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FORMULATION AND IN- VITRO EVALUATION OF FAST-DISINTEGRATING TABLETS OF FLUPIRTINE

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Abstract

Recent developments in fast-dissolving or disintegrating tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. The main objective of the present study was to prepare the orally disintegrating tablets of Flupirtine, a non-steroidal anti-inflammatory drug (NSAID) using different superdisintegrants by direct compression method. Different concentrations (4%, 8%, and 10%) of super disintegrants such as Primogel, Kollidon Cl, and Lycoat were used in the formulation. Mannitol was used as a bulking agent and to enhance the mouth feel and taste. The formulated tablets were evaluated for pre-formulation and post-formulation parameters and they were found to be satisfactory and within the official limits. All the tablets shown hardness 3-4.5kg/cm², friability of all the formulations was less than 1%, weight variation and drug content was found to be within official limits. Amongst all formulations, the optimized formulation F9 was prepared with Lycoat as a super disintegrant showed least disintegration time and faster dissolution.

Key Words: Flupirtine, Fast-disintegrating tablet, Direct compression method, Superdisintegrants.

Introduction

The major problem faced by many patients with conventional tablet dosage form is difficulty in swallowing. This problem is more apparent when drinking water is not easily available to the patient talking medicine. Hence, patients may not comply with prescription, which results in high incidence of ineffective therapy [1]. The fast-dissolving drug delivery system is rapidly gaining acceptance as an important novel drug delivery system. This delivery system emerged from the
desire to provide patient with more convenient medication, with better patient compliance than with conventional tablet dosage form. Bioavailability of the drug from this delivery system is significantly greater than from conventional tablets [2-4].

Flupirtine is a triaminopyridine derivative that functions as a centrally acting non-opioid (non-narcotic) analgesic; it also possesses a muscle relaxing effect. It has been in clinical use since 1984. The pharmacological and therapeutic properties of Flupirtine in pain states have been reviewed extensively [5]. It has unique spectrum of pharmacological activities [6-11] and is devoid of the typical side effects of natural or synthetic opioids, such as respiratory depression, constipation, tolerance, physical and/or psychological dependence, and liability to cause addiction. It is an NSAID, which is used in the treatment of acute pain conditions. It has also been reported that Flupirtine has biological half-life of 6½ hours, so it is desirable to formulate orodispersible tablet which would increase the bioavailability and give rapid onset of action by oral route. The antinociceptive activity of Flupirtine is similar to that of opioid agonists and mixed agonist antagonists but its mechanism of action is not based on the opioid mechanism. The morphine antagonist, Naloxone, did not inhibit the analgesic activity of Flupirtine. Furthermore, Flupirtine did not demonstrate any binding affinity for µ, or opioid receptors in the rat brain [12].

The performance of mouth dissolving tablets (MDT) depends on the technology used in their manufacture the basic approaches to develop MDT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation [13]. Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants [14].

In this study, an attempt has been made to formulate fast-dissolving tablet formulation of Flupirtine by using direct compression method.
Materials and Methods

Chemicals

Flupirtine was obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad (AP) and India. Sorbitol, Primogel, and Kollidon Cl were obtained from SD Find Chem. Ltd., Mumbai, India. Citric acid, sodium lauryl sulphate, Lycoat, Aspartame, Aerosi, Magnesium stearate and all other chemicals used were of analytical grade.

Preparation of Flupirtine Tablets

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique is applied in the current work because of the availability of improved excipients especially superdisintegrants and sugar-based excipients. Nine formulations were developed by varying concentrations of super disintegrating agents. The drug was mixed with proper portion of superdisintegrant. Care should be taken to confirm the proper mixing of drug and superdisintegrant. Then other excipients were added. Then the mixture is passed through sieve (Sieve No. 40). The mixture is blended with flavor, magnesium stearate, and microcrystalline cellulose. Finally, the blend is subjected for compressing using Rotary tablet punching machine. The prepared tablets were intended for further studies.

Evaluation Parameters of Tablet Blend

Pre-formulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form.

Hence, the following preformulation studies were performed on the formulated drug.

1. **Bulk density (Db)**[^15]

   It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve No. 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. The bulk density is calculated according to the following formula. It is expressed as g/ml.

   \[
   Db = \frac{M}{V_b}
   \]

   Where M is the mass of the powder

   Vb is the bulk volume of the powder
2. Tapped density (Dt)\textsuperscript{[16]}

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. It is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in g/ml and is given by the following formula.

\[ \text{Dt} = \frac{M}{Vt} \]

Where \( M \) is the mass of the powder

\( Vt \) is the tapped volume of the powder

3. Angle of Repose

The friction forces in a loose powder can be measured by the angle of repose (\( \theta \)). It is an indicative of the flow of properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

\[ \tan(\theta) = \frac{h}{r} \]

\[ \theta = \tan^{-1} \frac{h}{r} \]

Where \( \theta \) is the angle of repose

\( h \) is the height in centimeters

\( r \) is the radius in centimeters

The powder mixture was allowed to flow through the funnel fixed to a stand at a definite height (h).

The angle of repose was calculated by measuring the height and radius of the heap of powder formed.

4. Carr\'s Index (CI % Compressibility)

It indicates the powder flow properties. It is expressed in percentage and is calculated by using the formula.

\[ \text{CI} = \left( \frac{\text{Dt} - \text{Db}}{\text{Dt}} \right) \times 100 \]

Where \( \text{Dt} \) is the tapped density of the powder and
Db is the bulk density of the powder.

5. Drug-Excipient compatibility study

FTIR studies were carried out in order to determine any possible interaction between drug and excipients used. IR absorption spectrum of Flupirtine was determined using FT-IR Spectrophotometer.

Briefly about 2mg of sample was ground thoroughly with previously dried KBR at $120^\circ$ for 30 min, uniformly mixed with drug and kept in sample holder and the spectra was recorded over the wave number $400-4000^{-1}$. IR Spectrum of pure drug, physical mixture of ingredients of the formulation and optimized tablet were recorded.

Evaluation of Flupritine Tablets

The compressed tablets were evaluated for following parameters.

1. **Thickness**[^21]

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. The thickness of the tablet was measured by using digital vernier calipers.

2. **Weight variation (Uniformity)**[^21]

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. Weight variation specifications of the formulated tablets were compared with the specifications mentioned as per IP2010. The individual weights were compared with average weight.

3. **Hardness (Tablet crushing strength)**[^22]

Hardness is the force required to break a tablet across diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The hardness of tablets was tested using digital hardness test, the average of the tablets, was measured and recorded. The force measured was expressed in kg/cm^2.

4. **Friability**[^23]

Friability (F) is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation and shipment. Permitted friability limit is 1%.
Roche friabilator was used to measure the friability of the tablets. 10 tablets were weighed collectively and placed in a chamber of the friabilator. In the friabilator, tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of friabilator. It was rotated at a rate of 25 rpm. After 100 rotations the tablet were taken out from the friabilator and intact tablets were again weighed collectively. Percentage friability was calculated using the following equation

\[
\% F = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100
\]

5. **Disintegration time**[24]

The disintegration test was carried out using USP disintegration test apparatus type-II (Electrolab, Hyderabad, India). Six (6) tablets were taken randomly from each batch and placed each basket of the disintegration test apparatus and discs were placed over each tablet. Distilled water was used as the medium maintained at 37±2.0°C and observed the time taken for each tablet to disintegrate completely into fine particles was noted.

6. **In vitro dissolution study**[25]

The dissolution study was conducted using USP dissolution test apparatus type-II (Electrolab, Hyderabad, India). The dissolution test was performed in 900ml phosphate buffer (pH 6.8) as the dissolution medium at 100 rpm and 37±0.5°C. 5ml of aliquots were periodically withdrawn at predetermined time interval and equal amount of fresh medium was placed to maintain a constant volume. Each sample was analyzed photo metrically at 276nm against suitable blank using UV-Vis Spectrophotometer and drug content per tablet was determined.

**Results and Discussion**

The drug Flupirtine passed various test of identification and analysis. The pure drug Flupirtine and the solid admixture of drug and various excipients used in fast disintegrating tablet formulation were characterized by FT-IR spectroscopy to know the compatibility (Fig 1 & 2). Similar absorption bands (peaks) were observed with pure drug and pure drug with excipient, i.e., Lycoat. This result suggested that there was no physical or chemical interaction between Flupirtin and excipients such as superdisintegrating agents used in the manufacturing of fast dispersible tablets.
Nine different formulations (F1-F9) of Flupirtine were prepared with varying concentrations of superdisintegrants and, keeping other excipients constant, these tablets were manufactured by direct compression method. Total weight of individual tablet was kept constant at 250mg. Formulations F1-F3, F4-F6, and F7-F9 were manufactured by using Primogel, Kollidon chloride, Lycoat in 4%, 8% and 10% concentrations, respectively (Table 1).

**Table-1: Formulation design of Flupirtine fast disintegrating tablets.**

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupirtine</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Pre and Post-Compression Studies

The pre-compression studies performed on Flupirtine to find out bulk density, tapped density, angle of repose, Carr’s index a results clearly indicate that the values were within the limits and the results are shown in Table 2.

Table-2: Pre compression parameters of Flupirtine fast disintegrating tablets.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Batch No.</th>
<th>Angle of repose(°)</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>27.23</td>
<td>0.395±0.01</td>
<td>0.562±0.05</td>
<td>13.92±0.08</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>25.51</td>
<td>0.489±0.02</td>
<td>0.45±0.03</td>
<td>11.58±0.03</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>27.12</td>
<td>0.390±0.02</td>
<td>0.50±0.04</td>
<td>12.34±0.04</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>25.34</td>
<td>0.410±0.05</td>
<td>0.45±0.06</td>
<td>13.85±001</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>32.13</td>
<td>0.495±0.09</td>
<td>0.57±0.11</td>
<td>14.27±0.06</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>29.23</td>
<td>0.389±0.11</td>
<td>0.40±0.08</td>
<td>11.59±0.07</td>
</tr>
<tr>
<td>7</td>
<td>F7</td>
<td>26.48</td>
<td>0.391±0.07</td>
<td>0.42±0.12</td>
<td>14.22±0.03</td>
</tr>
<tr>
<td>8</td>
<td>F8</td>
<td>23.81</td>
<td>0.373±0.10</td>
<td>0.40±0.01</td>
<td>12.26±0.01</td>
</tr>
<tr>
<td>9</td>
<td>F9</td>
<td>24.13</td>
<td>0.494±0.10</td>
<td>0.40±0.03</td>
<td>11.45±0.02</td>
</tr>
</tbody>
</table>

The test results on weight variation of the tablets ranging from 196±1.32 to 199±1.01mg (Table 3), shows that all the tablets were not showing much variation in weight, i.e., the values are within the pharmacopoeial limits.
Table 3: Post compression parameters of Flupirtine fast disintegrating tablets.

<table>
<thead>
<tr>
<th>Batch No</th>
<th>Weight variation (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>D.T (sec)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>198±1.25</td>
<td>3.5 ± 0.1</td>
<td>5.1 ± 0.6</td>
<td>0.22 ± 0.03</td>
<td>41 ± 1.36</td>
<td>98.1± 0.25</td>
</tr>
<tr>
<td>F2</td>
<td>197±1.34</td>
<td>3.4 ± 0.1</td>
<td>4.5 ± 0.3</td>
<td>0.21 ± 0.01</td>
<td>57 ± 2.24</td>
<td>99.5 ± 0.38</td>
</tr>
<tr>
<td>F3</td>
<td>199±1.01</td>
<td>2.8 ± 0.1</td>
<td>4.2 ± 0.2</td>
<td>0.20 ± 0.03</td>
<td>45 ± 2.34</td>
<td>98 ± 0.58</td>
</tr>
<tr>
<td>F4</td>
<td>196±1.56</td>
<td>2.9 ± 0.1</td>
<td>4.1 ± 0.5</td>
<td>0.17 ± 0.03</td>
<td>35 ± 2.98</td>
<td>99 ± 0.65</td>
</tr>
<tr>
<td>F5</td>
<td>197±1.53</td>
<td>3.6 ± 0.05</td>
<td>4.0 ± 0.6</td>
<td>0.19 ± 0.02</td>
<td>56 ± 1.38</td>
<td>97.2 ± 0.78</td>
</tr>
<tr>
<td>F6</td>
<td>196±1.54</td>
<td>3.5 ± 0.06</td>
<td>4.4 ± 0.8</td>
<td>0.20 ± 0.04</td>
<td>60 ± 1.56</td>
<td>98.5 ± 0.65</td>
</tr>
<tr>
<td>F7</td>
<td>196±1.32</td>
<td>3.3 ± 0.04</td>
<td>4.2 ± 0.7</td>
<td>0.23 ± 0.02</td>
<td>58 ± 1.65</td>
<td>97.7 ± 0.38</td>
</tr>
<tr>
<td>F8</td>
<td>196±1.52</td>
<td>3.8 ± 0.05</td>
<td>5.5 ± 0.6</td>
<td>0.21 ± 0.04</td>
<td>70± 1.62</td>
<td>92.9 ± 0.29</td>
</tr>
<tr>
<td>F9</td>
<td>198±1.35</td>
<td>3.3 ± 0.06</td>
<td>4.3 ± 0.3</td>
<td>0.20 ± 0.01</td>
<td>55± 1.28</td>
<td>98.8 ± 0.89</td>
</tr>
</tbody>
</table>

The friability is needed for tablets to withstand the force of compression applied during the manufacture of tablets. The friability of the tablets was tested using Roche friabilator and the results show that all the values are within the normal limit, i.e., 0.17-0.23%, and the formulations F1 and F7 shown better results when compared to all other formulations (Table 3). The values obtained were <1 reveals that the tablets have good mechanical resistance.

Disintegration is an important parameter to know the breakdown of the particle. The disintegration test was conducted for all the formulated tablets shown in vitro dispersion time < 70 seconds, indicating that the Flupirtine tablets were better and effective drug. Among the formulations, F1, F3 and F4 showed drug release 41, 45 and 35 respectively, with better disintegrating capacity (Table 3).

The drug content of all the nine formulations of Flupirtine tablets were found to be within the range of 92.9-99.5% which were within the limits of BP specifications. The results are shown in Table 3.

The tablets (F1-F9) were evaluated for in vitro dissolution studies. Formulations F1-F3 were manufactured by using 8mg of Primogel, Kollidon Cl and Lycoat, in which 87.8±0.1 drug was released within 30 minutes which confirms within the limits by USP that states that not less than 80% of labeled amount of Flupirtine was released in 30 minutes. Formulations F4-F6 were manufactured by using 16mg of superdisintegrants showed 89.4±0.6 and formulations F7-F9 used 20mg of...
superdisintegrants exhibited 97.8±1.0 drug release in 30 minutes. This clearly indicates that increase in concentration of superdisintegrants increased the % release of the drug. The dissolution rate of F1-F9 formulations were tabulated in Table 4 & Fig. 3.

### Table-4: In-Vitro dissolution studies of Flupiritine fast disintegrating tablets.

<table>
<thead>
<tr>
<th>TIME</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>55.8±0.2</td>
<td>54.5±0.5</td>
<td>53.1±0.3</td>
<td>53.8±0.1</td>
<td>55.1±0.4</td>
<td>55.8±0.2</td>
<td>38.5±0.3</td>
<td>45.1±0.2</td>
<td>25.2±0.5</td>
</tr>
<tr>
<td>10</td>
<td>62.8±0.2</td>
<td>59.5±0.5</td>
<td>60.2±0.4</td>
<td>60.2±0.4</td>
<td>61.5±0.4</td>
<td>44.9±0.6</td>
<td>55.5±0.4</td>
<td>45.5±0.6</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>68.4±0.6</td>
<td>65.1±0.2</td>
<td>68.4±0.5</td>
<td>68.4±0.5</td>
<td>71.1±0.3</td>
<td>69.1±0.9</td>
<td>51.9±1.0</td>
<td>62.5±0.9</td>
<td>58.1±0.8</td>
</tr>
<tr>
<td>20</td>
<td>77.2±0.75</td>
<td>72.6±0.1</td>
<td>74.6±0.5</td>
<td>74.6±0.3</td>
<td>77.2±0.5</td>
<td>75.3±0.3</td>
<td>59.5±1.1</td>
<td>68.0±0.7</td>
<td>72.3±0.8</td>
</tr>
<tr>
<td>25</td>
<td>80.2±1.0</td>
<td>81.4±0.1</td>
<td>80.7±0.5</td>
<td>80.7±0.8</td>
<td>82.0±0.3</td>
<td>82.7±0.3</td>
<td>65.0±1.1</td>
<td>74.2±0.1</td>
<td>90.8±1.2</td>
</tr>
</tbody>
</table>

Fig-3: Percentage drug release of Flupiritine Fast disintegrating tablets (F1-F9).

The studies carried out in the investigation introduced two platform technologies that showed *in vitro* potential and to add significant advances to the field of orally fast-dissolving Flupiritine tablets. Some extended work is underway to explore the clinical performance of these ODTs in terms of patient acceptance, manual handling, mouth feeling upon disintegration and other *in vivo* data such as sites of absorption, GIT residence time and blood level curve. In terms of process development, determination the effect of the shape and size of the tablets as ODT characteristics would be
Conclusion

The use of superdisintegrants for preparation of fast-dissolving tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration/dissolution of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment.

The disintegration is reported to have an effect on dissolution characteristics as well. Prepared fast-disintegrating tablet gets dispersed in the mouth quickly and releases the drug fast.

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