STUDY OF DISSOLUTION IMPROVEMENT OF VARIOUS POORLY WATER SOLUBLE DRUGS BY SOLID DISPERSION MIXING WITH HPMC 6CPS AND PEG 6000
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Abstract
The aim of this work was to improve solubility of some poorly water soluble drugs (Atorvastatin, Carbamazepine, Etoricoxib, Fenofibrate, Furosemide, Glipizide, Ibuprofen and Spironolactone) by making solid dispersions. HPMC 6cps and PEG 6000 were used to improve the solubility. Dissolution studies were performed by preparing solid dispersions by solvent method. After studying all the results it can be said that PEG 6000 is a good vehicle to enhance the solubility of poorly water soluble drugs. Among drugs, Atorvastatin, Carbamazepine, Furosemide and Ibuprofen responded very well against PEG 600. For these drugs the release from the formulation reached around 50% only after 5 minutes. The release of these four drugs after 5 minutes were found 56.70%, 45.57%, 52.83% and 79.49% respectively. Where release from pure drugs after same time period were 40.18%, 32.70%, 8.95% and 36.59% for the respective drugs. Again for drugs with HPMC 6cps only and with HPMC 6cps and PEG 6000 Atorvastatin, Carbamazepine, Furosemide and Ibuprofen responded very well.

Keywords
Improve water solubility, Solid dispersion, Dissolution improvement.

1. INTRODUCTION
In order to ensure the optimum therapeutic effect of a drug it is necessary to prepare the proper dosage form. The enhancement of the drug dosage form formulation is connected with the application of new auxiliary substances or with new technological possibilities. Discovering a way to increase the solubility of poorly soluble drugs in order to improve their pharmaceutical and biological availability still remains one of the major technological problems. There are numerous ways of enhancing this process, of which the solid dispersion technique is more and more widely used and constantly improved1. 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. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles2. Generally, there are only two methods of preparing solid dispersions: fusion and solvent evaporation process. Atorvastatin12,13, Carbamazepine5,8,9, Etoricoxib16,17, Fenofibrate5,14,15, Furosemide5,10,11, Glipizide5,20,21, Ibuprofen5,18,19 and Spironolactone5,6,7 are some poor water soluble drugs which are included in the study and made solid dispersions with HPMC 6cps and PEG 6000 by solvent evaporation method.

2. MATERIALS AND METHODS

2.1 MATERIALS USED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Dr. Reddy’s Laboratories, India</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Sun Pharma, India</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>Cipla Ltd., India</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Ranbaxy Laboratories, India</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Ipca Laboratories, India</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Aurobido Pharma, India</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Dr. Reddy’s Laboratories, India</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aurobido Pharma, India</td>
</tr>
</tbody>
</table>
2.2. PREPARATION OF SOLID DISPERSION BY SOLVENT EVAPORATION METHOD

The solvent based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule and followed by removal of solvent by evaporation resulting in formation of a solid dispersion\textsuperscript{25}. Mixing at the molecular level is preferred, because this leads to optimal formulation and dissolution properties.

First of all 700 mg of each of the drugs were weighed and taken in vials and then polymers were added to it after proper weighing. Then the drug-polymer powders are mixed well physically and to these drug-polymer physical mixtures, solvent was added. Methanol was used as solvent for all the drugs except spironolactone; where acetone was used in stead of methanol, as solubility of this drug in methanol was not up to mark.

Solvent was added starting from a minimum amount and each time 0.5 ml of solvent was added to the existing content; i.e. 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, 3 ml and so on if necessary. After adding each fraction of the solvent sonication was performed in sonicator to avoid excess addition of solvent. Solvent was being added until uniform and clear dispersion was achieved.
As the boiling point of the solvent is low, it was easily evaporated by keeping the vials below dryer. After evaporation of the solvent vials were kept in desiccator for 48 hours. Finally formulations were withdrawn from vial, crushed in mortar and pestle and passed through 150 micron sieve. The samples were then ready for dissolution testing.

**Flow chart for the process of preparation of Solid Dispersion (Solvent Evaporation Method):**

![Flow chart](chart.png)

Table 2.8: Formulations of solid dispersions containing different drugs and polymer (and/or) carrier

<table>
<thead>
<tr>
<th>Codes</th>
<th>Drug</th>
<th>PEG 6000</th>
<th>HPMC 6cps</th>
</tr>
</thead>
<tbody>
<tr>
<td>F11</td>
<td>700 mg</td>
<td>300 mg</td>
<td>0 gm</td>
</tr>
<tr>
<td>F12</td>
<td>700 mg</td>
<td>300 mg</td>
<td>0 gm</td>
</tr>
<tr>
<td>F13</td>
<td>700 mg</td>
<td>0 mg</td>
<td>1 gm</td>
</tr>
</tbody>
</table>

Table 2.9: Different drugs with their dissolution medium

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dissolution medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Distilled water</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Distilled water</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>0.1 N Hydrochloric acid</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Distilled water</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Phosphate buffer (pH 5.8)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Simulated intestinal fluid without enzyme (pH 6.8)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Phosphate buffer (pH 7.2)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0.1 N Hydrochloric acid</td>
</tr>
</tbody>
</table>
2.3. CALIBRATION CURVES OF DIFFERENT DRUGS

**Atorvastatin Calibration Curve @ 243 nm, Medium: Methanol/Water**

\[ y = 0.045x - 0.0129 \]

\[ R^2 = 0.9995 \]

**Carbamazepine Calibration Curve @ 288 nm, Medium: Methanol/Water**

\[ y = 0.0508x + 0.0151 \]

\[ R^2 = 0.9976 \]

**Etoricoxib Calibration Curve @ 234 nm, Medium: Methanol/0.1N HCl**

\[ y = 0.0451x + 0.0091 \]

\[ R^2 = 0.9991 \]
Fenofibrate Calibration Curve @ 242 nm,
Medium: Methanol/Water

\[ y = 0.0524x + 0.0189 \]
\[ R^2 = 0.9957 \]

Furosemide Calibration Curve @ 274 nm,
Medium: pH 5.8 buffer

\[ y = 0.0066x - 0.0002 \]
\[ R^2 = 0.9976 \]

Glipizide Calibration Curve @ 276 nm,
Medium: Methanol/Water

\[ y = 0.0243x - 0.01 \]
\[ R^2 = 0.9989 \]
2.4. IN VITRO DISSOLUTION STUDY

In vitro dissolution study was performed in USP Type-II Dissolution Apparatus (Veego, India). The solid dispersion containing a fixed amount of drug was calculated and weighed by electric balance for dissolution. Dissolution medium was added in the baskets either 900 ml or 1000 ml depending on drug. The RPM for all the drugs were set 75. Temperature of the apparatus was set 37.5°C. Three formulations were taken in six baskets. Thus each formulation was taken in two baskets to perform duplicate to minimize the extent of error. Pure drug and drug solution (in methanol) were taken in next two baskets of the eight basket dissolution apparatus. The dissolution was performed for 1 hour. Two more baskets were needed for pure drug and the drug solution (in methanol). Thus dissolution of physical mixtures of two drugs was performed simultaneously in the eight basket dissolution tester.

After transferring the formulations into the baskets the dissolution apparatus was started. Stopwatch was maintained to monitor exact time interval. Samples from different baskets were withdrawn after 5, 10, 15, 20, 30, 40, 50 and 60 minutes. Each time 10 ml of sample was withdrawn by syringe filter and subsequently compensated by adding blank solution (dissolution medium).
Samples withdrawn were kept in test tubes which were already labeled according to the formula and time interval. The test tubes were covered by thin aluminium foil until UV-spectrometric readings were taken.

The dissolution samples were then analyzed spectrophotometrically by UV-VIS Spectrophotometer using the respective dissolution medium as the blank solution. The percent release of drugs from different formulations were calculated and then plotted in a graph against time in Microsoft excel worksheet.

Table 2.18: Formulation and dissolution medium for dissolution test.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Amount (mg)</th>
<th>Excepients</th>
<th>Dissolution Medium</th>
<th>RPM</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>F11</td>
<td>700</td>
<td>300</td>
<td>0.1% HCl (1000 ml)</td>
<td>75</td>
<td>242.00</td>
</tr>
<tr>
<td>F12</td>
<td>300</td>
<td>300</td>
<td>Dist. Water (1000 ml)</td>
<td>75</td>
<td>288.00</td>
</tr>
<tr>
<td>F22</td>
<td>700</td>
<td>300</td>
<td>5.8</td>
<td>75</td>
<td>274.00</td>
</tr>
<tr>
<td>F32</td>
<td>700</td>
<td>300</td>
<td>Phosphate Buffer pH</td>
<td>75</td>
<td>243.00</td>
</tr>
<tr>
<td>F33</td>
<td>700</td>
<td>300</td>
<td>Dist. Water (1000 ml)</td>
<td>75</td>
<td>288.00</td>
</tr>
<tr>
<td>F41</td>
<td>700</td>
<td>300</td>
<td>0.1 N HCl (0.2 900 ml)</td>
<td>75</td>
<td>234.00</td>
</tr>
<tr>
<td>F61</td>
<td>700</td>
<td>300</td>
<td>Dist. Water (1000 ml)</td>
<td>75</td>
<td>221.00</td>
</tr>
<tr>
<td>F71</td>
<td>700</td>
<td>300</td>
<td>Fluid (900 ml)</td>
<td>75</td>
<td>276.00</td>
</tr>
<tr>
<td>F81</td>
<td>700</td>
<td>300</td>
<td>Simulated Intestinal</td>
<td>75</td>
<td>288.00</td>
</tr>
</tbody>
</table>

3. RESULTS AND DISCUSSION

3.1. CALIBRATION CURVES OF DIFFERENT DRUGS

After studying all the calibration curves and their coefficient of determination (R<sup>2</sup>) values of a linear regression it was found that all the drugs have got R<sup>2</sup> values nearer to one. It was a clear indication of the linearity and accuracy of the calibration curves; which subsequently ensured correct calculation of results from dissolution data of different formulations of the drugs.
Table 3.1 Coefficient of determination ($R^2$) values for different drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Coefficient of determination ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>0.9995</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0.9982</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>0.9991</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>0.99</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.9976</td>
</tr>
<tr>
<td>Glipizide</td>
<td>0.9989</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.9982</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0.9987</td>
</tr>
</tbody>
</table>

3.2. DISSOLUTION STUDY

The solvent evaporation method for preparing solid dispersion includes dissolving the drug and the carrier in a common organic solvent, followed by evaporating the solvent at elevated temperature, under vacuum, or by freeze-drying or spray-drying the mixture. For this purpose, methanol was used as a common solvent.

Upon studying the dissolution profiles of solid dispersions of different drugs prepared by solvent evaporation method it is clear that solid dispersions showed higher dissolution rates than pure drugs.

Figure 3.1: Release pattern of different Atorvastatin solid dispersions

![Release pattern of different Atorvastatin solid dispersions](image1)

Figure 3.2: Release pattern of different Carbamazepine solid dispersions

![Release pattern of different Carbamazepine solid dispersions](image2)
Figure 3.3: Release pattern of different Etoricoxib solid dispersions

Figure 3.4: Release pattern of different Fenofibrate solid dispersions

Figure 3.5: Release pattern of different Furosemide solid dispersions
Figure 3.6: Release pattern of different Glipizide solid dispersions

![Glipizide graph]

- Medium: Simulated Intestinal Fluid (pH 6.8); RPM: 75

Figure 3.7: Release pattern of different Ibuprofen solid dispersions

![Ibuprofen graph]

- Medium: Phosphate buffer (pH 7.2); RPM: 75

Figure 3.8: Release pattern of different Spironolactone solid dispersions

![Spironolactone graph]

- Medium: 0.1% HCl; RPM: 75
Figure 3.9: Comparison of release pattern of different drugs with PEG at different time.
Figure 3.10: Comparison of release pattern of different drugs with PEG and HPMC at different time.
3.3. DISCUSSION

After studying all the results it can be said that PEG 6000 is a good vehicle to enhance the solubility of poorly water soluble drugs.
Dissolution studies were performed by preparing solid dispersions (solvent method).
Among these drugs, Atorvastatin, Carbamazepine, Furosemide and Ibuprofen [Figure 3.9] responded very well against PEG 600. For these drugs the release from the formulation reaches around 50% only after 5 minutes. The release of these four drugs after 5 minutes were found
56.70%, 45.57%, 52.83% and 79.49% respectively. Where release from pure drugs after same time period were 40.18%, 32.70%, 8.95% and 36.59% for the respective drugs.

Again for drugs with HPMC 6cps only [Figure 3.10] and with HPMC 6cps and PEG 6000 [Figure 3.11] Atorvastatin, Carbamazepine, Furosemide and Ibuprofen responded very well.

After studying dissolution profiles of solid dispersions prepared by solvent evaporation method [Figure 3.1 – 3.8] it can be concluded that except Fenofibrate, solid dispersions caused greater dissolution of drugs which are mainly poorly water soluble in nature.

After studying all the eight drugs, it was found that solid dispersion increased the dissolution to significant extent and it was almost 100% after 60 minutes for most of the drugs. Several mechanisms may be possible to the enhanced release of these drugs in the solid dispersion formulation with the water soluble polymer PEG 6000 and HPMC 6cps. The reduction of crystallinity of drug resulting in improved release may be a reason. In the dry state, drug particles were in close contact or adhered to the polymer particles as a result of mixing. When the mixture comes in contact with water, the polymer particles might have hydrated rapidly into the polymer solution, solubilizing the adjacent drug particles and subsequently releasing the drug into the medium.

After this study, PEG came out as a good device to increase the solubility of poorly soluble drugs. Solid dispersions prepared by both PEG and HPMC were found to exhibit best dissolution results for most of the drugs [Figure 3.10]. These polymers complimented each other to give rapid dissolution and better formulation. Among these drugs Fenofibrate [Figure 3.4] did not responded well with any of the combinations.

This study should be continued to the larger extent with more drugs and polymers to find out the suitable and perfect solid dispersion for individual drug.

4. CONCLUSION

It has been found that solid dispersions prepared by solvent evaporation method caused greater dissolution of drugs with poor water solubility. The combination of PEG and HPMC worked best in this study. Solid dispersion only by solvent evaporation method is examined here. But fusion and fusion-solvent method was not studied. These methods should also be studied for better understanding. Further study in this field is still required to establish this solid dispersion system so that in future it can be used effectively in commercial basis.

REFERENCES

3. Pharmaceutical solid dispersion technology, Muhammad J. Habib, 2001
5. British Pharmacopoeia 2010