“ENHANCING DISSOLUTION RATE OF NAPROXEN USING MODERN TECHNIQUES”

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ABSTRACT

In the present study an attempt has been made to increase the in vitro dissolution rate of poorly water-soluble drug naproxen, by employing novel solid dispersion methods are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drug. Naproxen formulations were prepared by using hot melt method, and solvent evaporation method using carrier like urea. The formulation were prepared with the above mentioned carriers in three different drug-carrier (w/w) ratios of 1:1, 1:3 and 1:5. The prepared solid dispersion was subjected for percentage practical yield, drug content, FTIR and DSC studies. Absence of significant drug-carrier interaction was confirmed by FTIR and DSC data. In-vitro release profiles of all solid dispersions (F-1 to F-6) were comparatively evaluated and also studied against pure naproxen. The drug release from all the solid dispersion displayed nearly zero-order release kinetics with r values ranging from approximately 0.906 to 0.998. Solid dispersion of formulation (F6) naproxen and urea combination prepared in (1:5) ratio showed excellent solubility and the dissolution rate was found to be 91.23% was selected as the best formulation in this study. Solubility of naproxen was increased as the concentration of carriers increased. Solvent evaporation method is most efficient and reliable method for enhancing dissolution of poorly water soluble drugs as compare to hot melt method.

KEYWORDS: Naproxen Urea Enhancement dissolution Solid dispersion, etc.
INTRODUCTION

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects, but poorly solubility of drug is major challenge for formulation scientist. About 40% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. To improve solubility and bioavailability of poorly soluble drug we use various methods or techniques. In this review we concentrated on improvement of the solubility of poorly water soluble drugs by applying various methods.[1]

Improving bioavailability by manufacturing process

There are three major approaches to overcome the bioavailability problems.

A) Pharmaceuticals approach: Modification of formulation, manufacturing processes or physiochemical properties of the drug is done.

B) Pharmacokinetic approach: Pharmacokinetics of drug is altered by modifying its chemical structure.

C) Biological approach: In this, route of drug administration may be changed such as parenteral form instead of oral form. Rate dissolution and its solubility are very important factors in third approach. The second approach of chemical modification has number of drawbacks such as being very expensive, time consuming, requires repetition of chemical studies, risk of precipitation and adverse effects. Moreover, the new chemical entity may suffer from another pharmacokinetic disorder or bear the risk of precipitating adverse effects. So generally only pharmaceutics approach is considered here.[2]

Figure no. i: Methods of preparation of solid dispersions to enhance the dissolution rate of poorly soluble drugs.[3-4]
Advantages of above methods
1. Rapid disintegration of oral tablets
2. As a formulation vehicle
3. Particles with improved wettability:
4. Particles with higher porosity
5. Drugs in amorphous state.[5]

Disadvantages of solid dispersions
1. Poor scale-up for the purposes of manufacturing.
2. Laborious and expensive methods of preparation.
3. Reproducibility of physicochemical characteristics.
4. Difficulty in incorporating into formulation of dosage forms.
5. Scale-up of manufacturing process.
6. Stability of the drug and vehicle.[6]

MATERIALS AND METHODS
Naproxen was obtained from Divis Laboratories Limited, Hyderabad has a gift sample. Urea, Potassium di-hydrogen phosphates were purchased from S.D. fine chemicals limited, Mumbai. All the carriers used were of analytical grade.

The solid dispersion of naproxen were prepared by using three different methods
1. Melt Method
2. Solvent evaporation method
3. Physical method

4.8 Preparation of solid dispersion of naproxen by melt method
Materials used
- Naproxen
- Urea

Procedure
Naproxen and urea were melt together in a china dish and mixed thoroughly both ingredients. After mixing the china dish was put on ice bath for cooling, and then resulted in damp mass. The damp mass passed through mesh no#60 and like this, other formulations with different proportion were prepared in various ratio of drug:excipient such as 1:1, 1:3, 1:5.[7]
4.9 Preparation of solid dispersion of naproxen by Solvent evaporation method

Materials used
✓ Naproxen
✓ Urea
✓ Methanol
✓ Chloroform

PROCEDURE
Naproxen was dissolved in a solvent blend of methanol and chloroform to get a clear solution in a 100ml round bottom flask. The excipient (urea) was then added and dispersed.

The solvent from mixture was removed by evaporation at 50º C under pressure while mixing the contents. The mass obtained was pulverized, mixed and passed through mesh no.60 co-evaporates were prepared in various ratio of drug: excipient such as 1:1, 1:3, 1:5.[8]

The objective of this project was to improve the solubility of poorly water soluble drug, namely naproxen by formulating ternary solid dispersions with a carrier and an adsorbent.

Table no. i: Composition of Naproxen solid dispersion

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Methods</th>
<th>Ratio</th>
<th>Drug (mg)</th>
<th>Excipient (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urea</td>
</tr>
<tr>
<td>F1</td>
<td>Melt dispersion method</td>
<td>1:1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>F2</td>
<td></td>
<td>1:3</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>F3</td>
<td></td>
<td>1:5</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>F4</td>
<td>Solvent evaporation method</td>
<td>1:1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>F5</td>
<td></td>
<td>1:3</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>F6</td>
<td></td>
<td>1:5</td>
<td>100</td>
<td>500</td>
</tr>
</tbody>
</table>

5.1 Evaluation Parameters
A. Determination of % practical yield

Determination of practical yield is useful to determine the efficiency of a preparation technique. The practical yield is calculated by using following equation:

\[
P_Y(\%) = \frac{\text{Practical mass(solid dispersion)}}{\text{Theoretical mass(solid dispersion)}} \times 100
\]

The prepared different formulation are weighed this gives the practical yield by using the above formula we calculated the percentage yield.[9]
B. Drug content uniformity studies
25 mg of each prepared solid dispersion formulation was accurately weighed and dispersed in 10 ml methanol and the mixture was shaken for 10 min. The methanol extracts were filtered and collected into 25 ml volumetric flask and made up to the mark with methanol by passing more solvent through the filter. The above solutions were suitably diluted with methanol and the absorbance was measured at 269.5 nm against methanol as a blank. The naproxen content was calculated using calibration curve.

C. Solubility’s studies
Naproxen is practically insoluble in water. To make a clear and thermodynamically stable solution, solubility studies with different solvents or combination of solvents (water, Ph 7.4 phosphate buffer and methanol.) were performed.

Excess Naproxen (100 mg) was added to stoppered conical flasks containing 15 ml of solvent. The flasks were kept on a sonicator 40KHZ frequency for 30 to 60 min. Suitable aliquots were withdrawn from filtered solutions (Watman No.1 filter paper) and analyzed for drug content spectrophotometrically at 261.6 nm against solvent blank. The experiments were run in triplicate.

Dissolution studies
Dissolution of naproxen from various dispersion method was studied in 900 ml of 7.4 phosphate buffer at 37 ±0.5°C using USP dissolution test apparatus II employing paddle stirrer at 100 rpm for 120 minute. A sample of dispersion formulation mixture equivalent to a 500 mg of neproxen was used in each test. At predetermined time intervals, 5 ml of the sample was withdrawn using a syringe fitted with a prefilter and simultaneously replacing with fresh 5 ml dissolution fluid. These collected samples were analyzed for naproxen content by measuring the absorbance at 261.5 nm. Percent of naproxen dissolved at various time intervals was calculated and plotted against time.

Infrared spectroscopy
Infrared spectroscopy is one of most powerful analytical techniques when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of a formulation. IR spectra of naproxen and its formulations were obtained by KBr pellet method using Perkin
Elmer FTIR series spectrometer in order to rule out drug-carrier interaction occurring during the formulation process.

RESULTS AND DISCUSSION

The technique of solid formulation was utilized in the present work to improve the \textit{in vitro} dissolution rate of water insoluble drug (naproxen). Solid dispersion of naproxen were prepared by using carriers (Urea,) by melt method, solvent evaporation method.

All the formulations prepared were found to be white or almost white in colour, fine and free flowing powders.

\% Practical yield and Drug content uniformity studies

Solid dispersions of Naproxen were prepared by using carriers like urea. All the solid dispersions prepared were found to be fine and free flowing powders. The results of percentage practical yield for all formulations of solid dispersions were found to be in the range of 89.00\% - 94.66\% (Table 2). The drug content estimated in various solid dispersion are given in Table-6 and were found to be within +2.5\% ranges of the expected percent drug content values, in IP limits. The low values of the standard deviation and coefficient of variation (< 2\%) for the estimated drug contents indicated the uniform distribution of the drug within the formulation prepared. (Table 2).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
SL.No & Formulation Code & \% Practical yield & Mean \% Drug Content*SD(CV) \\
\hline
1 & F1 & 89.00\% & 98.12±0.46 \\
2 & F2 & 89.25\% & 99.12±1.23 \\
3 & F3 & 90.16\% & 99.65±0.87 \\
4 & F4 & 91.50\% & 101.33±0.99 \\
5 & F5 & 92.00\% & 102.45±1.21 \\
6 & F6 & 92.16\% & 104.88±1.00 \\
\hline
\end{tabular}
\caption{\textbf{Table no. ii: \% Practical yield in all formulation}}
\end{table}

Solubility study

Phase solubility study was carried out in order in to ascertain effect of carriers on the solubility characteristics of naproxen. Solubility of naproxen was increased as the concentration of carriers increased. The results of saturation solubility studies are given in (Table 3). The solubility of pure drug in water, in PBS (pH 7.4) and methanol was found to be 27.04 ± 0.56, 53.06 ± 0.4 and 66.31±0.5 \textmu g/ml respectively. The solubility of solid dispersion of naproxen prepared by melt method in water, in PBS (pH 7.4) and methanol
were found in the range of 41.03 ± 0.84, 71.62±0.71, 74.73±0.26 5 µg/ml and The solubility of solid dispersion of naproxen prepared by solvent evaporation method in water, in PBS (pH 7.4) and methanol were found in the range of 59.84 ± 2.26, 79.60 ± 2.00 and 88.67± 2.63 µg/ml respectively.

**Table no. iii: Solubility studies of drug in all dispersions formulation**

<table>
<thead>
<tr>
<th>Samples</th>
<th>Solubility (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water</td>
</tr>
<tr>
<td>Pure drug(F0)</td>
<td>27.041 ± 0.5</td>
</tr>
<tr>
<td>F-1</td>
<td>30.944± 2.08</td>
</tr>
<tr>
<td>F-2</td>
<td>35.292± 2.51</td>
</tr>
<tr>
<td>F-3</td>
<td>41.039 ±0.84</td>
</tr>
<tr>
<td>F-4</td>
<td>51.281 ±2.18</td>
</tr>
<tr>
<td>F-5</td>
<td>48.432±1.83</td>
</tr>
<tr>
<td>F-6</td>
<td>59.848 ±2.65</td>
</tr>
</tbody>
</table>

**Figure no. ii: Solubility studies of drug in all dispersions formulation**

**In vitro drug release studies**

In vitro drug release studies were carried out in USP dissolution test apparatus (TDT-O8L Electrolab) by rotating paddle method at 100 rpm (apparatus II) using 900 ml of 0.1N HCl at 37±0.5o C as dissolution medium for 80 min. The data from the dissolution studies of naproxen in pure form, melt method, solvent evaporation method and physical mixtures it can be seen that, the pure form of the drug shows less dissolution i.e 44.13% in 80 min (given in table no.4).

All the formulation(F1-F6) showed cumulative % DR were found in the range of 8.79 to 91.23.all the formulation has been prepared by three methods showed solvent evaporation
method>hot melt method. *In vitro* release studies reveal that there is marked increase in the dissolution rate of naproxen from all the solid dispersions when compared to pure naproxen itself (Table 3). From the in-vitro drug release profile, it can be seen that formulation F-6 containing urea and drug (1:5 ratio of drug: carrier) shows higher dissolution rate compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. In the case of solid dispersions of naproxen with urea ratio of 1:5, the dissolution rate of drug increased while in the case of those prepared in the ratio of 1:1 and 1:3 the dissolution rate of drug was decreased (Figure no. iii ). This might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. The increase in dissolution rate is in the order of F6 >F3>F5>F2>F4 >F1. The regression coefficient (r) values for formulations F1 to F6 model that gave higher ‘r’ value was considered as best fit model. The r values were found to be higher in the Zero order model (0.953, 0.943, 0.975, 0.996, 0.991, 0.959.) than those in the first order model (0.845, 0.796, 0.861, 0.916, 0.853, 0.861.) with all the solid dispersion (pure naproxen, F1, F2, F3, F4, F5, F6 respectively) indicating that the dissolution of naproxen as such and from all the solid dispersion followed first order kinetics. The solid dispersions of the water-insoluble drug naproxen were successfully prepared by solvent evaporation technique using hydrophilic carriers. The in-vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure naproxen. Mechanisms involved are solubilization and improved wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals after dissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e urea.

**Mechanism of drug release**

The in vitro drug release data obtained from all the formulations were tabulated and fitted into three popular models of data treatment as follows.

- Cumulative percent drug released versus time plots (zero-order).
- Log cumulative percent drug remained verses time plots (first-order).
- When the data was plotted as log cumulative percent drug remaining versus time, the plots obtained were linear indicating first-order release kinetics. Cumulative percent drug released versus time plots (zero-order) the plots obtained were linear (Tables 17-20 and figures 13-22).
Dissolution parameters

The *in vitro* release parameter values (t<sub>25%</sub>, t<sub>50%</sub> and t<sub>75%</sub>) displayed by the various formulations range from 26 to 35 min (t<sub>25%</sub>), 56 to 65 min (t<sub>50%</sub>) and 75 to 83 (t<sub>75%</sub>) respectively. The formulations F6 (drug: urea ratio of 1:5) were found to be promising, which showed t<sub>25%</sub>, t<sub>50%</sub> and t<sub>75%</sub> values of 26, 56 and 75 respectively and released 91.23% drug within 80min respectively.

Table no. iv: Dissolution parameters for the solid dispersion formulations

<table>
<thead>
<tr>
<th>SL.NO</th>
<th>Formulation code</th>
<th>t&lt;sub&gt;25%&lt;/sub&gt; (min)</th>
<th>t&lt;sub&gt;50%&lt;/sub&gt; (min)</th>
<th>t&lt;sub&gt;75%&lt;/sub&gt; (min)</th>
<th>Cumulative% drug release in 80 mins.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F0</td>
<td>35</td>
<td>65</td>
<td>83</td>
<td>44.13</td>
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<tr>
<td>2</td>
<td>F1</td>
<td>31</td>
<td>62</td>
<td>78</td>
<td>79.78</td>
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<td>3</td>
<td>F2</td>
<td>29</td>
<td>61</td>
<td>76</td>
<td>85.44</td>
</tr>
<tr>
<td>4</td>
<td>F3</td>
<td>28</td>
<td>60</td>
<td>75</td>
<td>88.90</td>
</tr>
<tr>
<td>5</td>
<td>F4</td>
<td>29</td>
<td>58</td>
<td>77</td>
<td>80.15</td>
</tr>
<tr>
<td>6</td>
<td>F5</td>
<td>27</td>
<td>57</td>
<td>76</td>
<td>87.91</td>
</tr>
<tr>
<td>7</td>
<td>F6</td>
<td>26</td>
<td>56</td>
<td>75</td>
<td>91.23</td>
</tr>
</tbody>
</table>

Figure no. iv: Comparison of dissolution parameters (t<sub>25%</sub>, t<sub>50%</sub> and t<sub>75%</sub>) of solid dispersion of naproxen.
CONCLUSION

- The solid dispersion prepared by melt method and solvent evaporation method were found to be white in colour, fine and free flowing powders with uniform drug content.
- IR spectroscopic studies indicated that there was no drug-excipient interaction
- In vitro dissolution studies indicated that, an increase in drug-Excipients ratio showed an increase in drug release rate.
- In their 6 formulation (F1-F6) the Percentage practical yield for all formulations of solid dispersions were prepared among F6 found to be promising 92.16%.
- Solubility of naproxen was increased as the concentration of carriers increased.
- The drug release from all the solid dispersion displayed nearly first-order release kinetics with r values ranging from approximately 0.906 to 0.998.
- Formulation F6 prepared with a drug-carrier ratio of 1:5 (naproxen: urea) showed promising results in enhancing the dissolution rate of poorly water-soluble naproxen (91.23% drug release in 80 min).
- Short-term stability studies of promising formulation F6 indicates that there were no significant changes in drug content and dissolution parameter values after 3 months storage at 40° ± 2°C/75 ± 5% RH.

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REFERENCE


