CHARACTERIZATION AND SOLUBILITY ENHANCEMENT OF GLICLAZIDE SOLID DISPERSION USING PVP-K30 & K -90

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Abstract: The purpose of this study was to design Polyvinylpyrrolidone (PVP) based solid dispersions bearing gliclazide. Polyvinylpyrrolidone (PVP K-30 and K-90) based solid dispersions containing the drug in different mass ratio i.e. 1:1, 1:3, 1:5 and 1:7 were prepared using fusion method. The prepared solid dispersions were characterized for their drug content, phase solubility studies, fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry, x-ray diffraction, and in-vitro dissolution studies. All the formulations showed marked improvement in the solubility and dissolution rate of drug from solid dispersion is due to decrease in crystallinity of drug and additives. It was concluded that prepared solid dispersion of the gliclazide with Polyvinylpyrrolidone may improved the solubility and dissolution rate of the drug.

Keywords: Gliclazide, PVP, solid dispersion, Solubility.

INTRODUCTION

Diabetes is a metabolism disorder and its characteristic is raising blood sugar more than normal range and it happens because of dysfunction of Insulin which regulates blood sugar. According to International federation of Diabetes assessment in year 2003, 194 million diabetic people live in the world and its estimated that by year 2025 this number achieves 333 million [1]. In every 10 seconds, one person in the world passes away because of ignorance about Diabetes and ways to control it [2,3].Sulfonylureas (SUs) are among the oldest class of oral antihyperglycemic agents available for the treatment of type 2 diabetes. Gliclazide is a second-generation hypoglycemic sulfonylurea, which is useful in the treatment of type 2 diabetes mellitus [4]. Following oral administration, however, Gliclazide exhibits slow rate of absorption and inter individual variation in bioavailability. Stated problems of gliclazide might be due to its poor water solubility and slow dissolution rate [5,6]. But gliclazide exhibits good tolerability, low incidence of hypoglycemic effect, low rate of secondary failure, and low rate of progression of diabetic retinopathy [5,7]. 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, or cyclodextrin–hydroxypropylmethylcellulose. The authors in the present study investigated the physicochemical characteristics and dissolution behaviours of Gliclazide in solid dispersions by using polyvinylpyrrolidone K 30 and 90 (PVP K30 and 90). The possible interactions between Gliclazide and PVP K 30, 90 in both solid and liquid states was 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
Gliclazide was received as gift from Arion health care Baddi (Himachal Pradesh, India). Polyvinylpyrrolidone (PVP) K-30 and K 90 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 of gliclazide at four mass ratios (1:1, 1:3, 1:5 and 1:7) were prepared by the fusion method. PVP (K30 and K90) 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, then powdered in a mortar, sieved through a 100-mesh screen, and stored in a screw-cap vial at room temperature for further use.

Phase Solubility of Gliclazide
Solubility determinations were performed in triplicate according to the method of Higuchi and Connors [8]. 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 K 30 and 90 was added. Then, the samples were shaken at 25±0.5°C for 72h in a water bath (Rolex, Ambala, India). After 72 h, samples were 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 1700, PharmaSpec, Japan).

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.

Dissolution Studies
Dissolution studies of gliclazide in powder form, SDs, in triplicate were performed by using the US Pharmacopoeia (USP) model digital tablet dissolution test apparatus-2(6+2 station), (Lab India Ltd, Mumbai) at the paddle rotation speed of 50 rpm in 900 ml 0.1 N HCl at 37±0.5°C. The SDs equivalent to 30 mg of gliclazide were weighed using a digital balance and added into the dissolution medium. 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), prewarmed at 37±0.5 °C, was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. Dissolution studies were performed in triplicate (n=3).

Fourier-transform Infrared (FTIR) Spectroscopy
Fourier-transform infrared (FT-IR) spectra were recorded using an FT-IR spectrophotometer (Shimadzu). The samples (gliclazide, PVP K30 and 90 and its 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 (Shimadzu DSC-60 Thermal Analyzer) 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

RESULTS
Drug Content
Results depicted in Table 1 show that the drug concentration in solid dispersions ranged between 97.2 and 99.2.

<table>
<thead>
<tr>
<th>Solid dispersion mass ratio</th>
<th>(drug to PVP mass ratio)</th>
<th>Formulation code solid dispersion</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVP K30 (1:1)</td>
<td>SD k311</td>
<td>99.16±1.65</td>
<td></td>
</tr>
<tr>
<td>PVP K30 (1:3)</td>
<td>SD k313</td>
<td>98.6±2.23</td>
<td></td>
</tr>
<tr>
<td>PVP K30 (1:5)</td>
<td>SD k315</td>
<td>98.8±1.86</td>
<td></td>
</tr>
<tr>
<td>PVP K30 (1:7)</td>
<td>SD k317</td>
<td>99.2±1.58</td>
<td></td>
</tr>
<tr>
<td>PVP K90 (1:1)</td>
<td>SD k911</td>
<td>97.28±2.35</td>
<td></td>
</tr>
<tr>
<td>PVP K90 (1:3)</td>
<td>SD k913</td>
<td>98.73±2.05</td>
<td></td>
</tr>
<tr>
<td>PVP K90 (1:5)</td>
<td>SD k915</td>
<td>99.12±1.96</td>
<td></td>
</tr>
<tr>
<td>PVP K90 (1:7)</td>
<td>SD k917</td>
<td>98.45±1.75</td>
<td></td>
</tr>
</tbody>
</table>

Solubility and Dissolution Data Analysis

Phase-Solubility
The phase solubility diagram investigated in 0.1 N HCl (pH 1.2) was linear in a wide range of PVP K 30 and 90 concentrations and correspond to AL-type profiles [8]. The stability constant was found to be 0.201 and 0.34 ml⁻¹ mg⁻¹.
The value of apparent stability constant Ks, between drug–carrier combinations were computed from the phase-solubility profiles, as shown in Eqn1.

\[ K_s = \frac{\text{Slope}}{\text{Intercept} (1 - \text{Slope})} \]  

\[ G_{r0} = -2.303RT\log S_0/S_s \]  

where So/Ss is the ratio of molar solubility of gliclazide in aqueous solution of PVP K 30 and 90 to that of the same medium without PVP K 30 and 90. In solid dispersion of Gliclazide with 18% w/v PVP K 30 and PVP K 90 increase in solubility was found to be 3.83 and 4.81 fold respectively as shown in Table 2.

<table>
<thead>
<tr>
<th>PVP K30</th>
<th>Gliclazide (mg/ml) at 25°C</th>
<th>Gibbs free energy of transfer (J/Mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.75±0.03</td>
<td>0</td>
</tr>
<tr>
<td>18%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Dissolution studies

Q10, Q30 and Q60 values (percent drug dissolved within 60 min) are reported in Table 3. From Table 3, 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 PVP K 30 and PVP K 90 within 60 min compared to pure gliclazide. Dissolution was enhanced with SDs as the molecular weight of PVP increased from K 30 to K 90 at Q60min 80.02 to 80.20 % in ratio 1:1, 86.62 to 95.43 % in ratio 1:3, 93.27 to 97.47 % in ratio 1:5 and 92.76 to 96.82% in ratio 1:7. Increase in dissolution of gliclazide was approximately similar in the ratio 1:5 and 1:7 as shown in Fig. 1.

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

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dissolution Parameters (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q10min</td>
</tr>
<tr>
<td>GLZ: PVP K 30</td>
<td>12.42</td>
</tr>
<tr>
<td>GLZ: PVP K 90</td>
<td>55.20</td>
</tr>
<tr>
<td>SD1/3</td>
<td>64.62</td>
</tr>
<tr>
<td>SD1/5</td>
<td>68.40</td>
</tr>
<tr>
<td>SD1/7</td>
<td>67.80</td>
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</tbody>
</table>

Fig. 1: Percent drug released in 0.1 N HCl (pH 1.2) from solid dispersion of Gliclazide with PVP K 30 (a), and K 90 (b).

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 PVP K alone (Fig.2). In the SDs, the asymmetric vibration peak of the S=O is shifted with decreased intensity from 1349 cm⁻¹ to 1343 cm⁻¹ and 1348 cm⁻¹ in PVP K 30 and 90 respectively while the absorption of carbonyl (C=O) sulphonyl urea group at 1709 cm⁻¹ in pure gliclazide shifted towards higher wave number 1711 cm⁻¹ and 1717 cm⁻¹ in PVP K 30 and 90 respectively. A very broad band was also visible at 3443 cm⁻¹ and

3446 cm$^{-1}$ in PVP K 30 and 90 respectively which was attributed to presence of water.

Table 4: Stretching vibrations of Gliclazide and Solid Dispersion (SDs) of Gliclazide with PVP K 30 AND PVP K 90.

<table>
<thead>
<tr>
<th>Stretching</th>
<th>Pure Gliclazide</th>
<th>SDs with PVP K 30</th>
<th>SDs with PVP K 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-H</td>
<td>3373 cm$^{-1}$</td>
<td>3435 cm$^{-1}$</td>
<td>3444 cm$^{-1}$</td>
</tr>
<tr>
<td>C=O</td>
<td>1709 cm$^{-1}$</td>
<td>1711 cm$^{-1}$</td>
<td>1717 cm$^{-1}$</td>
</tr>
<tr>
<td>S=O</td>
<td>1349 cm$^{-1}$</td>
<td>1343 cm$^{-1}$</td>
<td>1348 cm$^{-1}$</td>
</tr>
<tr>
<td>C-H</td>
<td>2943 cm$^{-1}$</td>
<td>2954 cm$^{-1}$</td>
<td>2950 cm$^{-1}$</td>
</tr>
<tr>
<td>C=C</td>
<td>1644 cm$^{-1}$</td>
<td>1657 cm$^{-1}$</td>
<td>1655 cm$^{-1}$</td>
</tr>
</tbody>
</table>

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 PVP K 30 and PVP K 90 endotherm shows a broad endotherm ranging from 60°C to 100°C. Thermograms of SDs (Fig. 3) show the absence of a gliclazide melting peak and one exothermic peak at 272.9 °C, 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.

X-Ray Diffraction

The diffraction spectrum of pure gliclazide shows that the drug was of crystalline nature as demonstrated by numerous peaks observed at 20 of 10.79, 15.21, 16.95, 17.20, 18.26, 21.36, and 29.71etc in finger print region (Fig.4). Pure PVP shows absence of peaks in diffraction spectrum. 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 PVP increases (Fig.4) in the solid dispersion, relative reduction in diffraction intensity of gliclazide in PVP preparations at these angles suggests that the size of the crystals was more reduced to a microcrystalline form. Results of this study imply that gliclazide is present in a microcrystalline form in the SDs.[9].

DISCUSSION
Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting solvent method [9]. 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 of PVP K-30 and PVP K-90. An indication of the process of transfer of Gliclazide from pure water to the aqueous solution of PVP K30 and 90 may be obtained from the values of Gibbs free energy change. $\Delta G_{tr}$ values were all negative for PVP K-30 and K-90 at various concentrations indicating the spontaneous nature of drug solubilisation. The increase in the dissolution kinetics of Gliclazide from PVP Soluble dispersion might 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 PVP around it, thus reducing the hydrophobicity of their surfaces. This explains the improvement in the dissolution of solid dispersions. The shift of the peaks of gliclazide (FTIR), in SDs was as a result of physical interaction between gliclazide and PVP K 30 and K 90. The shift in the peaks associated with the gliclazide sulfonylurea group indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PVP K interacting with the oxygen atoms of the sulfonyl group. This led to the conclusion that the changes seen are a result of intermolecular hydrogen bonding between gliclazide and PVP K in the solid state. 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 PVP K 30 and 90 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 absence of a gliclazide melting peak in PVP K30 and 90 and suggest that gliclazide was 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 solids 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. The higher dissolution rates of solid dispersions can be ascribed to a number of factors which includes: The formation of higher energy metastable states of the components as a function of the carrier system being used and the proportion of carriers present [10]. Formation of amorphous forms of drug and carriers [11]. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, hence higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution (Betagiri, 1995) and cosolvent effect on the drug by the water-soluble carriers [10,11]. Furthermore, Intermolecular hydrogen bonds between drug and carrier [12] and local solubilisation effect of carrier at the diffusion layer [13] may be responsible for higher dissolution rate of solid dispersions as evident in the present study.

**CONCLUSION**

Vast number of technological advancements has been introduced for dissolution enhancement of poorly water-soluble drugs. Most of these techniques utilize inert carriers which improve the drug’s physicochemical properties like solubility, particle size, crystal habit etc. Some of the carriers are especially capable of forming highly water soluble amorphous forms when the drugs are dispersed in them or by size reduction (comixinization). Complexation of drug with suitable carrier also alters the solubility and dissolution characteristics due to extremely high aqueous solubility of the carrier. The solubility and dissolution rate improvements are also expected due to co-solvency effect and solubilisation effect of carriers in aqueous vehicles. In summary, it can be said that carrier induced physical modifications as evidenced in the present study is an important tool in designing and formulating immediate and fast release drug delivery systems.

**REFERENCES**


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