility study.** – Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors (17). 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 37 ± 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 a 0.45-μm membrane filter. After suitable dilution, the absorbance was measured at 226 nm. For the saturation solubility study, the same treatment was applied to solid dispersions and the concentration of gliclazide was determined.

**Dissolution study.** – Dissolution of gliclazide powder as such, from its physical mixtures and solid dispersions, was carried out with the USP dissolution test apparatus (18) at 37 ± 0.5 °C and the 100 rpm using 900 mL hydrochloric acid buffer (pH 1.2) and phosphate buffer (pH 7.4) as dissolution media. Samples of dissolution medium (5 mL) were withdrawn at predetermined time intervals and an equal volume of fresh dissolution medium was added. Test samples were filtered through Whatman filter paper No. 41, suitably diluted and assayed for gliclazide at 226 nm. The cumulative percentage of gliclazide dissolved was calculated from the regression equation generated from standard data.

**FT-IR study.** – FT-IR spectra were recorded using an FT-IR spectrophotometer (Shimadzu). The samples (gliclazide, polymers, physical mixtures and solid dispersions) were previously ground and mixed thoroughly with potassium bromide. Forty scans were obtained at a resolution of 4 cm⁻¹ from 4500 to 400 cm⁻¹.

**Differential scanning calorimetry study.** – The DSC measurements were performed on a DSC-60 (Shimadzu), differential scanning calorimeter with a thermal analyzer. Accurately weighed samples (about 5–10 mg) were heated in hermetically sealed aluminum pans under a nitrogen atmosphere at the flow rate of 20 mL min⁻¹ with a scanning rate of 15 °C min⁻¹ from 60 to 250 °C. An empty aluminum pan was used as a reference.

**X-ray diffraction study.** – The crystalline state of different samples was evaluated with X-ray powder diffraction. Diffraction patterns were obtained using an XPERT-PRO diffractometer (PANalytical) with a radius of 240 mm. The Cu Kα radiation (Kα 1.54060 Å) was Ni filtered. A system of diverging and receiving slits of 1° and 0.1 mm, respectively, was used. The pattern was collected with 40 kV of tube voltage and 30 mA of tube current and scanned over the 2θ range of 5–60°.

**RESULTS AND DISCUSSION**

Results depicted in Table I show that the drug concentration in physical mixtures and solid dispersions ranged between 98.2 and 99.4 and 98.7 and 101.3 %, respectively.
The mechanisms responsible for improved drug dissolution may be either drug/carrier interactions in solid state or drug/carrier interactions in liquid state or both. When the physical mixture is added to the dissolution medium, it may simply happen that the carrier, which dissolves first, modifies the hydrophilicity/lipophilicity or wettability of the drug or it may form a weak complex with the drug at the particle surface, resulting in drug dissolution. The results of the phase solubility study of physical mixtures simulating different drug: carrier mass ratios indicated that the phase solubility of drug was enhanced to 84 % as compared to the pure drug, gliclazide. Results are presented in Figure 1.

An increase in the saturation solubility of the drug can explain the improved dissolution of solid dispersions as per the Noyes and Whitney equation (19), since the saturation solubility of a compound is dependent on the size of the particles. Since it is possible to achieve reduction in particle size with a solid dispersion system, the saturation solubility studies were performed with these systems. The results on saturation solubility indicated that the solubility was enhanced by 37 to 128 % compared to gliclazide.

The cumulative release of gliclazide at various time intervals from the physical mixtures and solid dispersions made by using various concentrations of PEG 4000 are shown in Figs. 2a,b. Dissolution of the pure drug, gliclazide, in 0.1 mol L⁻¹ HCl (pH = 1.2) was only 41.2 %. Prepared physical mixtures and solid dispersions showed improvement in

<table>
<thead>
<tr>
<th>Physical mixture (drug to PEG mass ratio)</th>
<th>Drug content (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solid dispersion (drug to PEG mass ratio)</th>
<th>Drug content (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM 411 (1:1)</td>
<td>98.2 ± 1.9</td>
<td>SD 411 (1:1)</td>
<td>98.7 ± 0.7</td>
</tr>
<tr>
<td>PM 413 (1:3)</td>
<td>98.9 ± 0.5</td>
<td>SD 413 (1:3)</td>
<td>99.8 ± 2.5</td>
</tr>
<tr>
<td>PM 415 (1:5)</td>
<td>98.4 ± 0.5</td>
<td>SD 415 (1:5)</td>
<td>101.3 ± 1.8</td>
</tr>
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<sup>a</sup> Mean ± SD, n = 3.

![](image_url) Fig. 1. Phase and saturation solubility (X ± SD, n = 3).
dissolution characteristics. In the first 30 minutes, physical mixtures of PEG 4000 (1:1, 1:3 and 1:5) showed 55.7, 53.3 and 60.2 % drug release, and 67.2, 66.0 and 53.3 % drug release from solid dispersions (1:1, 1:3 and 1:5). After 120 min, physical mixtures showed 87.3, 88.1 and 90 % drug release, whereas solid dispersions showed 90.3, 95.9 and 96.9% drug release, respectively.

Dissolution of the pure drug, physical mixtures as well as solid dispersions was tested in phosphate buffer (pH = 7.4) for a period of 120 minutes. Dissolution of the pure drug was found to be 60.7 % in 120 minutes. Almost half of the drug was dissolved from physical mixtures and solid dispersions in the first 30 minutes. In the first 30 minutes, cumulative drug release from physical mixtures (1:1, 1:3 and 1:5) was 53.7, 56.5 and 60.7 %, respectively, while solid dispersions showed 60.7, 63.4 and 70.7 % release. After 120 min, solid dispersions (1:1 and 1:3) showed 96.0 and 96.6 % release whereas maximum release was obtained with 1:5 and was 99.6%. Results are presented in Figs. 2c,d.

Possible mechanisms of increased dissolution rates of solid dispersions have been proposed by Ford (19), and include a reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier, drug conversion to amorphous state and finally, a combination of the mentioned mechanisms. The increased dissolution rate in these cases can thus be attributed to several factors, such as the solubilization effect of the carrier, conversion to amorphous state, and improved wettability of gliclazide. In general, dissolution may be described by two processes: the rate of the interfacial or solid solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional or transport process of the solvated molecule to the bulk part of the dissolution medium (20). Water readily forms hydrogen bonds with the polar groups such as OH present in PEG 4000 and the –CH₃ and SO₂ groups in gliclazide. The strength of bonds between water and PEG 4000 and water and drug molecules may be stronger than or comparable with that between the molecules of the solid dispersions. Upon contact, water molecules solvate the polymers and gliclazide molecules, either in the crystalline or in amorphous form, and break the hydrogen bonds in the drug-carrier complexes.

The FT-IR spectra of gliclazide, PEG 4000, physical mixture (1:5) and solid dispersion (1:5) are presented in Figs. 3a-d. The spectrum of gliclazide showed a sharp concave curve at 1709 cm⁻¹ for the carbonyl group. A symmetric stretching peak at 1164 cm⁻¹ and an asymmetric stretching peak at 1350 cm⁻¹ were detected for the sulphonyl group. A peak at 3272 cm⁻¹ evidenced the amino group. The PEG 4000 spectrum showed important peaks at 3425 cm⁻¹ (OH stretch), at 1109 cm⁻¹ (C-O-C stretch) and at 2889 cm⁻¹ (CH stretch). In this case, any sign of interaction would be reflected by a change in C=O, S=O and NH vibrations in the spectrum of physical mixtures and solid dispersions, depending upon the extent of interaction. From the chemical structures, hydrogen bonding could be expected between the hydroxyl group of PEG 4000 and carbonyl function of gliclazide and hydrogen bonding between hydrogen atom of the NH of gliclazide and one of the ion pairs of the oxygen atom in PEG 4000. The spectra of solid dispersion and physical mixture did not indicate any well-defined interaction between gliclazide and PEG 4000.

The DSC thermograms of gliclazide, PEG 4000, PM 415 (1:5) and SD 415 (1:5) are presented in Figs. 4a-d. Gliclazide showed an endothermic reaction and its melting peak
Fig. 2. Release profile of gliclazide and a) physical mixtures in acid buffer; b) solid dispersions in acid buffer; c) physical mixtures in phosphate buffer; d) solid dispersions in phosphate buffer.
was at 172.3 °C. The thermal behavior of PEG 4000 exhibited a sharp but slightly broad endothermic peak at 59.2 °C. Physical mixture (PM) and solid dispersion (SD) showed a single sharp melting peak at 60.3 and 59.3 °C, respectively. Complete disappearance of the gliclazide melting peak observed in both PM and SD was attributable to complete miscibility of the drug in the melted carrier. The enthalpy of drug melting in solid dispersion ($\Delta H_m = 148.3 \text{ J g}^{-1}$) was gradually decreased as compared to the drug ($\Delta H_m = 126.9 \text{ J g}^{-1}$). This phenomenon could be attributed to the amorphous form of the drug in solid dispersion.

The diffraction spectra of pure gliclazide, PEG 4000, its physical mixture (1:5) and solid dispersion (1:5) are shown in Figs. 5a-d. The diffraction pattern of pure gliclazide showed that the drug was of crystalline nature, as demonstrated by numerous distinct peaks. Gliclazide’s numerous diffraction peaks were observed at 2θ of 10.5, 15.0, 16.7, 17.0, 17.8, 18.1, 18.4, 20.8, 21.1, 22.0, and 26.2, etc. (fingerprint region), indicating the crystalline nature of gliclazide. Pure PEG 4000 showed two peaks with highest intensity at 2θ of 19.3 and 26.2. The physical mixture and solid dispersion showed two peaks of highest intensity, at 2θ of 19.1 and 23.5 attributable to PEG 4000. Solid dispersion showed all peaks of the drug; however, the intensity of the peaks was reduced when compared to that of the drug and hence absent. The results indicate that the drug in solid dispersion was amorphous as compared to the pure drug; hence the dissolution of the drug was improved. PEG 4000 peaks in solid dispersion were the same and just superimposed, which ruled out the possibility of chemical interaction between gliclazide and PEG 4000.
CONCLUSIONS

The present work shows that the dissolution rate of gliclazide from solid dispersions with PEG 4000 improved to more than 90% compared to the pure drug. Further, all the solid dispersions performed better than the corresponding physical mixtures. Also, the saturation solubility of the drug when formulated into solid dispersion with the polymer was higher than that of phase solubility achieved in the presence of the polymer. IR spectra indicated no well-defined interaction between the drug and polymer. DSC thermograms of physical mixture and solid dispersion indicated complete miscibility of the drug in melted carrier. Amorphous nature of the drug in solid dispersion was confirmed by a decrease in enthalpy of drug melting in solid dispersion compared to the pure drug. XRD analysis indicated a reduction in drug crystallinity in solid dispersion.

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REFERENCES


**S A Ž E T A K**

**Priprava i karakterizacija gliklazid-polietilen glikol 4000 čvrstih disperzija**

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U radu je opisan učinak polietilen glikola 4000 (PEG 4000) na in vitro oslobađanje gliklazida iz čvrstih disperzija koje su pripravljene metodom taljenja ili fuzije. Čvrstim disperzijama i fizičkoj smjesi ljekovite tvari i nosača proučavana je topljivost faze i zasićenje te in vitro oslobađanje ljekovite tvari. Rezultati ukazuju da PEG povećava oslobađanje gliklazida u čvrstim disperzijama. Za karakterizaciju fizičkih smjesa i čvrstih disperzija upotrebljena je FT-IR spektroskopija, diferencijalna pretražna kalorimetrija i difraktometrija rendgenskog zračenja. Zaključeno je da je povećanje oslobađanja posljedica vlaženja, smanjenje kristaliničnosti i solubilizirajućeg učinka nosača te da se oslobađanje gliklazida može povećati pomoću hidrofilnog nosača.

**Ključne riječi:** gliklazid, čvrste disperzije, polietilen glikol

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