Enhancement of Dissolution Rate of Glimepiride using Solid Dispersions with Polyvinylpyrrolidone K 90

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Abstract
The aim of the present study was to enhance the dissolution rate of glimepiride using its solid dispersions (SDs) with polyvinylpyrrolidone K 90. The phase solubility behavior of glimepiride in presence of various concentrations of polyvinylpyrrolidone K 90 in phosphate buffer pH 7.4 was obtained at 37°C. The solubility of glimepiride increased with increase in amount of polyvinylpyrrolidone K 90 in buffer pH 7.4. Gibbs free energy ($\Delta G^\circ$) values were all negative. The solid dispersions of glimepiride with polyvinylpyrrolidone K 90 were prepared at 1:1, 1:3 and 1:5 (glimepiride: PVPK 90) ratio by kneading method. Evaluation of the properties of the solid dispersions was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy and X-ray diffraction (XRD) studies. The solid dispersions of glimepiride with polyvinylpyrrolidone K 90 exhibited enhanced dissolution rate of glimepiride. The mean dissolution time (MDT) of glimepiride decreases significantly in solid dispersions. The Fourier-transform infrared spectroscopic studies showed formation of intermolecular hydrogen bonding between glimepiride and polyvinylpyrrolidone K 90. The X-ray diffraction studies indicated the partially amorphous state of glimepiride in SD of glimepiride with polyvinylpyrrolidone K 90.

Keywords: Glimepiride, polyvinylpyrrolidone K 90, solubility, dissolution rate

INTRODUCTION
Glimepiride, 1-([p-(2-(3-ethyle-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl) phenyl) sulfonyl]-3-(trans-4-methylcyclohexyl) urea is a third generation of hypoglycemic sulfonurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM) 1, 2. Prior reports reveal that the drug shows more potential benefits over currently available sulfonureas such as lower dose, rapid onset of action, longer duration of action and lower insulin C-peptide level 3, 4. Glimepiride is a white crystalline powder, relatively insoluble in water (pKa=6.2). Glimepiride exhibits slow GI absorption rate and inter individual variations in its bioavailability due to its poor water solubility 1, 5, 6. From an economic point of view, low bioavailability of drug leads to wastage of more amount of drug after oral administration, in case of costly drug increases cost of formulation. The approach solid dispersion has been used to increase water solubility and dissolution rate of poorly water soluble drug and to solve bioavailability problems. Ammar et al., reported that the bioavailability and stability of glimepiride can be enhanced in its complex form with β-cyclodextrin 7, 8. However, there is no report on the preparation and evaluation of glimepiride solid dispersion with polyvinylpyrrolidone K 90.

In our previous study, the potentiality of improvement of solubility and dissolution rate of the gliclazide by preparing SDs with PEG 6000, PEG 8000 and polyvinylpyrrolidone K 90 was found 9-11. The authors investigated the physicochemical characteristics and dissolution behaviors of glimepiride in physical mixtures as well as solid dispersions with polyethylene glycol 20, 000 in a previous study 12. The primary objective of the present study is to enhance dissolution rate of glimepiride using solid dispersion with polyvinylpyrrolidone K90. The possible interactions...
between glimepiride and PVP K 90 in both solid state and liquid states were investigated. Interaction in the solid state was investigated by Fourier-transform infrared (FT-IR) spectroscopy and X-ray diffraction analysis (XRD). Interaction in solution was studied by phase solubility analysis and dissolution experiments.

**MATERIALS AND METHODS**

**Materials**

A gift sample of glimepiride was received from Aristo Pharmaceuticals Ltd., (Mumbai, India). PVP K 90 was received from Clariant (Germany).

**Methods**

**Preparation of SDs**

The SDs of glimepiride with PVP K 90 containing three different weight ratios (1:1, 1:3, 1:5) (glimepiride: PVP K 90) and denoted as SD1/1, SD1/3 and SD 1/5 respectively, were prepared by kneading method. In kneading method, a required amount of PVP K 90 was taken in a glass mortar along with 10% lactose. A required amount of glimepiride was added to mortar and kneaded thoroughly with a glass rod by using ethanol. The mixture was kept for drying in a desiccator. The hardened mixture was powdered in a mortar, sieved through a 100-mesh screen, and stored in screw-cap vial at room temperature until further use.

Physical mixtures of glimepiride with PVPK 90 containing three different weight ratios (1:1, 1:3, 1:5) and denoted as PM 1/1, PM 1/3 PM 1/5 were prepared separately. Glimepiride and PVPK 90 were accurately weighed, pulverized and mixed thoroughly by light trituration for 5 min in a mortar. The mixture was passed through a sieve no. 100.

**Phase Solubility Studies**

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors. The effect of concentrations of PVPK 90 on the equilibrium solubility of glimepiride in phosphate buffer pH 7.4 at room temperature was carried out by adding an excess of drug (50 mg) into a screw-capped glass vial containing 10 mL of phosphate buffer pH 7.4 and various amounts of the carrier (2-10% w/v). The samples were placed on a rotary shaker and agitated at room temperature for 48 hr. An aliquot of each solution was withdrawn and filtered through a 0.45-µm pore size Millipore membrane filter fitted with syringe holder. The assay of glimepiride was determined spectrophotometrically at 226 nm, a wave length at which PVPK 90 does not interfere.

The Gibbs free energy of transfer (ΔG°) of glimepiride from pure water to the aqueous solutions of carrier was calculated as

\[
\Delta G° = -2.303RT \log \frac{S_o}{S_5}
\]

Where \( \frac{S_o}{S_5} \) is the ratio of molar solubility of glimepiride in aqueous solution of PVP K 90 to that of the same medium without PVP K 90.

**Dissolution Studies**

Dissolution studies of glimepiride in powder form, SDs, and PMs were performed by using the U. S. Pharmacopeia (USP) model digital tablet dissolution test apparatus-2 (Veego Scientific Co.) at the paddle rotation speed of 50 rpm in 900 mL of phosphate buffer pH 7.4. The SDs or PMs equivalent to 10 mg of glimepiride was weighed using a digital balance (Ohaus Corp) and added into the dissolution medium. At the specified times (every 10 min for 1 hr), 10 mL samples were withdrawn by using syringe filter (0.45µm) (Sepyrane, Mumbai) and then assayed for glimepiride content by measuring the absorbance at 226 nm using the UV-Visible spectrophotometer (Shimadzu 1601PC, Japan). Fresh medium (10 mL), which was prewarmed at 37°C, was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), and calculated mean values of cumulative drug release were used while plotting the release curves.

**Fourier-Transform Infrared Spectroscopy**

Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR spectrometer-430 (Jasco, Japan). The samples (glimepiride 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 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 4600 to 300 cm⁻¹.

**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
monochromatic, 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), scan step time of 0.5s.

RESULTS AND DISCUSSION

Solubility Studies
Phase solubility experiments showed that the concentration of glimepiride in buffer pH 7.4 is notably affected by the presence of PVP K 90. The phase-solubility diagram investigated in buffer pH 7.4 was linear up to concentration 8% range of PVP K 90 concentrations and correspond to $A_n$-type profiles (Figure 1). These results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs. At 8% (w/v) concentration of PVPK 90, the solubility of glimepiride increased by 4.04 fold. An indication of the process of transfer of glimepiride from pure water to the aqueous solution of PVPK 90 may be obtained from the values of Gibbs free energy change. The values of Gibbs free energy associated with the aqueous solubility of glimepiride in presence of PVPK 90, $\Delta G_n$ values were all negative for PVPK 90 at various concentrations indicating the spontaneous nature of the drug solubilization. The values decreased by increasing PVPK 90 concentration, demonstrating that the solubilization more favorable as concentration of PVPK 90 increased.

Dissolution Studies
The results of the dissolution studies for individual samples (glimepiride alone, PMs and SDs) over the period of 1 hour are shown in Figure 2 and reported values are the mean of three determinations (CV<10%). $Q_{10}$, $Q_{30}$ and $Q_{60}$ values (percent drug dissolved in 30 minutes) are reported in Table 1. Onset of dissolution of pure glimepiride is very low about 36.08 % of drug being dissolved in 60 min. SDs of glimepiride with PVPK 90 considerably enhanced dissolution rates within 30 minute compared to pure glimepiride and PMs. Percentage dissolution efficiencies (%DE) values were computed, for comparative analysis all the formulations. The % DE values in the initial time period of dissolution study i.e. %DE$_{10min}$ provide relative information about both fast and slow releasing formulations. The value of % DE$_{30min}$ for the pure drug was increased to 33.80 % in PM (1:5) and up to 49.29% in SD (1:5). The change of DE$_{30min}$ of drug in its PMs and SDs is statistically significant (p<0.05).

In order to understand the extent of glimepiride dissolution rate enhancement from its SDs and PMs, the obtained dissolution data of pure glimepiride, SDs, and PMs were fit in Eq. 2

$$MDT_{n+1} = \frac{\sum T_{mid}(i)M}{\sum AM}$$

Here, i is dissolution sample number, n is number of dissolution sample times, T mid is time at the mid point between times Ti and T, and $AM$ is the amount of glimepiride dissolved (µg) between times Ti and T,i. In order to calculate the mean dissolution time (MDT) of pure glimepiride, SDs, and PMs, the mean (n=3) of cumulative drug release (µg) was used. The obtained values of MDT for pure glimepiride, SDs, and PMs are presented in Table 2. The MDT of glimepiride is 13.35 min, then it decreased to a greater extent 7.17 min after preparing its SDs with PVPK 90 at 1:5 (glimepiride: PVPK90) ratio.

The results of the dissolution study indicate an improvement of dissolution rate of glimepiride in solid dispersion. The rate of dissolution increases as concentration of PVPK 90 increases in SDs. The improvement of dissolution rate is possibly caused by several factors. Such factors are: a) the strong hydrophilic character of PVPK 90, which improves the water penetration and the wettability of the hydrophobic glimepiride, b) the optimal dispersion of glimepiride to PVPK 90, c) the absence of crystals (amorphous dispersions) corresponds to lower energy required for dissolution and d) the inter molecular hydrogen bonds and the molecular dispersion of glimepiride on PVP leads to partial miscibility, improving the hydrophilic characteristics of the drug substance via interactions within the polymer. The improvement of dissolution rate of glimepiride in PMs is due to increased wettability of the drug powder.

Fourier-Transform Infrared Spectroscopy
The IR spectra of SD and PM were compared with the
standard spectrum of glimepiride (Figure 3). IR spectrum of glimepiride is characterized by the absorption of carbonyl (C=O) sulphonyl urea group at 1708 and 1674 cm\(^{-1}\). Also the NH group which is located at 3369 cm\(^{-1}\) and 3288 cm\(^{-1}\) from the IR spectrum of glimepiride shifted to 3372 cm\(^{-1}\) and 3295 cm\(^{-1}\) in SD. The sulphonyl group bands are located at 1345 cm\(^{-1}\) and 1153 cm\(^{-1}\) in pure glimepiride. In SD, the asymmetrically vibration peak of S=O band was shifted from 1345 cm\(^{-1}\) to 1338 cm\(^{-1}\) with decreased frequencies. In SD, the symmetrically stretching vibration band of S=O was shifted from 1153 cm\(^{-1}\) to 1150 cm\(^{-1}\) with decreased frequencies. The spectrum of PVP K 90 exhibited important bands at 2953 cm\(^{-1}\) (C–H stretch) and 1652 cm\(^{-1}\) (C=O).

The shift in the peaks associated with C=O, S=O and NH group of glimepiride 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 drug and polymer. Intermolecular hydrogen bond expected to occur between the hydrogen atom of the NH group of glimepiride and one of the lone pairs electron of C=O group of polymer or/and C=O group of glimepiride and one of the hydrogen atom of PVP K 90. The FTIR data suggests formation of intermolecular hydrogen bonding between glimepiride and PVP K 90.

**X-Ray Diffractions (XRD)**

The diffraction spectrum of pure glimepiride showed that the drug was of crystalline nature as demonstrated by numerous peaks. Numerous diffraction peaks of glimepiride were observed at 20 of 13.41, 14.62, 16.67, 18.13, 19.18, 21.03, 21.11, 22.95 and 26.33 (finger print region) etc (Figure 4) indicating crystalline glimepiride. Pure PVP K 90 showed absence of peak. All principal peaks from glimepiride were present in their respective PM and SD with decreased intensity, which suggested that some portion of drug was converted into amorphous form. The X-ray diffraction findings also suggested that some portion of drug still existed in the same crystal structures of pure drug and/or formation of microcrystals but the relative reduction of diffraction intensity of drug in SD at these angles suggests that the drug partially converted into amorphous form.

**CONCLUSIONS**

The solubility and dissolution rate of glimepiride can be enhanced by the use of SDs of glimepiride with PVP K 90. The solubilization effect of PVP K 90, reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of glimepiride from its SDs and PMs.

**ACKNOWLEDGMENT**

The authors are grateful to Aristo Pharmaceuticals Pvt Ltd, Mumbai, India for gift sample of glimepiride. Mr. Sudarsan Biswal is grateful to the Principal, Royal College of Pharmacy and Health Sciences, Berhampur, for providing the required facilities for this work.

<table>
<thead>
<tr>
<th>Concentration of PVP K90 (% w/v)</th>
<th>Concentration of glimepiride (mg/ml) at 37°C</th>
<th>(\Delta G_{\text{sp}}^0) (J/Mol)</th>
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<tbody>
<tr>
<td>1. 0</td>
<td>0.12</td>
<td>0</td>
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<tr>
<td>2. 2</td>
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<td>5. 8</td>
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</tr>
<tr>
<td>6. 10</td>
<td>0.25</td>
<td>-1895.4</td>
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**Table 1. Effect of PVP K-90 concentration and Gibbs free energy on solubility glimepiride**
Table 2: In-vitro dissolution profile of glimepiride, physical mixture of glimepiride and solid dispersion of glimepiride in pH 7.4 buffer

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Dissolution parameters</th>
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<tr>
<td></td>
<td>$Q_{10\text{min}}$</td>
<td>$Q_{20\text{min}}$</td>
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<tr>
<td>Glimepiride</td>
<td>5.34</td>
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<td>PM 1 / 1</td>
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<td>11.59</td>
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<tr>
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<td>28.3</td>
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<tr>
<td>SD 1 / 5</td>
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</table>

Fig. 1: Phase solubility graph of glimepiride in pH 7.4 buffer
Fig. 2: In-vitro dissolution profiles of glimepiride, physical mixtures and solid dispersion of glimepiride with PVP K 90 in pH 7.4 buffers.

Fig. 3: FTIR Spectrograms of pure glimepiride (A), Pure PVP K 90(B), glimepiride -PVP K 90 PM (C), glimepiride -PVP K 90 SD (D).

Fig. 4: X-Ray Diffractograms of pure glimepiride (A), Pure PVP K 90(B), glimepiride -PVP K 90 PM(C), glimepiride -PVP K 90 SD (D).
REFERENCES


