Development and \textit{in-vitro} evaluation of Furosemide Solid Dispersion using different Water Soluble Carriers

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Keywords: Furosemide, PVP-K30, PEG6000, Solid dispersion

Objective: The objective of the present investigation was to improve solubility and dissolution characteristics of Furosemide, which might offer improved bioavailability. The bioavailability of the drug when taken orally is limited by the relatively low solubility. Furosemide is a loop diuretic (a ‘water pill’) used to treat congestive heart failure, oedema and sometimes hypertension.

Method: The solid dispersion of Furosemide was prepared by Solvent evaporation method by using 1:1, 1:2 and 1:3 ratios of drug and polymers (PVP K-30, PEG6000). The solid dispersion was prepared by solvent evaporation method. The prepared solid dispersion was evaluated for various parameters like uniformity of drug content, \textit{in-vitro} drug release and short term stability studies.

Results: The prepared dispersion showed marked increase in the dissolution rate of Furosemide than that of pure drug and the \textit{in vitro} release studies revealed that there was an improvement in the dissolution characteristics of drug when prepared as solid dispersions. Solid dispersion with PEG 6000 and PVPK30 gave better rate and extent of dissolution.

Conclusion: It can be concluded that the solid dispersions prepared with PEG6000 and PVP K30 and among all the formulations, F6 has highest solubility and in vitro dissolution rate.

Abstract:

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Introduction

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. Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract. The dissolution characteristics of poorly soluble drugs can be enhanced by several methods. Solid dispersion is one of the effective and widely used techniques for dissolution enhancement. \cite{1-3}
The formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilisation, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs, there is practical limitation of these techniques. In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome. This method, which was later termed as solid dispersion. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. [4-7]

Hence present study was focused to enhance the solubility of Furosemide by formulating into solid dispersion using PEG 6000 and PVP K 30. Furosemide is a loop diuretic (a ‘water pill’) used to treat congestive heart failure, oedema and sometimes hypertension. The major drawback in the therapeutic use and efficacy of Furosemide as oral dosage form is its very low aqueous solubility because of its hydrophobic nature. Poor aqueous solubility and slow dissolution rate of the drug leads to low oral bioavailability consequently irreproducible. Therefore, a better oral formulation was developed by increasing the water solubility of drug. [8]

Materials and Methods

Materials

Furosemide was gift sample from Lupine pharmaceutical industries Bhopal India. PVPK30 and PEG 6000 and all other reagents used were of analytical grade and obtained from S.D. Fine Chemicals, Mumbai, India

Methods

Preparation of solid dispersions by solvent evaporation method

Furosemide solid dispersions were prepared by solvent evaporation method using carriers (PVPK30 and PEG 6000). In the solvent evaporation method, minimal amount of methanol was used to dissolve Furosemide and the carriers by continuous stirring with a magnetic stirrer for an hour at room temperature. Methanol was removed under reduced pressure using a rotary evaporator kept at 40°C until all the solvents were evaporated. The solid dispersions formed were further dried in an oven at 40°C for 24 h.

All the resulting solid dispersions were scraped, pulverized in a mortar and sieved through a 60 mesh sieve. Following that, all solid dispersions were stored in amber glass vials and kept in the dessicator at 20±1°C until further analysis. [9-15]

Table 1: Formulation of Solid Dispersion

<table>
<thead>
<tr>
<th>Formulation</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug(mg)</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>PVP K-30 (mg)</td>
<td>80</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>PEG-6000 (mg)</td>
<td>-</td>
<td>-</td>
<td>80</td>
<td>160</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

Evaluation of Solid Dispersion

Solubility studies [16-18]

These studies were performed by taking in which the pure drug Furosemide and accurate weighed solid dispersion formulation which was theoretically equivalent to 80 mg of Furosemide added to a volume of distilled water at room temperature and gradually increases the volume of distilled water until it was not completely dissolves. The drug amount per part of volume was determined by using this technique. The studies were conducted in triplicate and whole process was repeated with different buffer solution and 0.1NHCl. The solubility of various dispersions was given in Table 3.

% Drug content [19-21]

The SD equivalents to 80 mg of Furosemide were taken and dissolved in methanol and filtered using 0.45 μm membrane filters. Then the filtrate was suitably diluted with buffer and drug content was determined by UV spectrophotometer at 276 nm with that of standard solution containing 80 mg of pure drug. The percentage of drug present in the solid dispersions was calculated by using following formula:

\[
\text{% Drug content} = \frac{\text{Conc. in formulation (practical)}}{\text{Total conc. in formulation (theoretical)}} \times 100
\]

In-vitro dissolution studies [22-24]

Dissolution rate studies of pure Furosemide and Furosemide solid dispersions were performed in Remi dissolution test apparatus with rotating paddles at 50 rpm employing 900ml of pH 4.5, 0.05M acetate buffer and the temperature was maintained at 37 ± 0.5 °C throughout the experiment. 5 ml of the samples were withdrawn at various time intervals. The absorbance of the samples was measured at 276 nm for determining the amount of drug release at various intervals. Each time the equal volume of buffer was added for maintaining the constant volume of dissolution medium. The dissolution studies were carried out with 10 mg of pure drug and an equivalent amount of preparations.
Aliquots of 5 mL were withdrawn at specified time intervals of 2, 4, 6, 8, 10, 20, 30, 40, 50, and 60 min and replaced with fresh media. The samples were filtered with Whatman filter paper (0.12 µm) and analysed spectrophotometrically at 276 nm for the dissolved drug.

Stability study [25]
All the formulations (F1 to F6) were kept at intermediate and accelerated conditions in stability chamber in the closed container. A portion of the sample was taken out at 0, 1 and 3 months and interval and tested them for drug content.

Table 2: Different stability study condition per the ICH guideline

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage Condition</th>
<th>Minimum time period</th>
<th>Sampling Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>30°C ± 2°C/65% RH ± 5% RH</td>
<td>3 months</td>
<td>0, 1 &amp; 3 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C/75% RH ± 5% RH</td>
<td>3 months</td>
<td>0, 1 &amp; 3 months</td>
</tr>
</tbody>
</table>

Results and Discussion

Solubility studies

Table 3: Solubility studies of Furosemide formulations (solubility in g/mL)

<table>
<thead>
<tr>
<th>pH</th>
<th>Pure drug</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1N HCl 1.2</td>
<td>4.37±0.13</td>
<td>15.84±0.21</td>
<td>28.43±0.13</td>
<td>38.67±0.15</td>
<td>50.43±0.14</td>
<td>60.96±0.16</td>
<td>75.36±0.15</td>
</tr>
<tr>
<td>0.05M Acetate Buffer 4.6</td>
<td>11.36±0.11</td>
<td>25.14±0.14</td>
<td>35.56±0.16</td>
<td>39.45±0.17</td>
<td>49.32±0.16</td>
<td>60.34±0.18</td>
<td>78.45±0.15</td>
</tr>
<tr>
<td>Phosphate Buffer 6.8</td>
<td>5.34±0.16</td>
<td>23.58±0.15</td>
<td>24.46±0.16</td>
<td>35.76±0.18</td>
<td>48.14±0.19</td>
<td>61.33±0.18</td>
<td>69.45±0.17</td>
</tr>
<tr>
<td>Phosphate Buffer 7.4</td>
<td>4.47±0.14</td>
<td>18.75±0.15</td>
<td>21.83±0.16</td>
<td>33.45±0.17</td>
<td>40.23±0.18</td>
<td>52.91±0.18</td>
<td>55.67±0.18</td>
</tr>
<tr>
<td>Water</td>
<td>0.32±0.11</td>
<td>6.58±0.13</td>
<td>14.64±0.12</td>
<td>18.53±0.14</td>
<td>23.54±0.15</td>
<td>28.67±0.17</td>
<td>33.12±0.18</td>
</tr>
</tbody>
</table>

% Drug content

The % Drug content of Furosemide solid dispersion was found to be maximum for F6 Formulation.

Table 4: Percentage drug content of formulations

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>82.45±3.5</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>84.67±4.23</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>86.23±3.45</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>88.35±5.23</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>92.85±3.65</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>93.59±6.26</td>
</tr>
</tbody>
</table>

n=3

In-vitro dissolution studies

The F6 formulation was found to produce maximum drug release of 64.56% after 60 min.

Stability study

The result in Table 5 shows no significant changes in appearance and in drug content. The highest percentage of degradation was observed in formulation F-6 after 3 months of storing in accelerated condition is found 1.89%. Hence it can be said that the formulations are stable at wide variation in storage condition for long time

Fig. 1: Drug release of pure drug, F1, F2, F3, F4, F5, and F6, formulation
Table 5: Drug content analysis after stability study of intermediate (IM) and accelerated (AC) conditions

<table>
<thead>
<tr>
<th>Formulation</th>
<th>0 months</th>
<th>1 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM</td>
<td>AC</td>
<td>IM</td>
</tr>
<tr>
<td>F1</td>
<td>82.45</td>
<td>82.45</td>
<td>82.22</td>
</tr>
<tr>
<td>F2</td>
<td>84.67</td>
<td>84.67</td>
<td>84.57</td>
</tr>
<tr>
<td>F3</td>
<td>86.23</td>
<td>86.23</td>
<td>86.14</td>
</tr>
<tr>
<td>F4</td>
<td>88.35</td>
<td>88.35</td>
<td>88.23</td>
</tr>
<tr>
<td>F5</td>
<td>92.85</td>
<td>92.85</td>
<td>92.75</td>
</tr>
<tr>
<td>F6</td>
<td>93.59</td>
<td>93.59</td>
<td>93.44</td>
</tr>
</tbody>
</table>

Conclusion

In conclusion, development and characterization of solid dispersion of Furosemide prepared with PVPK30 and PEG600 showed better solubility and drug content by solvent evaporation method. The in-vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure Furosemide. It was evident that the solid dispersion (SD) technique had improved the dissolution rate of drug. Finally, it could be concluded that solid dispersion of Furosemide using hydrophilic polymers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic bioavailability. In addition, these results indicate that dispersion technique can be an effective delivery system to improve the bioavailability of poor water soluble drugs like Furosemide.

References


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