Formulation and comparison of in vitro release profile of hydrophilic and hydrophobic polymer based Naproxen matrix tablets

Kumar Bishwajit Sutradhar, Tajnin Ahmed, Afia Ferdous and Riaz Uddin

ABSTRACT

The study was aimed to investigate the effect of polymer on the release profile of Naproxen from different percentages of HPMC 5cps and Kollidon SR based matrix systems. Different amount of HPMC and Kollidon SR were used to develop matrix builder in the four proposed formulations (F1-F4) for the study of release rate retardant effect at 25% and 35% of total weight of tablet matrix respectively. The tablets were prepared by direct compression method. The granules and tablets were evaluated for their physical properties and they did not show any significant variations and were found to have good physical integrity. The dissolution study of those proposed formulations were carried out in the simulated intestinal medium (pH 7.4) for 8 hours using USP paddle method with 50 rpm at 37±0.5°C. HPMC is hydrophilic and Kollidon SR is hydrophobic in nature. Statistically significant difference were found among the drug release profile from different percent of polymer and the release mechanisms were explored and explained with zero order, Higuchi and Korsmeyer equations. The release of Naproxen from F-1 and F-2 very closely followed Korsmeyer release kinetics where F-3 and F-4 best fitted with Higuchi model. The cumulative percent release of Naproxen was highest in F-2 containing 35% of HPMC. On the basis of results, it was found that the profile of F-1 formulation was the best among the four formulations. Between these two polymers, HPMC showed better percentage of release and Kollidon SR showed better release retardant effect.

Key words: Naproxen, Direct Compression, Sustained Release, HPMC 5cps, Kollidon SR.

INTRODUCTION

Sustained release dosage formulations by direct compression processes are presently gaining importance in order to achieve prolonged action without avoiding multiple doses taking which is commonly needed for maintaining therapeutic action of the drug for a stipulated period (Lordi, 1990). It is a very simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms (Longer and Robinson, 1990). Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semisynthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and release the drug at constant rate for desired time period (Lordi, 1990).

There are number of techniques applied in the formulation and manufacturing of sustained release dosage forms. However, the matrix tablet by direct compression has attracted much attention due its technological simplicity in comparison with other controlled release systems. Direct compression method has been applied for preparation of tablet matrix that
involved simple blending of all ingredients used in the formulations and then underwent direct compression. It required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate (Shangraw and Demarest, 1993). There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Kollidon SR is hydrophobic in nature whereas HPMC 5cps is a hydrophilic polymer that become hydrated, swollen and facilitates to diffuse the drug (Bidah and Vernaud, 1991).

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of moderate to severe pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, bursitis, and the treatment of primary dysmenorrhea (Howland, 2006).

Naproxen sustained release tablet matrix can be prepared by direct compression method by utilizing different grades of hydrophilic or hydrophobic polymers. These polymers can hold active ingredients firmly that depend on the concentration or ratio of the polymers used. In this study an attempt has been made to formulate Naproxen as sustained release tablet matrix with the addition of release retarding polymers HPMC 5cps and Kollidon SR in different ratios. The effects of polymer loading on drug release were recorded and release kinetics was evaluated.

MATERIALS AND METHODS

Materials

Naproxen was obtained as a gift sample from Eskayef Bangladesh Limited. HPMC 5cps and Kollidon SR both were collected from BASF, India. Magnesium stearate and microcrystalline cellulose (Avicel-101) were collected from Tasc Pharmaceuticals Ltd, India. Aerosil 200 was purchased from Degussa, Germany. Lactose was purchased from local market. Di-sodium hydrogen phosphate and sodium di-hydrogen ortho-phosphate were of analytical grade.

Equipments

UV Visible Spectrophotometer (HACH, model-DR/4000u); Dissolution Tester (PHARMA TEST, model-DT 70); Disintegration Tester (PHARMA TEST, D-63512); Hardness Tester (PHARMA TEST, Germany); Friability Tester (PHARMA TEST, Germany); Electric Balance (Denver Instrument, model-M-310); Digital pH Meter (LIDA Instrument, model-PHS-25); Single Punch Tablet Press (Single punch machine, India).

Table 1. Naproxen, HPMC 5cps, Kollidon SR and excipients used in the proposed formulation coded as F-1 to F-4.

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>Naproxen (mg)</th>
<th>HPMC 5cps (mg)</th>
<th>Kollidon SR (mg)</th>
<th>Mg-stearate (mg)</th>
<th>Aerosil (mg)</th>
<th>Lactose (mg)</th>
<th>Avicel-101 (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>100</td>
<td>65 (25%)</td>
<td>-</td>
<td>05</td>
<td>05</td>
<td>65</td>
<td>20</td>
<td>260</td>
</tr>
<tr>
<td>F-2</td>
<td>100</td>
<td>91 (35%)</td>
<td>-</td>
<td>05</td>
<td>05</td>
<td>65</td>
<td>20</td>
<td>260</td>
</tr>
<tr>
<td>F-3</td>
<td>100</td>
<td>-</td>
<td>65 (25%)</td>
<td>05</td>
<td>05</td>
<td>65</td>
<td>20</td>
<td>260</td>
</tr>
<tr>
<td>F-4</td>
<td>100</td>
<td>-</td>
<td>91 (35%)</td>
<td>05</td>
<td>05</td>
<td>39</td>
<td>20</td>
<td>260</td>
</tr>
</tbody>
</table>

Preparation of matrix Tablet

Drug, polymer and other excipients were weighed separately for 100 tablets per formulation as per proposed formulations. The proposed formulations were coded as F-1, F-2, F-3, and F-4. The amounts of drug and excipients were expressed in milligram unit. At first lactose, aerosol and polymer were mixed and sieved. Then Naproxen was added and mixed properly within 15 minutes and sieved again. Mg-stearate and avicel (MCC) was added and mixed properly within 5 minutes. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (260 mg). After compression the tablets were weighed and tablet weight was found 250 mg to 270 mg. The tablets were prepared by direct compression; the types and amounts of polymers used are shown in Table 1.

Preparation of phosphate buffer

Phosphate buffer at pH 7.04 was prepared with di-sodium hydrogen phosphate and sodium di-hydrogen ortho-phosphate. For preparing 9 litre phosphate buffer, 12.789g of di-sodium hydrogen phosphate and 2.043g of sodium di-hydrogen ortho-phosphate was taken in a plastic container, dissolved in and diluted with distilled water up to the mark. The pH of the buffer solution was adjusted using a pH meter.

Evaluation of Granules

Angle of repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granular cone was measured and angle of repose was calculated using the following equation (USP 30 and NF 25, 2007):

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

Where, h and r are the height and radius of the cone.

Carr’s compressibility index

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr’s compressibility index (I) which is calculated by using the following formula (USP 30 and NF 25, 2007):

\[ CI (%) = \left(\frac{TD - PD}{TD}\right) \times 100 / TD \]

Where, TD = Tapped Density, PD = Poured Density, CI = Carr’s compressibility index.
**Hausner Ratio**

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula (USP 30 and NF 25, 2007):

\[
\text{Hausner Ratio} = \frac{\text{TD}}{\text{PD}}
\]

Where, TD = Tapped Density, PD = Poured density.

**Tapped Density**

Tapped density is the ratio between mass of granules and volume of the granules after tapping. It is expressed by gm/cc (USP 30 and NF 25, 2007):

\[
\text{Tapped Density} = \frac{\text{Weight of granules}}{\text{Tapped volume}}
\]

**Evaluation of tablets**

**Tablet hardness**

The strength of tablet is expressed as tensile strength (kp). The tablet crushing load, which is the force required to break a tablet by compression. The hardness of the tablets was determined by diametral compression using a tablet hardness tester (Rudnie and Schwartz, 1990).

**Tablet thickness**

Tablet thickness can be measured using a simple procedure. 5 tablets were randomly taken from each formulation and their thickness was measured using Varnier calipers. The thickness was measured by placing tablet between two arms of the Varnier calipers (Rudnie and Schwartz, 1990).

**Tablet Friability**

The friability of the tablets was measured in a tablet friability tester. Tablets of a known weight \(W_0\) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed \(W\) again. Percentage friability was calculated from the loss in weight as given in equation as below (USP 30 and NF 25, 2007):

\[
\% \text{ of friability} = \frac{W_0 - W}{W_0} \times 100
\]

The weight loss should not be more than 1%. Determination was made in duplicate.

**Weight variation test**

The weights were determined to within ±1mg by using Denver Instrument (Model-M-310). Weight control is based on a sample of 20 tablets. Determination was made in duplicate (USP 30 and NF 25, 2007).

**In vitro dissolution study of the tablet matrix**

Dissolution studies were conducted according to USP method using apparatus II paddle at a speed of 50 rpm and the temperature was maintained at 37±0.5°C (USP 30 and NF 25, 2007). The total duration of dissolution was 8 hours in which for eight hours the tablet were subjected to simulated intestinal media (buffer pH 7.4). Firstly, basic buffer (900ml) was taken into six vessels and for each run, 3 tablets from two formulations were placed into six vessels respectively for 8 hour. At every one hour interval, 10ml samples were withdrawn from the dissolution medium and 10ml of fresh buffer solution was added to each glass vessel to compensate the volume loss. The process was performed for 8 hours to get a simulated picture of the drug release in the *in vivo* condition. The absorbance of the sample solutions were measured at 332 nm (USP 30 and NF 25, 2007) for Naproxen with UV Visible spectrophotometer (HACH, model-DR/4000µ). The amount of drug released from the samples was then calculated with the help of appropriate calibration curve constructed from reference standard (Klancke, 2003).

**Kinetic modeling of drug release**

Different kinetic models (zero-order and Higuchi’s equation) (Mockel, 1993; Higuchi, 1963) were applied to interpret the drug release kinetics from matrix system with the help of Equation 1-2.

\[
M_t = M_0 + k_0 t \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots (1)
\]

\[
M_t = M_0 - k_d t^{1/2} \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots (2)
\]

In these equations, \(M_t\) is the cumulative amount of drug released at any specified time \(t\) and \(M_0\) is the dose of the drug incorporated in the delivery system. \(k_0, k_d\) are rate constants for zero order, first order, and Higuchi’s model respectively. These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer kinetic equation (Korsmeyer et al., 1983) to ascertain the mechanism of drug release.

\[
\log \left( \frac{M_t}{M_\infty} \right) = \log k + n \log t \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots (3)
\]

Where, \(M_\infty\) is the amount of drug release after infinite time; \(k\) is the release rate constant which considers structural and geometric characteristics of the tablet; and \(n\) is the diffusion exponent or release exponent; indicative of the mechanism of drug release. For a tablet having cylindrical shape, when \(n\) is bellow 0.45, the Fickian diffusion phenomenon dominates, and \(n\) between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the \(n\) value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order release. In this case, the drug release is dominated by the erosion and swelling of the polymer (Peppas, 1985; Chueh et al., 1995). Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel et al., 1993).

\[
\text{MDT} = \left( \frac{n}{n+1} \right)^{1/2} \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots (4)
\]

**RESULTS AND DISCUSSION**

The physical properties of the powder blend and the prepared tablets were evaluated for flow properties of the powders;
i.e. angle of repose, Carr’s index, Hausner ratio (Table-2) and for physical characterization of the tablets; i.e. hardness, friability, diameter, thickness, average weight (Table-3).

Table 2: Flow characteristics of powders for formulations coded as F-1 to F-4.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Average Angle of Repose (θ)</th>
<th>Average Carr’s Index (%)</th>
<th>Average Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>26.22</td>
<td>13.51</td>
<td>1.13</td>
</tr>
<tr>
<td>F-2</td>
<td>27.17</td>
<td>18.69</td>
<td>1.18</td>
</tr>
<tr>
<td>F-3</td>
<td>30.71</td>
<td>19.83</td>
<td>1.15</td>
</tr>
<tr>
<td>F-4</td>
<td>31.01</td>
<td>20.45</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Table 3: Physical characterization of matrix tablets coded as F-1 to F-4.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (Kg/cm²) (n=5)</th>
<th>Friability (%) (n=10)</th>
<th>Diameter (mm) (n=5)</th>
<th>Thickness (mm) (n=5)</th>
<th>Average weight of each formulation (mg/tab) (n=10)</th>
<th>Weight variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>3.9</td>
<td>0.54</td>
<td>10.01</td>
<td>2.62</td>
<td>257</td>
<td>-0.01</td>
</tr>
<tr>
<td>F-2</td>
<td>3.7</td>
<td>0.51</td>
<td>10.15</td>
<td>2.57</td>
<td>266</td>
<td>0.02</td>
</tr>
<tr>
<td>F-3</td>
<td>4.5</td>
<td>0.43</td>
<td>10.04</td>
<td>2.61</td>
<td>262</td>
<td>0.01</td>
</tr>
<tr>
<td>F-4</td>
<td>4.2</td>
<td>0.42</td>
<td>10.07</td>
<td>2.60</td>
<td>263</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 4: Kinetic parameters of Naproxen release from the proposed formulations coded as F-1 to F-4.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% drug release after 8 hours</th>
<th>Zero Order</th>
<th>Higuchi</th>
<th>Korsmeyer</th>
<th>MDT (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K₀</td>
<td>R²</td>
<td>K₀</td>
<td>R²</td>
<td>n</td>
</tr>
<tr>
<td>F-1</td>
<td>67.80</td>
<td>4.784</td>
<td>0.972</td>
<td>24.116</td>
<td>0.992</td>
</tr>
<tr>
<td>F-2</td>
<td>93.13</td>
<td>11.695</td>
<td>0.942</td>
<td>36.240</td>
<td>0.973</td>
</tr>
<tr>
<td>F-3</td>
<td>54.20</td>
<td>6.433</td>
<td>0.923</td>
<td>20.294</td>
<td>0.989</td>
</tr>
<tr>
<td>F-4</td>
<td>41.31</td>
<td>4.671</td>
<td>0.912</td>
<td>14.863</td>
<td>0.993</td>
</tr>
</tbody>
</table>

To investigate the effect of polymer and their content level on drug release four formulations were prepared (Table-1). Formulation F-1 and F-2 best fitted with Korsmeyer kinetic model (R²=0.993 and R²=0.980 respectively) (Table-4). The value of release exponent (n) were 0.648 and 0.751 respectively which indicates that the release pattern of Naproxen from F-1 and F-2 prepared with hydrophilic polymer HPMC 5 cps followed anomalous transport mechanism, which appears to indicate a coupling of the diffusion and erosion mechanism (Korsmeyer et al., 1983). F-3 and F-4 prepared with hydrophobic polymer Kollidon SR best fitted with Higuchi kinetic model (R²=0.989 and R²=0.993 respectively) (Table-4). The values of release exponent (n) for the above formulations were 0.592 and 0.565 respectively which also indicates anomalous transport mechanism (coupling of the diffusion and erosion mechanism) (Korsmeyer et al., 1983).

MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice versa. The MDT value was also found to be a function of polymer content and polymer nature. MDT values for all the four formulas are listed in Table-4. From the table, it was observed that, MDT values were higher for those formulation which contained highest percentages of polymer (except F-2 which contain 35% HPMC 5cps). For example, T₅₀ (MDT) values for F-1, F-2, F-3 and F-4 were 5.959 hours, 2.917 hours, 7.518 hours and 13.033 hours respectively.

Effect of HPMC 5cps on the release of Naproxen loaded matrix tablets

Figure-1 shows the effect of different concentration of HPMC 5cps on drug release characteristics from Naproxen matrix tablets. A significant difference in release pattern was observed among the formulations of F-1 and F-2. Naproxen loaded F-1 and F-2 contained 65mg and 91mg of HPMC 5cps respectively. The average drug release was 67.80% and 93.13% after 8 hours of dissolution period. No formulation exerted any initial burst release. Generally drug release increases with less polymer content. But in case of F-2, it is clearly evident that drug release was increased with the increase of polymer. HPMC is a hydrophilic polymer and could potentially retard the release of a soluble drug, it could also facilitate the release of relatively insoluble drug due to its solubilizing effect (Lee et al., 1999).
Effect of Kollidon SR on the release of Naproxen loaded matrix tablets

Figure-1 elaborates the effect of different concentration of Kollidon SR on drug release characteristics of Naproxen matrix tablet. F-3 and F-4 contains 65mg and 91mg of Kollidon SR respectively. The average drug release was 54.20% and 41.31% after 8 hours of dissolution period. Kollidon is a hydrophobic polymer and could potentially retard the release of a soluble drug. It could not facilitate the release of relatively insoluble drug due to its hydrophobic characteristics. Kollidon SR was used at same concentration (25% and 35%) to formulate F-3 and F-4 respectively as HPMC 5cps was used in F-1 and F-2. But, the percentage of release is significantly less when Kollidon was used (lowest in F-4, 41.31%). It exerted a very high retention time compared to HPMC 5cps possibly due to its more viscous gel layer.

CONCLUSIONS

Naproxen sustained release matrix tablets were prepared using two different polymers. F-1 and F-2 were prepared using HPMC 5cps at 25 and 35% concentrations respectively and F-3 and F-4 were prepared with Kollidon SR at 25 and 35% concentrations. The release rate of Naproxen was found to be decreased with the increased concentration of both of the polymers. Kollidon SR was more rate retarding polymer than HPMC 5cps. F-1 and F-2 were best fitted to Korsmeyer model with release exponent (n) value showed the mechanism of Naproxen from these matrix tablets mainly governed by non-Fickian process. F-3 and F-4 were fitted to Higuchi model, showing the release mechanism was mainly by diffusion through pore formation. MDT value of F-4 (13.033 hours) was highest among the four formulations.

REFERENCES
