Formulation and Evaluation of Solid Dispersions of an Anti-diabetic Drug

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Abstract

The present work investigates the dissolution and bioavailability characteristics of an anti-diabetic drug, Glimepiride. Glimepiride, is an oral hypoglycemic drug and has problems in bioavailability and bioequivalence due to its poor water solubility. In the present study, dissolution studies were carried out by using USP XXIV apparatus, for the drug glimepiride, and its binary systems (both physical mixture as well as solid dispersions of glimepiride). Infrared (IR) Spectroscopy, Differential Scanning Calorimetry (DSC), and X-ray Diffractometry (XRD) were performed to identify any physicochemical interaction between the drug and the carrier and its effect on dissolution behavior. Tablets containing solid dispersion products were formulated and compared with the commercial product. The commercial product and the tablet formulation under investigation were than characterized for their various physicochemical properties such as weight variation, % friability, disintegration and in vitro dissolution profiles. IR Spectroscopy, XRD, and DSC showed no change in the crystal structure of glimepiride thus indicating the absence of any interaction between the drug and the polymer. A significant improvement in the dissolution of glimepiride in solid dispersion products has been observed (>85% in 5 minutes). Also tablets containing solid dispersion exhibited better dissolution profile than commercial tablets. Thus, the solid dispersion technique can be successfully used for the improvement of dissolution of glimepiride.

Key words: Solid Dispersion, Dissolution enhancement, Poorly soluble drugs, Antidiabetic drugs.

Introduction

Glimepiride is an oral anti-diabetic drug, which comes under the BCS (Biopharmaceutical Classification System) class 2 category drugs i.e. drugs, which are having high permeability and low solubility profiles. A drug substance is considered highly permeable when the extent of absorption in humans is determined to be ≥ 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose. A drug product is considered to be rapidly dissolving when ≥ 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions. Sparingly water-soluble drugs often exhibit low dissolution profile and oral bioavailability problems (1).

Various techniques such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrugs, drug derivitization, alteration in pH, addition of surfactants, and others (2, 3) have been employed in order to improve the dissolution and bioavailability of sparingly soluble drugs. Among the various approaches, the solid dispersion
technique has proved to be the most successful, simple and economic in improving the dissolution and bioavailability of poorly soluble drug (4).

Solid dispersion, which was introduced in the early 1970s (5) is a multicomponent system, having drug dispersed in and around hydrophilic carrier(s). It (solid dispersion technique) has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide (6), ketoprofen (7), tenoxicam (8), nifedipine (9), nimodipine (10), ursodeoxycholic acid (11), and albendazole (12). Various hydrophilic carriers, such as polyethylene glycols (13), polyvinylpyrrolidone (14), hydroxypropyl methylcellulose (15), gums (10), sugar (16), mannitol (17) and urea (11) have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs. Sekiguchi and Obi (18) were the first to propose the solid dispersion technique to improve the dissolution characteristics of poorly water-soluble drugs by the use of water-soluble carriers. Chiou and Rigelman, 1971 (5) have used the solid dispersion technique for dissolution enhancement of poorly water-soluble drugs by thoroughly dispersing the drug in a water-soluble carrier by solvent-melting methods. In this method, the drug is thoroughly dispersed in a water-soluble carrier by melting, solvent, or solvent-melting methods (5). Many water-soluble carriers have been employed for preparation of solid dispersion of poorly soluble drugs. The most common are polyethylene glycols (PEG) (19, 20), polyvinyl pyrrolidone (21, 22), lactose (23), β-cyclodextrin (24, 25), and hydroxypropyl methylcellulose (26). Moreover, Polyethylene glycol (PEG) is one of the most widely used carriers to prepare solid dispersions (27-29). This work investigated the possibility of developing glimepiride tablets, allowing fast, reproducible and complete drug dissolution, by using solid dispersion technique. Solid dispersions of Glimepiride in PEG 6000 were prepared by solvent evaporation method. Differential Scanning Calorimetry (DSC) curves, Infra-Red (IR) Spectroscopy and Powder X-Ray Diffraction (XRD) patterns of solid dispersions and physical mixtures were obtained using a Differential Scanning Calorimeter (DSC 60 Shimadzu Japan), FTIR (Jasco FTIR-5300 spectrophotometer (Tokyo, Japan) and XRD (Seimens D 5005 diffractometer) respectively.

Materials and Methods

Materials

For preparation of solid dispersions the following materials were used: Lactose (Sigma); PEG 6000 (BASF, India); Glimepiride (Zydus Recon) Bangalore. Chemicals used for buffer preparation were of reagent grade. All other materials used were of analytical grade.

Preparation of solid dispersions

Different ratios of solid dispersions (1:1, 1:2) were prepared by solvent evaporation technique using vacuum flash evaporator using methanol as solvent. The solvent was evaporated in the vacuum flash evaporator at 60°C until no trace of solvent was remaining. The residue was scrapped, collected and dried for 10 min. in oven at 40°C. After drying the mass was pulverized and passed through sieve no. 80 mesh. All these dispersions were then stored in the screw cap bottles for further analysis.

Physical mixtures of glimepiride were prepared by mixing glimepiride with the hydrophilic carriers for 5 min. in a mortar until a homogenous mixture was obtained. The resulting mixture was then sieved and 105-250 micron particle size fraction was obtained using 60- and 140 mesh screen. The powders were stored in screw cap bottles at room temperature until further analysis.

Estimation of drug content

Drug content of the preparations were estimated by dissolving weighed quantity of physical mixture (PM) or solid dispersion (SD) in minimum amount of methanol and then making
up the volume with water and then assayed for drug content spectrophotometrically at 229 nm.

An accurately weighed quantity of solid dispersion equivalent to 4 mg of drug were taken into 50 ml volumetric flask and then dissolved in minimum amount of methanol. This was then made up to the volume with water and was assayed for drug content by using UV double beam spectrophotometer at 229 nm. Three replicates were prepared and the average drug contents were estimated in the prepared solid dispersions (Table 1).

**Table 1:** Assay for the drug content in the binary mixtures

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ratio</th>
<th>Binary Mixtures</th>
<th>Assay (mg/50 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1:1</td>
<td>PM</td>
<td>96.14</td>
</tr>
<tr>
<td>2.</td>
<td>1:2</td>
<td>PM</td>
<td>96.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>95.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>95.85</td>
</tr>
</tbody>
</table>

**Fourier-Transform Infrared (FTIR) Spectroscopy**

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Jasco FTIR-5300 spectrophotometer (Tokyo, Japan). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm\(^{-1}\) and the resolution was 4 cm\(^{-1}\).

**Differential Scanning Calorimetry (DSC)**

DSC analysis was performed using DSC-60 Shimadzu (Japan) on 2-4 mg samples (Sartorius BP 210 S electronic microbalance, Goettingen, Germany). Samples were heated in an open aluminium pans at a rate of 10°C per min\(^{-1}\). Indium was taken as reference and the hold temperature was maintained at 300°C.

**X-Ray Powder Diffractometry**

The Powder X-Ray Diffraction (PXRD) pattern of all ingredients and all binary systems were recorded using an automated Seimens X-ray diffractometer (Seimens D5005, IISc, Bangalore).

**Dissolution rate studies**

Table 2 summarizes % drug dissolved in 5 minutes (DP\(_5\)), dissolution efficiency at 15 minutes (DE\(_{15}\)), and dissolution efficiency at 60 minutes (DE\(_{60}\)) for Glimepiride and its binary systems with carriers. Dissolution test was conducted using USP XXIV apparatus at 75 rpm. The dissolution medium was 900 ml of simulated gastric fluid. Solid products, (both solid dispersions as well as physical mixtures), each containing 4 mg of drug were subjected to dissolution. Samples were withdrawn at fixed time intervals, filtered (pore size 0.22 μm) and assayed spectrophotometrically for drug content at 229 nm. Each test was performed in triplicate. T\(_{50}\) values were evaluated directly from the dissolution data. (Table 3).

**Tablet preparation and characterization**

Tablets each containing 4 mg of the drug in solid dispersions (in PEG-6000) were prepared by wet granulation method as per the formulae given in Table 4. The blend of powders was compressed into tablets on a multi station tablet machine (Cadmach) to a hardness of 3-4 Kg/sq.cm. Tablets were tested for uniformity of weight (IP-1996). Prepared tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche Friabilator), weight variation, and drug content.

Estimation of Glimepiride in phosphate buffered saline (pH 7.8) was accomplished spectrophotometrically using an double beam UV spectrophotometer. The excipients used in the dissolution did not interfere in the method. In vitro dissolution studies of tablets containing solid dispersion and commercial tablet of glimepiride were carried out in 900-mL simulated gastric fluid.
Result and Discussion

Fourier Transform Infrared (FTIR) Spectroscopy

IR spectra of Glimepiride and its binary systems with PEG are presented (Figure 1). Pure glimepiride spectra has a sharp characteristic peaks at 1700, 1710, 1375, and 610 cm⁻¹. All the above characteristic peaks appears in the spectra of all binary systems at same wavenumber indicating no modification or interaction between the drug and carrier.

Differential Scanning Calorimetry

Thermal behavior of pure drug and corresponding drug carrier system are depicted (Figure 2). The DSC curve of Glimepiride profiles a sharp endothermic peak ($T_{peak} = 210^\circ C$) corresponding to its melting point, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and with reduced intensity, in both physical mixtures as well as solid dispersions.

**Table 2:** Percentage Dissolution and Dissolution Efficiency of Glimepiride from Different Binary Systems in Comparison With Original Drug

<table>
<thead>
<tr>
<th>S. No.</th>
<th>System</th>
<th>DP₅ %</th>
<th>DE₁₅ %</th>
<th>DE₆₀ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Glimepiride</td>
<td>10.10±1.0</td>
<td>9.0±0.87</td>
<td>16.58±1.36</td>
</tr>
<tr>
<td>2.</td>
<td>PM1</td>
<td>25.30±2.3</td>
<td>22.50±1.91</td>
<td>36.80±2.84</td>
</tr>
<tr>
<td>3.</td>
<td>PM2</td>
<td>34.10±2.7</td>
<td>32.90±2.61</td>
<td>53.06±3.74</td>
</tr>
<tr>
<td>4.</td>
<td>SD1</td>
<td>70.10±3.8</td>
<td>63.45±4.34</td>
<td>85.62±5.37</td>
</tr>
<tr>
<td>5.</td>
<td>SD2</td>
<td>85.40±1.3</td>
<td>77.20±2.76</td>
<td>93.20±0.95</td>
</tr>
</tbody>
</table>

*Glimepiride is the drug, DP₅, % dissolved at 5 minutes; DE₁₅ and DE₆₀, dissolution efficiency at 15 and 60 minutes).
†All values are mean of 3 readings ± SD.

**Table 3:** T₅₀ values of the Marketed Tablets and the SD containing Tablet formulations of Glimepiride and PEG.

<table>
<thead>
<tr>
<th>Preparations</th>
<th>T₅₀ values (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketed</td>
<td>60</td>
</tr>
<tr>
<td>SD containing formulation</td>
<td>4</td>
</tr>
</tbody>
</table>

**Figure 1:** FTIR Spectra of Glimepiride and various binary systems with PEG

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This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data indicate no interaction between the components of binary system. The intensity of the peaks of solid dispersions was smaller than those of the pure drug and the corresponding physical mixture at same weight ratio. These results suggested that glimepiride became partially amorphous during dispersion into PEG matrix.

**X-ray Diffractometry**

X-ray diffractometry (XRD) spectra of pure drug and its binary systems with carriers are presented (Figure 3). The x-ray diffractogram of Glimepiride has sharp peaks at diffraction angles (2\(\theta\)) 13.8°, 17.01°, 18.1°, 19.1°, 21.2° and 26.5° showing a typical crystalline pattern.

The diffraction pattern of glimepiride showed that glimepiride has high crystallinity because of the presence of numerous peaks. PEG is found to be amorphous powder having no crystalline structures. The XRD peaks of crystalline glimepiride in all the physical mixtures were similar to those in the pure drug, indicating that the crystallinity of glimepiride did not change in the physical mixtures.

The crystalline structure of glimepiride in all the solid dispersions was different from that of the pure drug and the corresponding physical mixture as indicated from the differences in their XRD patterns. The number of peaks and the peak height was reduced in all the solid dispersions as the polymer concentration increased. These findings suggest that the glimepiride crystals got converted to the amorphous form in the polymer matrix in solid dispersions with higher weight.
ratios of the polymer. IR and DSC studies support the same hypothesis, as is confirmed by x-ray diffractometry.

**Dissolution rate studies**

Dissolution profiles of original drug crystals and drug-carrier binary systems are presented (Figure 4). As is evident from the graph that the solid dispersion (SD) technique has improved the dissolution rate of Glimepiride to a great extent, the results indicate that within the two solid dispersion ratios, SD2 (DE\textsubscript{60} = 93%) showed maximum enhancement in dissolution rate than the SD1. Moreover, SD1 also produced comparable results in terms of dissolution efficiency (DE\textsubscript{60} = 85%). Physical mixtures (PM) also improve dissolution rate by a significant extent as compared with drug alone (P < 0.001). The order of efficiencies of products based on DE values is SD2 > SD1 > PM2 > PM1 > Glimepiride. This enhancement of dissolution of Glimepiride from drug-carrier systems can be attributed to several factors. The mechanism of dissolution rate improvement from solid dispersion is reviewed by Ford (30). Lack of crystallinity, i.e., amorphization, increased wettability, dispersibility and particle size reduction are considered to be the important factors for the enhancement of dissolution rate. As indicative from the dissolution data of the physical mixtures, improvement could be attributed to higher wettability and dispersibility. Dry mixing of drugs with a hydrophilic carrier results in greater wetting and increases surface available for dissolution by reducing interfacial tension between the hydrophobic drug and the dissolution media. During dissolution studies, it was noted that drug-carrier system sinks immediately, whereas pure drug keeps floating on the surface for a longer time interval. Furthermore, kneading results in uniform distribution of drug in the polymer crust in a highly dispersed state. Thus, when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available. Moreover, other factors such as absence of aggregation and/or reagglomeration phenomenon during dissolution and particle size reduction could be attributed to a better dissolution profile (31).

**Tablet preparation and characterization**

On the basis of in vitro dissolution efficiency, the SD2 binary system was selected to formulate the tablet of glimepiride. Tablet characteristics of the optimized formulation (SD2) are tabulated in Table 4. In vitro dissolution studies of the optimized formulation confirmed the results obtained with the solid binary mixtures. SD2 tablets showed good dissolution efficiency (DE\textsubscript{60} = 81.38%) and rapid dissolution (DP\textsubscript{5} = 65.13%). When compared with commercial formulation (Figure 5), tablets formulated with the binary mixture (SD2) clearly performed better and a significant enhancement in dissolution characteristics was observed (P < 0.001). A significant increase in DP\textsubscript{60} (% dissolved in 60 minutes) was found with SD2 with respect to commercial formulation.

**Conclusion**

Finally, solid dispersions are known for their dissolution rate–enhancing properties of
poorly soluble drugs, such as CsA. (Leuner C, 2000; Sethia S, 2003; Kaushal AM, 2004) (11-13). The study shows that the dissolution rate of glimepiride may be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method. Hence glimepiride-PEG binary systems could be considered for formulation of fast-dissolving tablets of glimepiride.

**Acknowledgement**

Authors would like to thank Principal, PES college of Pharmacy, Bangalore for providing all the necessary facilities to carve out this research work. Further, authors would also like to thank Manipal college of Pharmacy for assisting in the DSC studies, and the Indian Institute of Sciences (IISc), Bangalore for conducting the XRD studies of the samples.

**Table 4** Composition for the SD2-containing Tablets:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glimepiride</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>PEG-6000</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Starch</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>Magnesium Sterate</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Lactose</td>
<td>113</td>
</tr>
</tbody>
</table>

**Table 5.** Percentage Dissolution and Dissolution Efficiency of Glimepiride from Tablets Containing solid dispersion (SD2) and Commercial Formulation A

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation</th>
<th>DP₅ %*</th>
<th>DP₁₅ %*</th>
<th>DE₆₀ %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SD2</td>
<td>65.13±4.81</td>
<td>76.41±4.91</td>
<td>81.38±2.94</td>
</tr>
<tr>
<td>2</td>
<td>Marketed product</td>
<td>24.49±1.91</td>
<td>32.37±4.12</td>
<td>43.16±3.16</td>
</tr>
</tbody>
</table>

*All determinations are mean of 3 readings ± SD. DP₅ and DP₁₅, % dissolved at 5 minutes and 60 minutes respectively, DE₆₀, dissolution efficiency in 60 minutes.
References


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