Formulation and evaluation of naproxen sodium rapimelts by direct compression method

Naga Subba Reddy Jekku1, T.S Nagaraja1, Bharathi1 and M. Devi Reddy2

1, Department of Pharmaceutics, SJM College of Pharmacy, Chitradurga, (Karnataka) –India
2, Department of Pharmaceutics, Krishna Teja College of Pharmacy, Thirupathi, (Andhra Pradesh) -India

Abstract

Naproxen sodium is an analgesic NSAID (non steroidal anti inflammatory drug) used for the treatment of pain, inflammation, fever and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, migraine and dysmenorrhea. However, the gastric discomfort caused by drug results in poor patient compliance associated with its conventional dosage forms. Hence the present investigation was undertaken with a view to develop Rapimelt tablet of naproxen, which offers quick on set of action of drug and minimizes the problem of gastric discomfort associated with it. Thus improves patient compliance, generates rapid response, enhances bioavailability and also reduces the dose of drug. In this study, rapimelt tablets were prepared by direct compression method using three different superdisintegrants e.g. sodium starch glycolate, croscarmellose sodium and crospovidone in three different concentrations e.g. 2%, 4% and 6% along with other excipients. The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time and dissolution rate. In the present work efforts have been made to prepare and evaluate Rapimelt tablets of Naproxen with different concentrations of superdisintegrants sodium starch glycolate, CCS and Crospovidone by direct compression technique. Release profile of F-9 having 6% Crospovidone in direct compression method was found to have maximum release of 97.56 % at the end of 30 minutes. The drug release from all batches was found to be concentration dependent. Hence the formulation of F-9 fulfills the objective of the present study. F-12 fulfills the objective of the present study.

Key-Words: Rapimelts, Naproxen sodium, Sodium starch glycolate, Crosscarmellose sodium

Introduction

With the increase in the average human life, drug administration for elderly patients has become more important. Due to a decline in swallowing ability with age, a great many elderly patients complain that it is difficult to take medication in the form of tablets. Recently, useful dosage forms, such as rapimelt tablets or rapidly disintegrating or dissolving tablets have been developed and applied clinically. This dosage form can also improve compliance in children, as well as, for local action within oral cavity as local anesthetics for toothache, cold sore or teething product. Rapimelt tablets may also be another option in emergency. Naproxen is a non-steroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. Naproxen sodium is an odourless crystalline powder, white to creamy in color. It is soluble in methanol and water.

* Corresponding Author
E.mail: subbu.naga14@gmail.com

The basic approach used in the development of the Rapimelt tablets is the use of superfine disintegrates. The main objective of this research is to study the effect of concentration of different superfine disintegrants on drug release of Naproxen Sodium by direct compression method.

Material and Methods

Tablets containing 250 mg of Naproxen Sodium were prepared by direct compression method and the various formulae used in the study6. Total nine formulations with different concentration of CCS (F1, F2, F3), SSG (F4, F5, F6) and Crospovidone (F7, F8, F9) were prepared. The drug, diluents, superdisintegrants and sweetener are passed through sieve #60. The powder blend was compressed in to tablets on ten station rotary punch-tableting machine(Rimek mini press-1, Model RSB-4, Karnavati Engineering, Ahmedabad). The prepared tablets were evaluated for various parameters like...
hardness, friability, weight variation, thickness, wetting time, disintegration time, dissolution study and dissolution efficiency.8

**Compression of tablets by using direct compression technique:**
To the blended powders finally magnesium stearate and talc were added. The mixed blend of drug and excipients was compressed into tablets weighing 250 mg using a flat faced punches of 8 mm diameter in a rotary tablet press (Rimek mini press- 1, Model RSB-4, Karnavati Engineering, Ahmedabad). A minimum of 50 tablets were prepared for each batch.

**Evaluation of naproxen sodium rapimelt tablets**
Pre compression parameters
Angle of Repose:9
Angle of repose was determined using funnel method4. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \( \theta \) is the angle of repose, h is height of pile; r is radius of the base of pile.

**Bulk Density**10
Apparent bulk density (\( \rho_b \)) was determined by pouring the blend into a graduated cylinder4. The bulk volume (\( V_b \)) and weight of powder (\( M \)) was determined. The bulk density was calculated using the formula

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

**Tapped Density**10
The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (\( V_t \)) occupied in the cylinder and weight (\( M \)) of the blend was measured. The tapped density (\( \rho_t \)) was calculated using the following formula

\[ \rho_t = \frac{M}{V_t} \]

**Compressibility Index**11
The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules was determined by Carr’s or compressibility index (I), which is calculated by using the following formula

\[ I = \frac{pt - pb}{pt} \times 100 \]

**Post compression parameters**
All prepared Rapimelts were evaluated for its uniformity of weight, hardness, friability and thickness, in vitro disintegration time, wetting time, in vitro drug release according to official methods shown in Table 3.

**Hardness**12
The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

**Friability**13
Ten tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was measured as per the following formula.

\[ \text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \]

**Weight Variation**14
Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5% (USP XX).

**Disintegration time**15
The *in vitro* disintegration test was carried out at 37°C in 900ml of distilled water. The *in vitro* disintegration time of 5 tablets from each formulation was determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in seconds for complete disintegration of the tablet with no mass remaining in the apparatus was measured.

**Wetting time**16,17
Wetting time is an important step in the disintegration process. Wetting is closely related to the inner structure of tablet and to the hydrophilicity of excipients. The method reported by Yunexia was used to measure tablet wetting time.8 A piece of tissue paper folded twice was placed on the distilled water (6ml) which was taken in a small petridish (6.5cm diameter).One tablet was placed on the paper and the time for complete wetting of the tablet was measured.

**In vitro drug release studies**18
In *In Vitro* dissolution studies for all the prepared tablets were carried out using USP paddle method at 50 rpm in 900 ml of 6.8 pH phosphate buffer as dissolution media, maintained at 37 ± 0.5°C. 5 ml of samples, were
withdrawn from the dissolution medium at the specified regular intervals, filtered through Whatmann filter paper and release of the drug was determined spectrophotometrically at 272nm. An equal volume of pre warmed (37ºC) fresh medium was replaced into the dissolution medium after each sampling, to maintain the constant volume of the dissolution medium throughout the test. Then the cumulative percentage of drug release was calculated and represented graphically (Figure-2 and 3).

Results and Discussion
Nine formulations of Naproxen Sodium were prepared with concentration of three superdisintegrants: Sodium Starch glycolate, Croscarmellose sodium, Crospovidone and Avicel 101 were used as a direct compressible vehicle. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.50-0.56 g/cm3 and the tapped density between 0.61-0.66g/cm3. Using these two density data compressibility index was calculated. The Hausner’s ratio was found between 1.17-1.23 and the compressibility index was found between 15.152 and 19.048 % and the compressibility -flowability correlation data indicated a fairly good flowability of the blend. The good flowability of blend was also evidenced with angle of repose (range of 26 – 31º), which is below 40º indicating good flowability. Tablets were prepared using direct compression technique. Precompression parameters shown in table no: 2. The hardness of the tablets between 3.1–3.5kg/cm². The weight variation of the tablets between 248–251 mg. The thickness of the tablets between 2.56 – 3.42 mm. Friability of the tablets was found below 1 % indicating a good mechanical resistance of tablets. Wetting time is closely related to the inner structure of the tablet. This showed that wetting process was very rapid in almost all formulations. This may be due to ability of swelling and also capacity of water absorption and causes swelling. The in vitro disintegrating time is measured by the time taken to undergo complete disintegration of the tablets. Rapid disintegration within the seconds was observed in all the formulations. Comparision of disintegration time and wetting time done by drawing graph shown in figure no: 1. The results showed that tablet containing Crospovidone having low disintegrating time as compare to other superdisintegrants. The concentration of superdisintegrants increases as the disintegrating time decreases. The in vitro disintegrating time of the tablets was found to be less than 50 sec. Post compression parameters shown in table no: 3. All the formulations showed enhanced dissolution rate as compared to superdisintegrants. The maximum increase in the dissolution rate was observed with Crospovidone amongst the three superdisintegrants. In the present work release profile of F-9 having 6% Crospovidone in direct compression method was found to have maximum release of 97.56 % at the end of 30 minutes. The drug release from all batches was found to be concentration dependent. Hence the formulation of F-9 fulfills the objective of the present study.

Conclusion
The use of superdisintegrants for preparation of Rapimelt tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well. Prepared Rapimelt tablets gets dispersed in the mouth quickly and releases the drug fast. Fig. 3 show the cumulative percentage of Naproxen Sodium Sodium released from formulated tablet with different concentration of Sodium Starch Glycolate and Croscarmellose sodium, and Crospovidone. It is clear that the dissolution and disintegration of Naproxen Sodium Sodium has improved considerably in batch F9 as compared to other formulations, Batch F9 tablet showed good dissolution efficiency and rapid dissolution. The study shows that the dissolution rate of Naproxen Sodium Sodium can be enhanced to a great extent by direct compression technique with the addition of superdisintegrants and no extreme changes in formulation F9 during stability studies.

Acknowledgement
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References


### Table 1: Composition of Rapimelt tablets of Naproxen Sodium

<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>
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<tr>
<td>Naproxen Sodium</td>
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<td>100</td>
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<td>100</td>
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<td>100</td>
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<td>10</td>
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<td>10</td>
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<td>Crospovidone</td>
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<td>5</td>
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<td>Sodium saccharine</td>
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<tr>
<td>Mg. stearate</td>
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Table 2: Pre compression parameters of Naproxen Sodium Rapimelts

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bulk density (g/cc) ±SD, n=3</th>
<th>Tapped density (g/cc) ±SD, n=3</th>
<th>Angle of repose (degree) ±SD, n=3</th>
<th>Carr’s index (%) ±SD, n=3</th>
<th>Hausner’s Ratio ±SD, n=3</th>
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<tr>
<td>F1</td>
<td>0.52 ± 0.004</td>
<td>0.62 ± 0.01</td>
<td>26.28 ± 1.26</td>
<td>16.12 ± 0.80</td>
<td>1.19 ± 0.04</td>
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<td>F2</td>
<td>0.50 ± 0.003</td>
<td>0.61 ± 0.01</td>
<td>28.53 ± 1.20</td>
<td>18.03 ± 0.90</td>
<td>1.22 ± 0.02</td>
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<td>F3</td>
<td>0.56 ± 0.002</td>
<td>0.66 ± 0.02</td>
<td>29.39 ± 1.27</td>
<td>15.15 ± 1.55</td>
<td>1.17 ± 0.70</td>
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<td>F4</td>
<td>0.51 ± 0.007</td>
<td>0.63 ± 0.02</td>
<td>28.43 ± 1.46</td>
<td>19.04 ± 1.13</td>
<td>1.23 ± 0.06</td>
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<tr>
<td>F5</td>
<td>0.50 ± 0.009</td>
<td>0.61 ± 0.02</td>
<td>30.38 ± 1.31</td>
<td>18.03 ± 0.93</td>
<td>1.22 ± 0.07</td>
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<td>F6</td>
<td>0.53 ± 0.002</td>
<td>0.63 ± 0.31</td>
<td>31.03 ± 1.40</td>
<td>15.87 ± 1.42</td>
<td>1.18 ± 0.11</td>
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<tr>
<td>F7</td>
<td>0.53 ± 0.002</td>
<td>0.64 ± 0.01</td>
<td>28.32 ± 1.52</td>
<td>17.18 ± 1.0</td>
<td>1.20 ± 0.02</td>
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<td>F8</td>
<td>0.52 ± 0.005</td>
<td>0.62 ± 0.01</td>
<td>29.08 ± 1.20</td>
<td>16.12 ± 1.52</td>
<td>1.19 ± 0.04</td>
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<tr>
<td>F9</td>
<td>0.55 ± 0.003</td>
<td>0.66 ± 0.02</td>
<td>30.21 ± 1.70</td>
<td>16.66 ± 1.20</td>
<td>1.20 ± 0.03</td>
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</tbody>
</table>

Table 3: Post compression parameters of Naproxen Sodium Rapimelts

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Weight variation ±SD, n=3</th>
<th>Hardness (Kg/cm²) ±SD, n=3</th>
<th>Friability (%) ±SD, n=3</th>
<th>Thickness (mm) ±SD, n=3</th>
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<tbody>
<tr>
<td>F1</td>
<td>250±1.05</td>
<td>3.8±0.14</td>
<td>0.65±0.03</td>
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<td>F2</td>
<td>251±1.02</td>
<td>3.8±0.11</td>
<td>0.64±0.07</td>
<td>3.39±0.09</td>
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<tr>
<td>F3</td>
<td>250±0.99</td>
<td>3.6±0.16</td>
<td>0.59±0.05</td>
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<td>F4</td>
<td>250±1.15</td>
<td>3.7±0.15</td>
<td>0.70±0.03</td>
<td>2.96±0.08</td>
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<tr>
<td>F5</td>
<td>248±1.32</td>
<td>3.5±0.13</td>
<td>0.74±0.01</td>
<td>2.72±0.05</td>
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<td>F6</td>
<td>249±1.10</td>
<td>3.4±0.15</td>
<td>0.58±0.06</td>
<td>2.68±0.02</td>
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<td>F7</td>
<td>249±1.32</td>
<td>3.4±0.12</td>
<td>0.64±0.05</td>
<td>2.65±0.09</td>
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<tr>
<td>F8</td>
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<td>3.3±0.13</td>
<td>0.75±0.06</td>
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<td>F9</td>
<td>250±1.15</td>
<td>3.1±0.12</td>
<td>0.48±0.08</td>
<td>2.56±0.06</td>
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Fig. 1: Comparison of disintegration time and wetting time done by drawing graph

Fig. 2: Cumulative % drug Release Vs Time in min from prepared batches F-1, F-2, F-3, F-4 & F-5 of Rapimelts of Naproxen Sodium prepared by direct compression method

Fig. 3: Cumulative % drug Release Vs Time in min from prepared batches F-6, F-7, F-8 & F-9 of Rapimelts of Naproxen Sodium prepared by direct compression method