SURFACE SOLID DISPERSION OF GLIMEPIRIDE FOR ENHANCEMENT OF DISSOLUTION RATE

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ABSTRACT: Surface solid dispersions using water-insoluble carriers like crospovidone, croscarmellose sodium, sodium starch glycolate, pre-gelatinized starch, potato starch and Avicel PH 101 were investigated to enhance the dissolution rate of the glimepiride, a poorly water insoluble drug. The effect of various carriers on dissolution profile was studied using presence absence model. The surface solid dispersion on crospovidone with drug to carrier ratio of 1:19 showed highest dissolution rate with the dissolution efficiency of 81.89% in comparison to pure drug (22.88%) and physical mixture (35.96%). The surface solid dispersion on crospovidone was characterized by powder X-ray diffractometry, differential scanning calorimetry, Fourier transform infrared spectroscopy, gas chromatography and scanning electron microscopy. The optimized dispersion was formulated into tablets by wet granulation method. These tablets, apart from fulfilling the official and other specifications, exhibited higher rates of dissolution and dissolution efficiency values.

Key words: Glimepiride, Crospovidone, Croscarmellose, Sodium starch glycolate, Pre-gelatinized starch, Potato starch, Avicel PH 101, Surface Solid Dispersion., Presence absence model, Solvent deposition.

INTRODUCTION

The effort to improve dissolution and solubility of poorly and practically water insoluble drugs remains one of the most challenging tasks in drug development. Several methods have been introduced to increase dissolution rate and thereby oral absorption and bioavailability of such drugs¹. Among various approaches, solid dispersion has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability². Only a few solid dispersion products are however commercially available³,⁴. The surface solid dispersions can overcome some of the shortcomings of the conventional solid dispersions. The carriers used in surface solid dispersion are water-insoluble, porous materials and hydrophilic in nature. Many commonly used tablet excipients like microcrystalline cellulose, silicon dioxide, sodium starch glycolate, potato starch, croscarmellose, crospovidone have been used as carriers for surface solid dispersion. The release of drug from the carrier material depends on hydrophilic nature, particle size, porosity and surface area of the carriers⁵. Larger the surface area available for surface adsorption of the drug, better is the release rate. For those carriers that have larger surface area like silicon dioxide, smaller amount of carrier can give increased dissolution rate⁶. Surface solid dispersion technique has been extensively used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water soluble drugs...
Glimepiride is one of the third generation sulphonylurea, antidiabetic drug which stimulates insulin release. It is used for treatment of non-insulin-dependent diabetes mellitus. Glimepiride is classified under class II according to biopharmaceutical classification system. The drug shows low, pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37°C (≤0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. This poor solubility may cause poor dissolution and unpredicted bioavailability. However, only a few attempts have been made to improve its bioavailability. Literature cites reports of formation of inclusion complex with cyclodextrin and preparation of solid dispersions using water soluble carriers to improve the dissolution rate of glimepiride and subsequently its bioavailability.

Since the dissolution rate and extent for many drugs are influenced by the rate and extent of dissolution, it was postulated to improve the dissolution rate of glimepiride in vivo dissolution rate is rate limiting step in drug absorption. Surface solid dispersion (SSD) was selected as the method of choice since it would be easier in subsequent formulating and processing of tablets. The carriers used were crospovidone, croscarmellose, sodium starch glycolate, pregelatinized starch, Avicel PH 101 and potato starch. The SSDs were prepared at various drug-to-carrier weight ratios by solvent evaporation method. The optimized SSD was characterized and formulated into tablets.

**MATERIALS AND METHODS**

**MATERIALS**

Glimepiride, crospovidone, pregelatinised starch, croscarmellose sodium and Avicel PH 101 was obtained as gift sample from Dr.Reddy’s laboratories, Hyderabad, India. Pharmaceoical grades of sodium starch glycolate and other tablet excipients were procured from Nehal traders, Hyderabad, India. The solvents used were analytical reagent grade from SD Fine Chem, Mumbai, India.

**PREPARATION OF SURFACE SOLID DISPERSION AND PHYSICAL MIXTURE**

The SSDs of glimepiride and either carrier at 1:9 and 1:19 drug to carrier ratio were prepared by solvent evaporation method. The required amount of glimepiride was dissolved in dichloromethane. The carrier was dispersed in the drug solution. The solvent was removed using rotary evaporator, under reduced pressure at 40-45°C. The mass was passed through a 100 # sieve and the powders were subsequently dried at 40°C in a tray drier for 3hrs until a constant mass was obtained. The powder was stored in desiccators for further studies. Physical mixtures (PM) containing one part of drug and 19 parts of either carrier were prepared by manually shaking in a glass bottle for 30 minutes. The powders mixtures were sifted through 100# sieve and were freshly prepared prior to analysis. Results were confirmed on three batches for all carriers.

**PRESENCE ABSENCE MODEL**

A presence absence model for screening and studying the effect of carrier on dissolution profile was designed. Excipients like Avicel PH 101, potato starch, sodium starch glycolate, pregelatinized starch, croscarmellose and crospovidone (denoted as level A, B, C, D, E and F respectively) were screened for their suitability as carrier for preparation of SSD of glimepiride. The model was postulated as

\[ y = \beta_0 + \beta_A X_A + \beta_B X_B + \beta_C X_C + \beta_D X_D + \beta_E X_E + \beta_F X_F + \varepsilon \]  

(1)

The factor takes any one of the possible levels (A,B,….or F) and the coefficients are not independent but related to one another by,

\[ \beta_A + \beta_B + \beta_C + \beta_D + \beta_E + \beta_F = 0 \] and \[ X_A + X_B + X_C + X_D + X_E + X_F = 1 \]  

(2)

Estimates of coefficient in model are given by following equation

\[ b_0 = 1/6(y_1 + y_2 + y_3 + y_4 + y_5 + y_6) \]  

(3)

\[ b_A = y_1 - b_0; b_B = y_2 - b_0; b_C = y_3 - b_0; b_D = y_4 - b_0; b_E = y_5 - b_0; b_F = y_6 - b_0 \]  

(4)

where;

\[ y = \text{Experimental response, percent drug release at 15 minutes (t_{15})} \]

\[ \beta_0 = \text{Constant; true or theoretical response} \]

\[ \beta = \text{E(b) expectation of b where b is the coefficient of the model} \]

\[ \varepsilon = \text{Experimental error (random error)} \]
important carrier affecting the dissolution of the drug from SSD to be identified immediately.

**EFFECT OF BATCH SIZE AND CHANGE IN SOLVENT**

The optimized SSD on crospovidone (1:19) was also prepared using methanol as a solvent. The effect on dissolution profile and XRD pattern was determined. The batch size was increased to 10X using dichloromethane/methanol as solvent and the effect on dissolution profile was obtained.

**CALIBRATION CURVES BY BLANK CORRECTION METHOD**

Methods reported were employed to correct the interference of the carriers. Stock solutions were prepared by dissolving 100mg of drug in 100ml of methanol. Aliquots were diluted with appropriate buffer solution to obtain calibration curves in the region of 1 to 20 mcg/ml. To blank out interference of the carriers on UV measurements, stock suspension of the carriers were prepared in appropriate buffer solution. Aliquots of these suspensions were added to drug solutions so as to obtain a 1:19 drug-to-excipient ratio on dilution. The suspensions were suitably diluted, filtered through 0.45μm membrane filter before determination of the absorption at a λmax of 236nm. The blanks used were corresponding buffers plus appropriate carrier. The method obeyed Beer’s law in the concentration region of 1 to 20 mcg/ml. The method was precise (RSD < 1.2%) and accurate (RSD <1.72%) based on average of six independent determination.

**DISSOLUTION STUDIES**

In-vitro dissolution studies of samples were carried out as per conditions reported by using USP apparatus II paddle method by dispersed powder technique. Accurately weighed sample equivalent to 2mg of glimepiride was placed in a dissolution vessel and 900ml of 7.8pH phosphate buffer dissolution medium, maintained at 37±0.5°C was transferred into the vessel and rotated at 75 rpm. An aliquot of 10ml was withdrawn at different time intervals and filtered through 0.45μm membrane filter. An equal volume of fresh dissolution medium was immediately replaced. The concentration of glimepiride at each sampling time was analyzed spectrophotometrically at 236nm by blank correction method. Dissolution of each sample was performed 12 times and mean of all determinations was used to calculate drug release profile. Amount of drug released at 5, 15 and 30 minutes were calculated and tabulated as t5, t15 and t30 respectively. A model independent parameter, the dissolution efficiency (DE75) was employed to compare dissolution profiles of different samples. The dissolution data was fitted into first order, Hixson-Crowell cube root and Higuchi model to analyze the mechanism of the drug release rate kinetics from the prepared SSD and physical mixtures.

**ASSAY**

The amount of drug was determined by blank correction method. Accurately weighed samples (n=3) equivalent to 10mg of drug was taken in a 100ml volumetric flask, a volume of 20ml methanol was added and sonicated for 20min to dissolve the drug. The volume was made to 100ml with pH 7.8 buffer solution. The dispersion was filtered using 0.45μm membrane filter. A 10ml aliquot of the above solution was taken and diluted to 100ml with buffer solution. An equivalent quantity of carrier that would be present in the SSD sample was taken and treated in a manner similar to the sample. The absorbance of sample solution was determined at 236nm against carrier blank.

**FTIR SPECTROSCOPY**

FTIR spectra of drug, PM and SSD were obtained. About 5mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 cm⁻¹ to 625 cm⁻¹ in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

**SOLVENT RESIDUE**

The residual solvents; dichloromethane and methanol were monitored by gas chromatography on a Agilent GC 6890N with 7694E Headspace sampler, fitted with flame ionization detector. Packed column was BD-624 capillary column. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. Temperature of oven was 60°C injection port 140°C and detector 250°C. Oven was programmed at 5°C/min for 10min., 15°C/min upto 250°C.

**POWDER X-RAY DIFFRACTION ANALYSIS (XRD)**

X-ray diffraction of drug, physical mixture and SSD prepared using dichloromethane and methanol as solvents were obtained on a D-5000 Siemens X-ray diffractometer, using Cu Kα radiation (wave length=1.5406Å). The data were recorded over a scanning 2θ range of 2θ to 65° at step time of 0.045 steps/0.5 sec.
DIFFERENTIAL THERMAL ANALYSIS (DSC)

dsc analysis of drug, PM and SSD prepared using dichloromethane as solvent were obtained on a PerkinElmer Thermal Analyzer equipped with a monitor and printer. The instrument was calibrated with indium standard. Accurately weighed about 3.5mg of sample was placed in an open, flat bottom, aluminum sample pans. Thermo grams were obtained by heating the sample at a constant rate 10.00°C/min. A dry purge of nitrogen gas (20 ml/min) was used for all runs.

SCANNING ELECTRON MICROSCOPY (SEM)

The surface morphology of glimepiride SSD on crospovidone (1:19) and PM were observed by scanning electron microscope (SEM). Beforehand, the samples were mounted on alumina stubs using double adhesive tape, coated with gold in Hitachi HUS-GB vacuum coating unit and observed in Hitachi S-300 N Scanning electronic microscope at a voltage of 10 Kv.

PREPARATION AND EVALUATION OF TABLETS

Based on the dissolution profile, glimepiride SSD on crospovidone (1:19) was selected as the carrier for the preparation of tablets of surface solid dispersion. Tablets were formulated by wet granulation method using 10% of starch paste and compressed on a 10 station rotary tablet compression machine. Other ingredients incorporated in the tablets were lactose 30%, microcrystalline cellulose 17%, talc 2% and magnesium stearate 1%. The tablets prepared were evaluated for parameters like weight variation, hardness, friability, disintegration time, assay, content uniformity, drug release and compared with marketed glimepiride tablet. Results were confirmed on three independent batches.

RESULTS AND DISCUSSION

All SSD and the physical mixtures were found to be fine and free flowing powders. Low coefficient of variation (2-4%) in the percent glimepiride content of the preparations indicated uniformity of the drug content in each batch prepared. The content of drug in SSD was slightly below the theoretical values (around 96%), probably due to solvent evaporative losses. These losses were much higher when lower carrier ratios were used hence SSD were prepared with higher carrier ratios. Glimepiride showed very poor dissolution rate in all basic pH solutions (table 1). The drug took approximately 4 hours to release 100% of the amount and DE₃₀ was only around 16 to 23%. All carriers studied displayed enhancement in dissolution rate. The improvement in dissolution was marginal for Avicel PH 101 and potato starch. At 1:19 ratio, carriers like pre-

The improvement in dissolution was marginal for Avicel carriers studied displayed enhancement in dissolution rate. The solvent employed in the preparation of SSD was found to have a significant impact on the dissolution profile of glimepiride. A 10% reduction in the values of t₅, t₁₅ and DE₃₀ was observed when methanol was used as a solvent to prepare SSD (table 1). The reason attributed to this change could be due to slightly less solubility of glimepiride in
methanol. This study was conducted to assess whether chlorinated solvent like dichloromethane can be replaced with less toxic solvents like methanol. However, no significant change in assay, content uniformity and dissolution profile was noticed when the batch size was increased, suggesting its feasibility for scale up.

FTIR spectra of glimepiride (figure 3) revealed the presence of peaks at 3369 and 3288 cm\(^{-1}\) due to N-H stretch for urea, peaks at 1345 and 1153 cm\(^{-1}\) corresponding to the sulphonamide group and peaks at 1708 and 1674 cm\(^{-1}\) corresponding to carbonyl group. The IR spectra of physical mixture matched with those of drug and crospovidone when superimposed. No specific conclusions could be drawn from the IR spectra of the SSD. The spectra predominantly revealed many peaks of crospovidone. The characteristic N-H stretching mode of amide exhibited a broadening. Other peaks showed overlapping with spectra of crospovidone. Further characterization was done using XRD and DTA to determine the interaction.

XRD of SSD (figure 4) prepared by using dichloromethane and methanol revealed a reduction in peak intensity when compared with XRD of plain drug and physical mixture. The characteristic peaks identified in the drug XRD or the physical mixture was not detected. Decrease in peak intensities was probably due to dilution and may be due to some change in crystal habit or conversion to an amorphous form. No new peak was detected, hence the possibility of any conversion to polymorphic form was ruled out. SSD prepared using dichloromethane as solvent showed reduced crystalline properties when compared to SSD of methanol. This could account for increased dissolution efficiency of the SSD prepared with dichloromethane when compared to SSD prepared using methanol as solvent.

DSC of the pure drug showed a sharp peak at 217.28° C corresponding to the melting point of glimepiride (figure 5). The peak showed an onset at 214.43°C. The enthalpy change \( \Delta H \) was calculated as 139.2 J/gm. Crospovidone showed a broad peak at 78.60°C with peak onset from 40.48°C. The \( \Delta H \) for this peak was calculated as 332.29 J/gm. DSC of SSD showed peaks characteristic of crospovidone and the drug with no additional peaks. However, the peak of crospovidone had shifted to 91.05°C, while the drug showed a sharp melting point peak at 217.32°C and with peak onset from 213.04°C. From DSC, it can be concluded that drug and carrier showed no interaction.

Residual solvent concentration in SSD of glimepiride prepared using dichloromethane and methanol was performed by gas chromatography. The levels of methanol and dichloromethane were below detectable limits (LOD was 10ppm and 1ppm respectively). Hence, it can be concluded that solvent deposition method was efficient in removal of solvents from SSD well below permissible levels. The SEM of physical mixture showed dusting of drug powder on the carrier, while the SEM of surface solid dispersion showed a more porous nature of carrier with fine crystals of drug deposited on it when compared to physical mixture. This particular change in structure may be one of the causes for increase in dissolution rate (figure 6).

Tablets containing SSD of glimepiride: crospovidone in 1:19 ratio were prepared by wet granulation technique using starch paste as a binder. The tablets complied with the official specifications. The results of various quality control parameters evaluated for the prepared tablets were, disintegration time (1.45 min), hardness (5-6 kg/cm\(^2\)), friability (0.8%), weight variation (102.25), assay (101.5%). The dissolution profile of these tablets prepared using SSD was comparable with plain SSD and marketed product (table 1).

CONCLUSIONS

Surface solid dispersions technique was successful in improving the dissolution rate of glimepiride. The nature and the amount of the carrier used played an important role in the enhancement of the dissolution rate. This surface solid dispersion could then be incorporated successfully, into a tablet by conventional wet granulation technique.
Table 1: Dissolution parameters of glimepiride from Surface solid dispersions, Physical Mixtures and formulated tablets

<table>
<thead>
<tr>
<th>Excipient Formulation</th>
<th>Drug Excipient ratio</th>
<th>t_{5} ± SD</th>
<th>t_{15} ± SD</th>
<th>t_{30} ± SD</th>
<th>DE_{30}</th>
<th>K x 10^{3} (min^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride (^1) Pure, untreated</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17.20±0.91</td>
<td>30.98±0.91</td>
<td>16.46 7.9(0.9882)</td>
</tr>
<tr>
<td>Glimepiride (^2) Pure, untreated</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.22±1.38</td>
<td>33.12±0.54</td>
<td>18.85 8.7(0.9820)</td>
</tr>
<tr>
<td>Glimepiride (^3) Pure, untreated</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>26.56±1.38</td>
<td>35.91±2.63</td>
<td>22.88 9.2(0.9827)</td>
</tr>
<tr>
<td>Avicel PH101 SSD</td>
<td>1:9</td>
<td>18.50±4.34</td>
<td>26.58±5.59</td>
<td>40.94±4.31</td>
<td>24.88 11.4(0.9863)</td>
<td></td>
</tr>
<tr>
<td>Potato Starch SSD</td>
<td>1:9</td>
<td>20.82±4.51</td>
<td>29.65±5.14</td>
<td>48.18±6.21</td>
<td>29.91 16.8(0.9510)</td>
<td></td>
</tr>
<tr>
<td>1:19</td>
<td>18.50±4.34</td>
<td>26.58±5.59</td>
<td>40.94±4.31</td>
<td>24.88 11.4(0.9863)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>1:19</td>
<td>20.82±1.28</td>
<td>28.13±1.95</td>
<td>47.43±0.54</td>
<td>29.60 12.2(0.9380)</td>
<td></td>
</tr>
<tr>
<td>Pre gelatin starch SSD</td>
<td>1:9</td>
<td>28.07±1.65</td>
<td>40.10±1.20</td>
<td>56.77±1.60</td>
<td>38.68 17.1(0.9535)</td>
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</tr>
<tr>
<td>1:19</td>
<td>43.91±2.40</td>
<td>52.86±2.76</td>
<td>64.64±4.03</td>
<td>48.94 19.1(0.9187)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycolate SSD</td>
<td>1:9</td>
<td>39.02±2.90</td>
<td>51.71±2.52</td>
<td>65.15±4.15</td>
<td>47.56 19.1(0.9178)</td>
<td></td>
</tr>
<tr>
<td>1:19</td>
<td>45.84±3.49</td>
<td>54.93±3.60</td>
<td>69.18±5.09</td>
<td>51.31 25.2(0.9574)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>1:19</td>
<td>14.49±1.28</td>
<td>24.83±1.31</td>
<td>43.94±1.34</td>
<td>24.77 13.6(0.9773)</td>
<td></td>
</tr>
<tr>
<td>Croskarmelllose SSD</td>
<td>1:9</td>
<td>49.65±3.36</td>
<td>67.02±4.14</td>
<td>86.44±4.83</td>
<td>62.23 44.8(0.9721)</td>
<td></td>
</tr>
<tr>
<td>1:19</td>
<td>61.77±3.13</td>
<td>72.65±3.10</td>
<td>87.56±2.64</td>
<td>67.83 53.9(0.9772)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>1:19</td>
<td>20.37±1.88</td>
<td>31.32±2.06</td>
<td>43.95±1.86</td>
<td>29.60 12.4(0.9611)</td>
<td></td>
</tr>
<tr>
<td>Crospovidone SSD</td>
<td>1:9</td>
<td>62.74±2.26</td>
<td>72.37±3.55</td>
<td>87.08±3.62</td>
<td>68.61 45.6(0.9635)</td>
<td></td>
</tr>
<tr>
<td>1:19</td>
<td>81.21±1.54</td>
<td>88.48±1.66</td>
<td>95.70±3.92</td>
<td>81.89 73.3(0.9253)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:19(m)</td>
<td>72.28±3.00</td>
<td>82.53±4.15</td>
<td>92.41±2.42</td>
<td>75.59 59.9(0.9365)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>1:19</td>
<td>27.96±3.94</td>
<td>37.68±3.23</td>
<td>52.21±2.16</td>
<td>35.96 16.1(0.9632)</td>
<td></td>
</tr>
<tr>
<td>Tablets</td>
<td>1:19</td>
<td>75.51±3.66</td>
<td>88.62±1.61</td>
<td>99.69±2.71</td>
<td>84.66 207.5(0.9720)</td>
<td></td>
</tr>
<tr>
<td>Marketed Tablets -</td>
<td>83.30±2.60</td>
<td>96.26±2.56</td>
<td>102.52±5.40</td>
<td>87.65 200.3(0.9550)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1, 2, 3 – dissolution performed in phosphate buffer media of pH 6.8, 7.4 and 7.8 respectively.
PM- physical mixture, SSD- Surface solid dispersion, (m)- SSD prepared with methanol as solvent.
SD – standard deviation, Figures in brackets are correlation coefficient (r) values.

Figure 1: In vitro dissolution profile of glimepiride, glimepiride: crospovidone surface solid dispersion (SSD) at 1:9 and 1:19 ratio and physical mixtures (PM) of glimepiride and crospovidone (1:19)
Figure 2: Pareto chart for effect of carrier on surface solid dispersion of glimepiride at 1:19 drug carrier ratio. A - Avicel PH 101, B - Potato starch, C - Pre gelatin starch, D - Sodium Starch Glycollate, E - Croscarmellose, F - Crospovidone.

Figure 3: FT-IR of glimepiride formulations. KEY: 1 - glimepiride; 2 - crospovidone; 3 - glimepiride: crospovidone (1:19) surface solid dispersion; 4 - glimepiride: crospovidone (1:19) physical mixture.
Figure 4: PXRD of glimepiride formulations. KEY: 1 - glimepiride; 2 - crospovidone; 3 - glimepiride: crospovidone (1:19) physical mixture; 4 - glimepiride: crospovidone (1:19) surface solid dispersion using dichloromethane; 5 - glimepiride: crospovidone (1:19) surface solid dispersion using methanol.

Figure 5: DSC thermograms of glimepiride (1), crospovidone (2) and SSD of glimepiride and crospovidone at 1:19 ratio (3).
Figure6: Scanning Electron Microscopy of glimepiride: crospovidone (1:19) formulations. A- physical mixture at 250X, B- physical mixture at 5000X, C- surface solid dispersion at 250X and D- surface solid dispersion at 2000X.

REFERENCES


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