**ABSTRACT**

The aim of the study was to investigate the use of liquisolid technique in improving the dissolution profiles of naproxen in solid dosage form. This study was designed to evaluate the effect of different formulation variables i.e type of non volatile liquid vehicles and carriers on drug dissolution rates. The liquisolid tablets were formulated with two different liquid vehicles, namely polyethylene glycol 400 and propylene glycol and with two different carrier materials namely microcrystalline cellulose (Avicel pH 101) and dicalcium phosphate. Silica gel was used as coating material and sodium starch glycolate was used as disintegrating agent in all formulations. The liquid loading factors for liquid vehicle was calculated to obtain the optimum amounts of carrier and coating materials necessary to produce acceptable flowing and compactable powder admixtures capable of producing tablets. The ratio of carrier to coating powder was kept constant in all formulations at 20 to 1. Before compression, powdered mass were evaluated for various parameters like weight variation, hardness, drug content uniformity, and disintegration time. The in-vitro release characteristics of the pure drug, drug from marketed tablets (as reference) and liquisolid technique (test sample), were studied. X-Ray Diffraction (XRD), differential scanning calorimetry (DSC) and Fourier-Transform infrared spectroscopy (FT-IR) were performed to determine the drug-excipient interaction. The results showed that liquisolid formulations of naproxen exhibited higher percentage of drug release than marketed formulation. And it was concluded that there was no interaction between drug and excipients.

**Keywords:** Liquisolid compacts, Naproxen, Dissolution, content uniformity

1. **INTRODUCTION**

About 40% of the drug candidates identified via combinatorial screening programmes are poorly water soluble. The aqueous solubility for poorly water-soluble drugs is usually less than 100 μg/mL. The dissolution rate is the rate-limiting factor in drug absorption for class II (low solubility and high permeability) and class IV (low solubility and low permeability) drugs as defined in the Biopharmaceutics Classification System, BCS. Poorly water soluble drugs are difficult to formulate using conventional techniques. Different techniques have been reported in the literature to achieve better drug dissolution rates. For example, (a) reduce the particle size via micronisation or nanosisation to increase the surface area; (b) use of surfactants; (c) inclusion with cyclodextrins; (d) use of pro-drug and drug derivatisation; (e) formation of solid solutions or amorphous solids and (f) microencapsulation and inclusion of drug solutions or liquid drugs into soft gelatin capsules or specially coated hard gelatin capsules. Among various techniques to overcome the solubility issue, several researchers reported that the formulation of liquisolid tablets is one of the most promising techniques for promoting drug dissolution. It is established that soft gelatin capsule preparations containing a solubilised liquid drug show higher and more consistent bioavailability than the conventional oral dosage forms because the active ingredient(s) is already in solution. In fact, liquisolid tablets deliver active ingredient(s) in a similar mechanism as co-extended drug solutions or liquid drugs into soft gelatin capsules or specially coated hard gelatin capsules.

The technique of liquisolid compacts has been successfully employed to improve the in vitro release of poorly water soluble drugs such as carbamazepine, lamotrigine, diphenhydramine, piroxicam, indomethacin, naproxen, furosemide, and prednisolone.

Naproxen, (6-methyl-2-naphthyl acetic acid) non-steroidal anti-inflammatory drug, is a weak acid (pKa = 4.15) which is practically insoluble in water and the major problem associated with the formulation and effectiveness of the naproxen is its variable oral absorption due to insufficient aqueous solubility at gastrointestinal pH, thus making dissolution the rate-determining step in the gastric absorption of naproxen. Various approaches have been tried to enhance the dissolution properties of naproxen, such as formation of naproxen sodium, solid dispersion, complexation with cyclodextrins, drug particle size reduction and formation of naproxen disintegrant agglomerates using a crystallo-coagulation technique. To the best of our knowledge, there are currently no liquisolid dosage forms available on the market. However, commercial products using liquisolid technology may be available, in the future, on the market based on this research and similar studies.

The main objective of this work is to develop and explore a new formulation to enhance the bioavailability of a highly permeable and a poorly soluble non steroidal anti-inflammatory drug naproxen by following liquisolid compacts. And to compare the invitro drug release profile of formulated liquisolid tablets with marketed conventional tablet.

2. **MATERIALS AND METHODS**

2.1. **Materials**

Naproxen was generously provided by Ranbaxy (India). Avicel PH 101 and Silica gel were generously provided by Okasa Pharmaceuticals (India). Polyethylene glycol, propylene glycol, and DCP, were purchased from SD Fine Chemicals (India). All other reagents and chemicals were of analytical grade.

2.2. **Use of a mathematical model to design liquisolid compacts**

The formulation design of liquisolid systems was done in accordance with the new mathematical model. In this study, polyethylene glycol and propylene glycol were used as a liquid vehicles, Avicel PH 101 (Mycro crystalline Cellulose-MCC), and Dicalcium Phosphate (DCP) were used as carrier materials and Silica gel was used as coating material, respectively. The concentration of the drug in liquid vehicle and the carrier; coating ratio was kept constant in all formulations. According to new theories, the carrier and coating powder mate-
Table 1: Formulations of Liquisolid Compacts

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug</th>
<th>Solvent</th>
<th>Carrier</th>
<th>Coating material</th>
<th>Disintegrating agent</th>
<th>Total weight</th>
<th>Loading factor (Lw)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Naproxen-100 mg</td>
<td>PEG-60mg</td>
<td>MCC-330 mg</td>
<td>Silica gel-16.5 mg</td>
<td>SSG</td>
<td>531.8 mg</td>
<td>0.181</td>
</tr>
<tr>
<td>F2</td>
<td>Naproxen-100 mg</td>
<td>PEG-60mg</td>
<td>DCP-325 mg</td>
<td>Silica gel-16.25 mg</td>
<td>SSG</td>
<td>526.25 mg</td>
<td>0.184</td>
</tr>
<tr>
<td>F3</td>
<td>Naproxen-100 mg</td>
<td>PG-55mg</td>
<td>MCC-329 mg</td>
<td>Silica gel-16.45 mg</td>
<td>SSG</td>
<td>525.45 mg</td>
<td>0.167</td>
</tr>
<tr>
<td>F4</td>
<td>Naproxen-100 mg</td>
<td>PG-55mg</td>
<td>DCP-324 mg</td>
<td>Silica gel-16.20 mg</td>
<td>SSG</td>
<td>519.96 mg</td>
<td>0.169</td>
</tr>
</tbody>
</table>

3. Determination of solubility

Saturated solutions were prepared by adding excess naproxen to the liquid vehicle and shaking on a shaker for 48 h at 25°C with constant vibration. The solutions were filtered through a 0.45 micron filter, diluted with water, and analyzed with a Shimadzu 1700 UV-Vis spectrophotometer at 230 nm with respect to a blank sample (the blank sample was a solution containing the same concentration used without the drug). Determination was carried out in triplicate for each sample to calculate the solubility of Naproxen.

2.4. Preparation of liquisolid compacts

Calculated quantities of naproxen and liquid vehicle were accurately weighed in a 20-mL glass beaker and then mixed well. The resulting medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps5. In the first, the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using an aluminum spatula. Then Carrier: Coating material (20:1) was added to this mixture and blended in a mortar. This provided the final formulation that was compressed into tablets using a 12mm single punch tablet compression machine after addition of 5% sodium starch glycolate as disintegrating agent.

2.5. Precompression studies:

2.5.1 Flow properties

Flow properties of liquisolid formulation were studied by angle of repose, Carr’s index, and Hausner’s ratio11. Each analysis was carried out in triplicate. Bulk density measurements were carried by placing a fixed weight of powder in a graduated cylinder, and the volume occupied was measured and the initial bulk density was calculated. The cylinder was then tapped at a constant velocity until a constant volume was obtained. The tapped density was then calculated. The angle of repose was calculated by the fixed-height cone method. All studies were done in triplicate.

2.5.2 X-ray powder diffraction (XRD)

The cavity of the metal sample holder of the X-ray diffractometer was filled with ground sample powder and then smoothed with a spatula. X-ray diffraction pattern of naproxen samples was obtained using the X-ray diffractometer (Siemens, Model DS8000, Germany) at 40 kV, 30 mA and a scanning speed of 4 degree/min over the range 10–80 (2θ), using Cu radiation of wavelength 1.5405 Å.

2.5.3 Infra red spectra analysis

The infra red spectra of formulations were recorded by the KBr method using a Fourier transform infrared spectrophotometer (FTIR-8400S). A base-line correction was made using dried potassium bromide and then the spectrum of the pure drug, liquisolid system was obtained.

2.5.4 Differential Scanning Calorimetry

DSC thermograms of naproxen pure drug, all liquisolid formulations were obtained with DSC Refrigerated Cooling System (Model Q1000, TA Instruments, UK). Samples (0.8–6.3 mg) were weighed and transferred into the equipment for analysis in sealed hermetically aluminium pans. The instrument was calibrated with sapphire and indium before running the samples. Thermal behaviour of the samples was investigated at a scanning rate of 10°C/min, from 0°C to 250°C.

2.5.5 Content uniformity studies

The granules were crushed and powder containing 100 mg of Naproxen was dissolved in 100ml of methanol. The solution was passed through a whatmann (NO.1) filter and analyzed spectrophotometrically at 230nm after sufficient dilution with Phosphate buffer pH 7.4.

2.6. Evaluation of liquisolid compacts

The hardness of liquisolid compacts was determined using a Pfizer hardness tester (Pfizer). The mean hardness of each formula was determined. The friability of prepared liquisolid compacts was determined using a digital tablet friability tester (Roche). Weight variation was performed as per IP. Disintegration test was conducted by using Electrolab disintegration testing apparatus. Each evaluation was done in triplicate.

2.7. In vitro drug release studies

Studies were done on a six-station USP dissolution apparatus I (Electrolab). All batches of tablets were evaluated (n = 3) using 900 mL of 7.4 pH Phosphate buffer. Temperature was maintained at 37 ± 0.5°C throughout the study and stirring was done at 50 rpm. Samples were periodically collected, filtered through a 0.45 micron filter, and replaced with fresh dissolution medium. After filtration through Whatman filter paper 41, the concentration of naproxen was determined spectrophotometrically at 230 nm (Shimadzu 1700 UV-Vis Spectrophotometer). The actual amount of released drug was determined from the calibration curve (n = 3).

3. RESULTS

3.1 Determination of Solubility of Naproxen

Determination of solubility is most important aspect in formulation of liquisolid systems. It is needed ascertain formation of molecular dispersion of the drug in non-volatile solvent such as polyethylene glycol and propylene glycol. The solubility of naproxen in polyethylene glycol and propylene glycol was found to be 119.24 ± 0.1 mg/ml and 87.21± 0.2 mg/ml respectively.

3.2 Precompression studies for liquisolid systems

3.2.1 Flow properties: Results of angle of repose, consolidation index and hausner’s ratio are given in the table no 2.

Table 2: Results of Angle of repose, Consolidation Index and Hausner’s ratio

<table>
<thead>
<tr>
<th>No</th>
<th>Tapped density</th>
<th>Bulk density</th>
<th>Angle of repose</th>
<th>Consolida</th>
<th>tion index</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.87</td>
<td>0.74</td>
<td>28.1</td>
<td>14.9</td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.86</td>
<td>0.71</td>
<td>28.3</td>
<td>17.4</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.81</td>
<td>0.71</td>
<td>29</td>
<td>12.3</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.82</td>
<td>0.72</td>
<td>29.5</td>
<td>12.2</td>
<td>1.13</td>
<td></td>
</tr>
</tbody>
</table>

Fig 1: XRD of Naproxen pure drug
3.2.3 Infra red spectra analysis

Fig 2: XRD of Naproxen liquisolid compacts prepared with PEG+MCC

Fig 3: XRD of Naproxen liquisolid compacts prepared with PEG+DCP

Fig 4: XRD of Naproxen liquisolid compacts prepared with PG+MCC

Fig 5: XRD of Naproxen liquisolid compacts prepared with PG+DCP

Fig 6: FTIR of Naproxen pure drug

Fig 7: FTIR of Naproxen liquisolid compacts prepared with PEG+MCC
3.2.4 Differential Scanning Calorimetry

Fig 11: DSC of Naproxen pure drug

Fig 12: DSC of Naproxen liquisolid compacts prepared with PEG+MCC

Fig 13: DSC of Naproxen liquisolid compacts prepared with PEG+DCP
3.2.5 Content Uniformity:

Table 3: Results of Content Uniformity:

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Content uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>99.8 ± 0.12</td>
</tr>
<tr>
<td>F2</td>
<td>100.1 ± 0.12</td>
</tr>
<tr>
<td>F3</td>
<td>101.1 ± 0.21</td>
</tr>
<tr>
<td>F4</td>
<td>101.4 ± 0.11</td>
</tr>
</tbody>
</table>

3.3. Evaluation of liquisolid tablets

Table 4: Results of hardness, friability, weight variation and disintegration time

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight Variation (%)</th>
<th>Disintegration Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5 ± 0.2</td>
<td>0.13 ± 0.024</td>
<td>531 ± 1.4</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>F2</td>
<td>6 ± 0.3</td>
<td>0.135 ± 0.024</td>
<td>526 ± 1.6</td>
<td>2.6 ± 0.4</td>
</tr>
<tr>
<td>F3</td>
<td>4 ± 0.2</td>
<td>0.219 ± 0.032</td>
<td>525 ± 1.5</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>F4</td>
<td>4 ± 0.3</td>
<td>0.126 ± 0.023</td>
<td>519 ± 1.7</td>
<td>3.6 ± 0.2</td>
</tr>
</tbody>
</table>

DISCUSSION

4.1 Application of new mathematical model for design of liquisolid systems

Naproxen was selected as model drug for this study as it is poorly soluble in water and thus ideal candidate for evaluating rapid release potential of liquisolid tablets. Liquisolid hypothesis states that drug candidate dissolved in liquid nonvolatile vehicle and incorporated into carrier material having porous structure and closely matted fibers in its interior, phenomenon of both adsorption and absorption occurs. This concludes that drug in the form of liquid medication is absorbed initially in the interior of particles of carrier and after saturation of this process it gets adsorbed into internal and external surfaces of carrier. Coating materials such as silica gel which have high adsorptivity and greater surface area lead the liquisolid systems desirable flow properties.

4.2 Percompression studies for liquisolid systems

4.2.1 Flow properties

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Results of measurements such as angle of repose, Carr’s index, and Hausner’s ratio are represented in the Table 2. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose = 40° indicate powders with poor flowability. The results are according to this statement. Also results of Carr’s index and Hausner’s ratio show good flow behavior.

4.2.2 X-ray Diffraction Studies

Sharp distinct characteristic peaks at 2θ diffraction angles for Naproxen at 19.26°, 22.69°, and 24.07° indicated its crystalline state (Figure 1). Liquisolid powder X-ray diffraction pattern (Fig. 2-5) showed absence of these distinct peaks. Hence absence of specific peaks (constructive reflections) in liquisolid system revealed that Naproxen has been completely converted to molecular form or solubilized form. This lack of crystallinity in the formulation might be due to solubilization of drug in liquid vehicle which was absorbed into carrier material and adsorbed onto carrier and coating materials. Whereas, presence of certain naproxen peaks is due to the fact that after saturation of absorption process, adsorption occurs on the surface of carrier. Thus, solubilization of naproxen in liquisolid system will lead to improved dissolution rate, and therefore bioavailability of naproxen.

4.2.3 Infra red spectra analysis

Samples of pure naproxen, liquisolid formulations were subjected to FT-IR spectroscopic analysis, and their spectra at 400–4000 cm⁻¹ are shown in (Fig. 6-10). The characteristic absorption bands of naproxen are the C=O stretching region, which are between 1600 and 1800 cm⁻¹. A reduction in intensity of
4.2.4 DSC: The DSC of pure naproxen is shown in (Fig. 11), while the DSC profiles of all liquisolid formulations are presented in Fig. 12-15. DSC is one of the most common applications to determine and predict the physicochemical interaction between components in a formulation. The thermogram of pure naproxen (Fig. 11) showed a sharp endothermic peak (Tm = 154.2°C, C, Tm = 157.9°C) due to drug melting. The sharp endothermic peak indicated that the naproxen was in crystalline anhydrous state. DSC thermograms of liquisolid formulations (Fig. 12-15) revealed a peak which was markedly broadened, the intensity was reduced, and a broad peak was observed. This is indicative of complete solidification of naproxen and/or interactions between the naproxen and the excipients [23]. The broad peak in the DSC profiles of liquisolid formulations might be correspondence to the melt and decomposition of the whole liqusiolid system. The melting point of a substance is closely related to its solubility via latent heat of fusion. A substance with a higher heat of fusion is more difficult to melt and therefore less soluble. Generally, crystal with weak bonds has a low-melting point and low heat of fusion. On the contrary, crystal with strong bonds gives high melting point and high heat of fusion. The structure of the drug crystal has to be disrupted in order to disperse or solubilize in a solvent. Accordingly, high melting point usually reflects low solubility [24].

5. CONCLUSION
In conclusion, this study showed that liquisolid technique could be a promising strategy in improving dissolution of insoluble drugs and formulating immediate release solid dosage forms. The results generated in this study described the relationship between formulation variables and dissolution profiles. The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as naproxen. Enhanced dissolution rates obtained in the present study in turn indicates increase in oral bioavailability due to increased wetting and surface area available for dissolution. This novel approach to the formulation may be helpful to improve oral bioavailability. Liquisolid formulation containing Polyethylene glycol as the solvent, DCP as the carrier and silica gel as coating material has shown faster dissolution rate when compared to other formulations, hence it can be regarded as the optimum formulation for the formulation of naproxen liquisolid tablets. The key step in formulating a successful liquisolid tablets is determination of optimal flowable liquid retention Potential (F-value).

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7. REFERENCES

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