ENHANCEMENT OF SOLUBILITY OF BICALUTAMIDE DRUG USING SOLID DISPERSION TECHNIQUE

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ABSTRACT
Bicalutamide is poorly soluble drug which is non-steroidal androgen having pKa 12. Aqueous in vitro solubility of bicalutamide is low at 50 μg/mL at pH 7 and 37°C. The drug exhibits low bioavailability related to its poor water solubility. Therefore, bicalutamide bioavailability can be improved by increasing its solubility. Solid dispersion technique is most effective technique to improve solubility of drug. Solid dispersions of bicalutamide were prepared by using solvent evaporation technique using HPMC and surfactant like SLS. Solubilities were calculated by using in vitro dissolution technique. 1:4 drug: HPMC ratio was found efficient with 2% SLS concentration.

Keywords: Bicalutamide, Solid Dispersion, HPMC, SLS.

INTRODUCTION
Chiou and Riegelman defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”.

Enhancement of bioavailability of hydrophobic drugs is one of the major challenges in drug development. Of the plethora of pharmaceutical technologies available to address this issue, solid dispersion is one of the useful methods for the dispersion of the drug into an inert, hydrophilic polymer matrix[1,2]. Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability of a range of hydrophobic drugs. Although a large number of studies have been published but the mechanisms underpinning the observed enhancement of the rate of drug release is not yet understood[3,4].

The poorly water soluble drugs are characterised by insufficient bioavailability (low dissolution rates) and absorption in the gastro-intestinal tract. Different methods have been used to increase the dissolution and bioavailability of poorly water soluble drugs including micronisation the use of surfactants[5] and the formation of solid...
dispersions. Solid dispersions display an enhanced solubility of drug because of the conversion of the drug’s crystal lattice into an amorphous form, particle size reduction and increased wettability by the hydrophilic polymer. Therefore, the same pharmacological results can be obtained from a reduced amount of drug given to the patient\(^{[6]}\).

Various methods used for preparation of solid dispersion system. These methods are given below.

1. Melting method.
2. Solvent method.
3. Melting solvent method (melt evaporation).
4. Melt extrusion methods.
5. Lyophilization techniques.
7. Electrospinning.

Bicalutamide is poorly soluble drug which is non-steroidal androgen having pKa 12. Aqueous in vitro solubility of bicalutamide is low at 50 g/mL at pH 7 and 37°C. The drug exhibits low bioavailability related to its poor water solubility. Bicalutamide is a BCS class II compound, i.e., water-insoluble, lipophilic, and highly permeable. Therefore, bicalutamide bioavailability can be improved by increasing its solubility\(^{[7-9]}\).

In our present study, we have formulated solid dispersions of bicalutamide and Hydroxy Propyl Methyl Cellulose (HPMC) with 2% SLS concentration. We have examined improved solubility of this Solid dispersion using in-vitro dissolution studies.

MATERIALS AND METHODS:

Bicalutamide was obtained as free gift sample from Khandelwal Laboratories, Thane, India. Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Lauryl Sulphate (SLS), Ethanol and Acetone were purchased from SD fine chemicals, Mumbai. All ingredients used were of Analytical grade quality.
FORMULATION:

Preparation of solid dispersion of Bicalutamide:

Solid dispersions of Bicalutamide were prepared by using solvent evaporation technique using water ethanol system and acetone. Each formulation of solid dispersion of Bicalutamide were prepared by varying Hydroxy Propyl Methyl Cellulose (HPMC) concentration and keeping Sodium Lauryl Sulphate (SLS) concentration constant (2%). Solid dispersions were prepared in the ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 of Drug: HPMC and 2% SLS of total weight of mixture. Quantities are given in table 1.

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Drug: Excipient</th>
<th>Quantity taken in gm.</th>
<th>SLS in 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bicalutamide</td>
<td>HPMC</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>1:1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>1:2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>3.</td>
<td>1:3</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>4.</td>
<td>1:4</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>5.</td>
<td>1:5</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
</table>

Bicalutamide was dissolved in Acetone (15%) till clear solution appears. HPMC were dissolved separately in water: ethanol (3:1) system till clear solution appears. Then both solutions mixed and SLS was added to above solution. Then volume was adjusted with either water-ethanol mixture or acetone until the formation of a clear solution, if necessary. The solvents were evaporated at 50°C under reduced pressure in a rota evaporator and they were further dried in desiccators over silica gel for 24 hrs. to remove all the residual solvents. The dried mass were collected and passed through 60 #, and packed in a separate closed container.

Preparation of physical mixture:

The physical mixture of drug and polymer was prepared by simple mixing in the mortar in the same ratios as solid dispersion taken. So, the physical mixture of bicalutamide: HPMC in 1:1, 1:2, 1:3, 1:4 and 1:5 ratio taken in separate morters. SLS was added to each mortar ie 0.2, 0.3, 0.4, 0.5, and 0.6 respectively. The above mixtures
mixed properly using pestle. The dry powder was collected and stored in packed container.

This physical mixture and plain drug is used to compare dissolution profile of respected solid dispersion.

EVALUATION OF SOLID DISPERSION:

Determination of Percentage yield:
The yield of the final solid dispersion of all ratios was calculated by using the final weight of solid dispersion after drying and the initial weight of drug and polymer used for preparation of solid dispersion.

The following formula is used for calculation of percent yield:

\[
\% \text{ yield} = \frac{\text{practical weight of solid dispersion}}{\text{theoretical weight of solid dispersion}} \times 100
\]

Determination of drug content:

Powdered solid dispersion and physical mixture equivalent to 10 mg bicalutamide drug accurately weighed and transferred to 100 ml volumetric flask. About 20 ml ethanol added and flask shaken gently to dissolve complete residue. Then make up volume with ethanol which gives resulting solution of 100µg/ml. 1 ml of resulting solution was taken in 10 ml volumetric flask and volume was make up with ethanol. The absorbance of this solution was taken at 272 nm in UV spectrophotometer. And drug content was determined.

Determination of solubility:

The solubility of solid dispersions of bicalutamide was determined in the distilled water. Excess amount of bicalutamide solid dispersion was added to the 10 ml of distilled water in beaker. These solutions were stirred on magnetic stirrer for 4 hours. Due to this equilibrium is achieved. Then this solution was centrifuged at 2000 rpm for 10 min. The supernatant solution was filtered by using whatman filter paper grade 41. One ml of this filtered solution was taken and diluted with respective medium and absorbance was taken on UV spectrophotometer at 272 nm.
In-vitro dissolution studies:
Dissolution studies of solid dispersion were performed separately in 900ml of medium 0.1 N HCl. This study was carried out by using USP apparatus Type II (Paddle). RPM of paddle is set at 50 RPM and temperature condition kept maintained at 37°C ± 0.5 °C. The samples were estimated for amount of bicalutamide dissolved by measuring their absorbance at 272nm. Samples were taken at time interval of 5, 15, 30, 45, 60, 75, 90 min.
Dissolution studies of plain drug and physical mixtures also performed as per above procedure.

RESULT AND DISCUSSION:

Percentage yield:
Percentage yield of solid dispersions were calculated and reported in table 2. The highest percentage yield was found in solid dispersion having ratios of 1:4. Ratio 1:5 has slightly lower percentage yield than 1:4.

**TABLE 2: PERCENTAGE YIELDS OF SOLID DISPERSIONS.**

<table>
<thead>
<tr>
<th>Sr no.</th>
<th>Solid dispersion</th>
<th>Percentage yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>94.43</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>94.56</td>
</tr>
<tr>
<td>3</td>
<td>1:3</td>
<td>96.78</td>
</tr>
<tr>
<td>4</td>
<td>1:4</td>
<td>97.89</td>
</tr>
<tr>
<td>5</td>
<td>1:5</td>
<td>97.53</td>
</tr>
</tbody>
</table>

Drug content:
Drug content was determined as per procedure and reported in the table 3. Highest drug content was observed in the ratio 1:4 and 1:5 solid dispersions.
### TABLE 3: DRUG CONTENT OF SOLID DISPERSIONS AND PHYSICAL MIXTURES.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Drug: solubilizers ratio</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Solid dispersion</td>
</tr>
<tr>
<td>1.</td>
<td>1:1</td>
<td>98.8</td>
</tr>
<tr>
<td>2.</td>
<td>1:2</td>
<td>99.34</td>
</tr>
<tr>
<td>3.</td>
<td>1:3</td>
<td>99.48</td>
</tr>
<tr>
<td>4.</td>
<td>1:4</td>
<td>99.86</td>
</tr>
<tr>
<td>5.</td>
<td>1:5</td>
<td>99.72</td>
</tr>
</tbody>
</table>

Solubility:
Solubility study of solid dispersion was done as per procedure and obtained results were reported in table 4. Maximum solubility was observed in the solid dispersions having ratio 1:4 and 1:5.

### TABLE 4: SOLUBILITIES OF SOLID DISPERSIONS.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Solid dispersion</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>0.23</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
<td>1:3</td>
<td>0.67</td>
</tr>
<tr>
<td>4</td>
<td>1:4</td>
<td>0.71</td>
</tr>
<tr>
<td>5</td>
<td>1:5</td>
<td>0.69</td>
</tr>
</tbody>
</table>

In-vitro dissolution studies:
Dissolution studies of plain drug, Physical mixtures and solid dispersions were performed as per procedure. The dissolution profile showed in Graph 1, Graph 2 and Graph 3 respectively.
Graph 1
Dissolution profile of plain bicalutamide drug.

Graph 2
Dissolution profiles of Solid dispersions
According to these results, pure drug released less than 42% of active content at the end of the 3 hrs. because of its poor solubility, at the same time physical mixtures of different ratios were also released the active content less than 64% at the end of 1.5 hrs., but the solid dispersion having ratio 1:4 released active content more than 90% at the end of the 1 hr. indicating that the solubility was significantly increased by solid dispersion method.

CONCLUSION:
Solid dispersion of bicalutamide and HPMC (1:4) prepared by solvent evaporation method exhibit higher rate of dissolution as compared to plain drug and Physical mixtures. The results obtained by different characterization techniques clearly indicate that the solid dispersion 1:4 was most promising combination for solubility enhancement. Finally the results concluded that, bicalutamide- HPMC solid dispersion technique results in increase in the solubility and dissolution rate of the bicalutamide, suggesting a possible enhancement of its oral bioavailability. The dispersion of bicalutamide and HPMC lends an ample credence for better therapeutic efficacy.

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REFERENCES:


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