FORMULATION DEVELOPMENT AND EVALUATION OF LIQUISOLID SYSTEMS TO IMPROVE THE DISSOLUTION RATE OF KETOPROFEN

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ABSTRACT

Liquisolid compacts were used to formulate water insoluble drugs in non-volatile solvents and converting into acceptably flowing and compressible powders. The main objective of present investigation was to enhance the dissolution rate of water insoluble drug ketoprofen by using liquisolid technique. Several liquisolid tablets were prepared by using different carrier materials such as microcrystalline cellulose (Avicel pH-101), starch, dicalcium phosphate and lactose, and coating material such as silica gel, respectively. Polyethylene glycol 400 was used as non volatile water miscible liquid vehicle. The liquid loading factors for such liquid vehicle was calculated to obtain the optimum amounts of carrier and coating materials necessary to produce acceptable flowing and compactable powder admixtures viable to produce compacts. The ratio of carrier to coating material was kept constant in all formulations at 20 to 1. Before compression, powdered mass were evaluated for various parameters like flow properties, content uniformity etc. All the prepared formulations were compressed using 12mm punch after addition of 5 % Sodium starch glycolate (super disintegrating agent) to each formulation. The formulated liquisolid tablets were evaluated for post compression parameters such as weight variation, hardness, drug content uniformity, percentage friability 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) and Fourier-Transform infrared spectroscopy (FT-IR) were performed. The results showed that liquisolid formulations of ketoprofen exhibited higher percentage of drug release than marketed formulation. And it was concluded that there was no interaction between drug and excipients.

KEY WORDS: Liquisolid compacts; Ketoprofen; Dissolution; content uniformity

1. INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability.
Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced\(^1\). As large proportions of new drug candidates have poor aqueous solubility, various formulation strategies were reported to overcome such a problem. Among these techniques is complexation with cyclodextrins, micronization, solid dispersion, co-precipitation and recently, the technique of ‘liquisolid compacts’. Several studies have shown that the liquisolid technique is a promising method for promoting dissolution rate of poorly water soluble drugs\(^2-8\). In liquisolid compact, a liquid medication is converted into acceptably flowing and compactible powder forms. The term ‘liquid medication’ implies liquid lipophilic (oily) drug and solution or suspension of poorly water soluble drugs carried in suitable water miscible non-volatile liquid systems termed the liquid vehicle. By simple blending with suitable excipients ‘carrier and coating materials’, the liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compactible powder\(^9\). Since drug dissolution is often the rate limiting step in gastrointestinal absorption, the significant increase in wetting properties and surface area of drug particles available for dissolution from liquisolid compacts may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability.

The technique of liquisolid compacts has been successfully employed to improve the In Vitro release of poorly water soluble drugs such as carbamazepine\(^{10}\), famotidine\(^{11}\), piroxicam\(^4\), indomethacin\(^5\), hydrocortisone\(^2\), naproxen\(^7\), furosemide\(^{12}\), and prednisolone\(^{10}\). Ketoprofen, (RS) 2-(3-benzoylphenyl)-propionic acid, is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. The major problem associated with the formulation and effectiveness of the ketoprofen 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 ketoprofen\(^{13}\). Therefore, ketoprofen establishes a good candidate for testing the potential of rapid-release liquisolid compacts.

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 ketoprofen 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: Ketoprofen was generously provided by Ranbaxy (India). Avicel PH 101 and Silica gel were generously provided by Okasa Pharmaceuticals (India). Polyethylene glycol, DCP, Starch and Lactose 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\(^9\). In this study, polyethylene glycol was used as a liquid vehicle, Avicel PH 101 (Mycro crystalline Cellulose-MCC), Dicalcium Phosphate (DCP), Starch and Lactose were purchased from SD Fine Chemicals (India). All other reagents and chemicals were of analytical grade.
concentration of the drug in polyethylene glycol and the carrier: coating ratio was kept constant in all formulations. According to new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability and compressibility. The excipient ratio $R$ of the powder is defined as

$$R = \frac{Q}{q} \quad (1)$$

Where $R$ is the ratio of the weight of carrier ($Q$) and coating ($q$) materials present in the formulation. The liquid load factor ($L_d$) is defined as the ratio of the weight of liquid medication ($W$) to the weight of the carrier powder ($Q$) in the system, which should be present in an acceptably flowing and compressible liquisolid system, i.e.,

$$L_d = \frac{W}{Q} \quad (2)$$

The flowable liquid retention potential ($\Phi$ value) of powder excipients was used to calculate the required ingredient quantities. Therefore, powder excipients ratios $R$ and liquid load factors $L_d$ of the formulations are related as follows:

$$L_d = \Phi + \Phi \left( \frac{1}{R} \right) \quad (3)$$

Where, $\Phi$ and $\Phi$ are the $\Phi$ values of carrier and coating materials, respectively. Hence, to calculate the required weights of the excipients used $\Phi$ and $\Phi$ from Eq. 3 are constants, and thus $L_d$ was calculated according to the ratio of carrier:coating materials ($R$). Using the above mathematical model, liquisolid compacts were formulated as summarized in Table 1.

### 2.3. Determination of solubility:

Saturated solutions were prepared by adding excess ketoprofen to the polyethylene glycol 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 260 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 Ketoprofen.

#### 2.4. Preparation of liquisolid compacts

Calculated quantities of ketoprofen and polyethylene glycol 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 steps. 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 ratio. 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.

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 of pure drug and then smoothed with a spatula. X-ray diffraction pattern of ketoprofen samples was obtained using the X-ray diffractometer (Siemens, Model D5000, 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. All the liquisolid formulations containing all the excipients to be present in the final formulation were analysed in the same way before compression of the tablets.

2.5.3 Infra red spectra analysis

The infra red spectra of pure drug and all liquisolid 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 Content uniformity studies:

The granules were crushed and powder containing 100 mg of Ketoprofen was dissolved in 100 ml of methanol. The solution was passed through a whatmann (NO.1) filter and analyzed spectrophotometrically at 260 nm 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).

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 100 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 ketoprofen was determined spectrophotometrically at 260 nm (Shimadzu 1700 UV-Vis Spectrophotometer). The actual amount of released drug was determined from the calibration curve (n = 3).

2.8. Statistical methods:

One Way ANOVA was conducted for dissolution studies of various formulations to determine whether there is any significant variation between prepared liquisolid formulations and marketed formulation. Test was conducted at 99% confidence interval and 0.001 % level of significance where the F critical value is 3.68. If the obtained F value is greater than critical value, it can be concluded that there will be significant difference between liquisolid formulations and marketed formulation.

3. RESULTS

3.1 Determination of Solubility of Ketoprofen in polyethylene glycol

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. The solubility of ketoprofen in polyethylene glycol was found to be 134.24 ± 0.1 mg/ml.
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.

3.2.2 X-ray Diffraction Studies: XRD curves of pure drug and all liquisolid formulations were shown in fig no 1-5 respectively.

3.2.3 Infra red spectra analysis: FTIR curves of pure drug and all liquisolid formulations were shown in fig no 6-10 respectively.

3.2.4 Content Uniformity: FTIR curves of pure drug and all liquisolid formulations were shown in fig no 6-10 respectively. Content uniformity values obtained for all liquisolid formulations (F1-F4) were given in the Table No 3.

3.3 Evaluation of liquisolid tablets:
Results of hardness, friability, weight variation and disintegration time of each liquisolid formulation (F1-F4) were represented in Table No 4.

3.4 In Vitro dissolution studies: In Vitro Drug release values obtained for all formulations of liquisolid tablets, pure drug and marketed formulation were tabulated in table no. 5. From the table it was observed that formulation 1 containing PEG as solvent and MCC as carrier has shown faster drug release among all formulation. Hence its drug release was compared graphically with % drug release obtained with pure drug and marketed formulation (Fig 12).

4. DISCUSSION

4.1 Application of new mathematical model for design of liquisolid systems

Ketoprofen 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 grater surface area lead the liquisolid systems desirable flow properties16.

4.2 Precompression 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 $\geq 40^\circ$ 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 20 diffraction angles for Ketoprofen at 11.525°, 14.105°, 18.2560 and 22.190° 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 Ketoprofen 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 ketoprofen peaks is due to the fact that after saturation of absorption process, adsorption occurs on the surface of carrier. Thus, solubilization of ketoprofen in liquisolid system will lead to improved dissolution rate, and therefore bioavailability of ketoprofen 20.

4.2.3 Infra red spectra analysis: The IR spectrum showing percentage transmission (T%) versus wave number of pure drug is shown in Fig. 6 with characteristic peaks of aromatic C=O stretching at 1700 cm⁻¹ and 1650 cm⁻¹, respectively. From the figure it is evident that pure drug in liquisolid compact (fig 7-10) undergoes no chemical reaction with any of the excipients used in the preparation of liquisolid compacts.

4.2.4 Content Uniformity

The percentage of drug uniformity was found to be between 98%-102% of Ketoprofen, which was within acceptable limits. The values obtained were given in the Table No. 3.

4.3 Evaluation of liquisolid tablets:

Results of hardness, friability, weight variation and disintegration time are represented in Table 4. There should be certain amount of strength or hardness and resistance to friability for the tablet, so that tablet should not break during handling. However, it has also effect on tablet disintegration and drug dissolution. Average hardness of liquisolid tablet ranges from 3 ± 0.2 to 5 ± 0.3 kg/cm². Compactness of tablet may be due to hydrogen bonding between Avicel PH 101 and drug molecules. As polyethylene glycol is an alcoholic compound, it might show hydrogen bonding due to presence of hydroxyl groups and may contribute to compactness of tablets. Friability studies of liquisolid tablets are in the range of 0.125% to 0.292%. This indicates that acceptable resistance is shown by liquisolid tablets to withstand handling. Weight variation was found to be in the range of ± 1.5 to ± 1.7 for all the formulations, indicating that all formulations passed the test. Disintegration time was found to be in the range of 2.5 ± 0.4 to 3.4 ± 0.3 min. Faster disintegration time indicate rapid release rates. These are in accordance with dissolution rates.

4.4. In Vitro dissolution studies:

Dissolution rates of liquisolid formulations were compared with pure drug and marketed formulation (Table 5). Liquisolid formulations initially show greater release than marketed formulation. This is indicated by percentage release at 10 min. The statistical analysis (One Way ANOVA) showed that there is significant difference in dissolution rates compared to marketed formulations (P < 0.05, F = 3773.48). All liquisolid tablets show greater than 98% drug release after 30 min. Formulation 1 containing PEG as non volatile liquid and MCC as carrier was selected as best formulation among all liquisolid formulations and compared the dissolution time of this formulation with marketed formulation and pure drug graphically (Fig 12). According to “Diffusion layer model” for dissolution, dissolution rate is in proportion to concentration gradient in stagnant diffusion layer. Not only the concentration gradient, drug dissolution is directly proportional to surface area available for dissolution. As liquisolid tablets contain a drug dissolved in polyethylene glycol, the drug surface available for dissolution is highly increased. In short, drug is present in the form of molecular dispersion, after its disintegration in the dissolution media. As all the dissolution tests for Ketoprofen liquisolid tablets were conducted at...
constant speed (100 rpm) and in same dissolution medium, the thickness of stagnant diffusion layer and diffusion coefficient for drug dissolution will be almost identical. Hence, molecularly dispersed drug in liquisolid tablets may be responsible for greater dissolution rates compared to marketed formulations. This will also reflect enhanced oral bioavailability.

CONCLUSION
The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as Ketoprofen. Polyethylene glycol was used as a liquid vehicle. 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.

ACKNOWLEDGEMENTS
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REFERENCES
11. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets for mulation: In Vitro and in


### Table 1: Formulations of Liquisolid Compacts

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug (mg)</th>
<th>Solvent</th>
<th>Carrier</th>
<th>Coating material</th>
<th>Disintegrating agent</th>
<th>Total weight</th>
<th>Liquid Loading factor ($L_f$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>Polyethylene glycol - 55mg</td>
<td>Micro Crystalline Cellulose- 329mg</td>
<td>Silica gel-16mg</td>
<td>Sodium Starch Glycollate</td>
<td>525mg</td>
<td>0.167</td>
</tr>
<tr>
<td>F2</td>
<td>100</td>
<td>Polyethylene glycol - 55mg</td>
<td>Di Calcium Phosphate- 324mg</td>
<td>Silica gel-16mg</td>
<td>Sodium Starch Glycollate</td>
<td>519mg</td>
<td>0.169</td>
</tr>
<tr>
<td>F3</td>
<td>100</td>
<td>Polyethylene glycol - 55mg</td>
<td>Starch- 324mg</td>
<td>Silica gel-16mg</td>
<td>Sodium Starch Glycollate</td>
<td>519mg</td>
<td>0.169</td>
</tr>
<tr>
<td>F4</td>
<td>100</td>
<td>Polyethylene glycol - 55mg</td>
<td>Lactose-329mg</td>
<td>Silica gel-16mg</td>
<td>Sodium Starch Glycollate</td>
<td>525mg</td>
<td>0.167</td>
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Table 2: Results of Angle of repose, Consolidation Index and Hausners ratio

<table>
<thead>
<tr>
<th>S.NO</th>
<th>TAPPED DENSITY</th>
<th>BULK DENSITY</th>
<th>ANGLE OF REPOSE</th>
<th>CONSOLIDATION INDEX</th>
<th>HAUSNERS RATIO</th>
</tr>
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<tbody>
<tr>
<td>F1</td>
<td>0.88</td>
<td>0.75</td>
<td>28</td>
<td>14.7</td>
<td>1.17</td>
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<tr>
<td>F2</td>
<td>0.85</td>
<td>0.7</td>
<td>28.5</td>
<td>14.9</td>
<td>1.18</td>
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<tr>
<td>F3</td>
<td>0.8</td>
<td>0.7</td>
<td>29</td>
<td>12.5</td>
<td>1.14</td>
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<tr>
<td>F4</td>
<td>0.82</td>
<td>0.72</td>
<td>29.56</td>
<td>12.1</td>
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Table 3: Results of Content Uniformity

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<tr>
<th>Formulations</th>
<th>Content uniformity (%)</th>
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<tbody>
<tr>
<td>F1</td>
<td>99.5 ± 0.12</td>
</tr>
<tr>
<td>F2</td>
<td>100.2 ± 0.13</td>
</tr>
<tr>
<td>F3</td>
<td>101.1 ± 0.21</td>
</tr>
<tr>
<td>F4</td>
<td>101.3 ± 0.10</td>
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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>
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<tr>
<td>F1</td>
<td>4 ± 0.2</td>
<td>0.145 ± 0.025</td>
<td>525±1.5</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>F2</td>
<td>4 ± 0.3</td>
<td>0.153 ± 0.024</td>
<td>519±1.5</td>
<td>2.5 ± 0.4</td>
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<tr>
<td>F3</td>
<td>3 ± 0.2</td>
<td>0.292 ± 0.032</td>
<td>519±1.5</td>
<td>3.4 ± 0.3</td>
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<tr>
<td>F4</td>
<td>5 ± 0.3</td>
<td>0.125 ± 0.021</td>
<td>525±1.7</td>
<td>2.6 ± 0.2</td>
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Table 5: Results of % Drug Release of various formulations of Ketoprofen

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Drug Release after</th>
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<tr>
<td></td>
<td>10min</td>
</tr>
<tr>
<td>F1</td>
<td>101.81</td>
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<tr>
<td>F2</td>
<td>82.30</td>
</tr>
<tr>
<td>F3</td>
<td>92.48</td>
</tr>
<tr>
<td>F4</td>
<td>56.22</td>
</tr>
<tr>
<td>Pure Drug</td>
<td>16.46</td>
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<tr>
<td>Marketed</td>
<td>26.72</td>
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</table>

Fig 1: XRD of Ketoprofen pure drug

Fig 2: XRD of Ketoprofen liquisolid compacts prepared with MCC

Fig 3: XRD of Ketoprofen liquisolid compacts prepared with DCP

Fig 4: XRD of Ketoprofen liquisolid compacts prepared with Lactose
Fig 5: XRD of Ketoprofen liquisolid compacts prepared with Starch

Fig 6: FTIR of Ketoprofen pure drug

Fig 7: FTIR of Ketoprofen liquisolid compacts prepared with DCP

Fig 8: FTIR of Ketoprofen liquisolid compacts prepared with Lactose

Fig 9: FTIR of Ketoprofen liquisolid compacts prepared with MCC

Fig 10: FTIR of Ketoprofen liquisolid compacts prepared with MCC
Fig 11: Dissolution Graph of Liquisolid Formulations

Fig 12: Comparative Dissolution Graph of Ketoprofen