Optimization of Polymer Concentration for Designing of Oral Matrix Controlled Release Dosage Form

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Abstract

Patient’s compliance can be enhanced by using extended release drug delivery systems which allow decreasing the number of daily doses, and helping to maintain uniform drug levels and increase the safety margin for high-potency drugs. Hydroxypropyl methylcellulose (HPMC) is the most commonly used hydrophilic polymer for the preparation of oral controlled drug delivery systems. This research was conducted with the aim of developing matrix based oral controlled release tablets for the drug diclofenac sodium using different viscosity grades of HPMC (K15M) and to compare the drug release characteristics with those of a commercial product, Voltaren® SR 100. Similarity factor (f2) values in between test formulation and marketed preparation was calculated to choose the best formulation. The release kinetics from various matrices was also studied. Increasing in polymer content reduced the rate of drug release. At the same polymer content in the matrix, the drug release was most sustained with tablets prepared using HPMC (K15M). Out of all the formulations studies, matrix tablets containing 40% of HPMC (K15M) showed comparable dissolution profile to that of the marketed preparation as indicated by a similarity factor value of (f2) 88.30%. The release of drug from marketed preparation and matrix with HPMC (K15M) 40% was found to be a diffusion drug mechanism as per Higuchi equation.

Keywords: Diclofenac sodium, HPMC (K15M), Dissolution, Drug kinetics studies, f2 value

1 Introduction

Treatment of a disease in most cases requires maintaining a desired drug plasma concentration level over a prolonged period of time. The most common approach to minimizing patient non-compliance is by using extended release drug delivery systems to decrease the number of doses.

The development of oral controlled release dosage forms came to restrict systems to certain regions and to improve the therapeutic effect of the drug. Hydrophilic matrix systems are among the most widely used for the preparation of controlled drug release dosage forms. The concentration and viscosity grade of the polymer can modify the drug release rate.

Diclofenac sodium (Figure 1) being a class II drug within the biopharmaceutics classification system (BCS) is sparingly soluble in water but freely soluble in methanol, soluble in ethanol and is slightly soluble in acetone. It is usually prescribed as once-a-day controlled release tablets for management of painful arthritis conditions to reduce the inflammation and thereby reduce pain. An effort was therefore made to develop simple and effective controlled release Diclofenac sodium tablets using a polymer matrix system with uniform in vitro release properties. Hydroxypropyl Methylcellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems. As reported by Ford et al (1985) as the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix.

The objective of the present study was to develop matrix based oral controlled release dosage form for the drug Diclofenac sodium using different concentration of Hydroxypropyl methylcellulose (HPMC) and to compare the drug release characteristics with those of a...
commercial product, Voltaren® SR 100.

**Figure 1** Structure of Diclofenac sodium

### 2 Materials and Methods

#### 2.1 Materials

Diclofenac sodium supplied by CCM UPHA Pharmaceuticals Manufacturing (M) Sdn. Bhd. while Voltaren® SR100, used as reference was purchased from a local pharmacy. HPMC (Methocel K15M Premium) Lactose, Magnesium stearate, Talcum, Aerosil 200 and Povidone 30 procured from Pharmaniaga Manufacturing Berhad (Selangor, Malaysia).

#### 2.2 Preparation of matrix control release tablets

Diclofenac sodium matrix tablets were prepared by using direct compression method with a 10 mm round concave punch at constant hardness. Various concentrations 20, 30, 40 and 50% of HPMC (K15M) polymer were used for the formulations of the series of tablets containing a constant amount of Diclofenac sodium by varying the composition of excipients. The composition of the formulations prepared is as shown in Table 1 and Figure 2 respectively.

#### 2.3 Evaluations of the prepared matrix tablets

##### 2.3.1 Weight variation

Weight variation was calculated as per method described in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than 7.5 mg and no tablets differ in weight by more than double that percentage.

##### 2.3.2 Tablets hardness

The hardness of 10 tablets was examined by using hardness tester (Guoming® YD-1 Tablet Hardness Tester). The point of fracture of the tablet was taken as the crushing strength of the tablets.

##### 2.3.3 Thickness

The thickness was determined using a vernier caliper. Ten individual tablets of each formulation were used.

### Table 1 Composition of matrix tablet formulations

<table>
<thead>
<tr>
<th>Name of component</th>
<th>Quantity per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac sodium (mg)</td>
<td>100 100 100 100</td>
</tr>
<tr>
<td>HPMC K15M (mg) (20%)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>(30%)</td>
</tr>
<tr>
<td></td>
<td>(40%)</td>
</tr>
<tr>
<td></td>
<td>(50%)</td>
</tr>
<tr>
<td>Lactose DCL (mg)</td>
<td>65.55</td>
</tr>
<tr>
<td>Povidone 30 (mg)</td>
<td>65.55</td>
</tr>
<tr>
<td>Magnesium stearate (mg)</td>
<td>3</td>
</tr>
<tr>
<td>Talc (mg)</td>
<td>3</td>
</tr>
<tr>
<td>Aerosil 200 (mg)</td>
<td>3</td>
</tr>
</tbody>
</table>

#### 2.3.4 Friability

Twenty tablets were weighed and placed into a Guoming® CS-2 tablet friability tester (Tianjin Guoming Medicinal Equipment Co., Ltd). The samples underwent 25 rotations per minute, for 4 minute, and were then reweighed. This process was repeated for all formulations and the percentage friability was calculated.

#### 2.3.5 In -vitro dissolution study
Drug release from the various matrix tablets and reference was determined by using the USP dissolution apparatus—II, paddle method (Labindia DS 8000) at a speed of 100 rpm. The test was conducted using 900 ml of 0.05M phosphate buffer pH 7.5 as a dissolution medium, maintained at temperature of 37°C ± 0.5°C. Samples of 5 ml volume each were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 & 12 hours using a manual collection method. The amount of drug released was determined at 290 nm using an ultraviolet (UV) Spectrophotometer (Thermo Sci. Evolution 60).

2.4 Analysis of drug release
2.4.1 Similarity factor calculation

The similarity factor test (f2) is used to compare the dissolution profiles of different formulations. The similarity factor is the logarithmic reciprocal square root transformation of the sum of squared error and it is to measure the similarity in the percent (%) of dissolution between the two curves (FDA Guidelines 2000).

\[
f_2 = 50 \times \log \left[ \frac{1}{n} \sum_{t=1}^{n} \left( \frac{R_t - T_t}{\text{mean}} \right)^2 \right]^{-0.5} \times 100\]  
(Equation 1)

Where,

- \(n\) is the number of dissolution sample times,
- \(R_t\) and \(T_t\) are the individual or mean percent dissolved at each time point,
- \(t\) for the reference and test dissolution profiles, respectively.

Two dissolution profiles are considered similar when the \(f_2\) value is 50 or more than 50.

2.4.2 Drug release kinetics

To study the kinetic profile of drug release from the formulations, data was treated according to zero-order (Cumulative percentage of drug released versus time), first-order (Log cumulative percentage of drug remaining versus time), Higuchi (Cumulative percentage of drug released versus square root of time), Korsmeyer-Peppas (Log cumulative percentage of drug released versus log time), and Hixson-Crowell (Cube root of cumulative percentage of drug remaining versus time) equations 10-14.

2.5 Statistical analysis

The data obtained from different formulations were analyzed by one-way analysis of variance (ANOVA) procedure using the Statistical Package for the Social Science (SPSS) program (SPSS Statistics 22.0). When there was a statistically significant difference, a post-hoc Tukey test was then conducted to detect the differences among the pairs. A statistically significant difference was considered at \(p < 0.05\).

3 Results and Discussion

3.1 Evaluation of the prepared matrix tablets

Physical characteristics of the various matrix tablets are represented in Table 2. All the formulations prepared showed good pharmacotechnical characteristics. The hardness of all the matrix tablets prepared ranged between 6.5-9.8 kg, diameter at 10mm, thickness between 3.1-4.3 mm, and the friability was less than 0.5%. The friability results of all the formulations were within the limit as stated in the British Pharmacopoeia (2008) which is F<1%.
3.2 In-vitro drug release

Diclofenac sodium 300 mg tablets were prepared with different concentrations (20, 30, 40 and 50%) of HPMC (K15M). Tablets were uniform in weight and hardness. Figure 3 shows the mean percentage of drug release profiles of Diclofenac sodium from various tablet formulations. It was found that the rate of drug release decreased as the content of polymer was increased (F1-F4). The order of drug release was F1 > F2 > F3 > F4. These findings were in good agreement with the results published by some researchers using different concentrations of HPMC (K15M) as release retarding agent for various drugs such as promethazine hydrochloride, aminophylline, propranolol hydrochloride and indomethacin. The mechanism of drug release from this type of polymer may be due to water penetration and polymer relaxation to form a viscous, rubbery gel layer. This rubbery layer controls drug release by the viscous resistant force to drug diffusion or matrix erosion. The retarding effect depends on the viscosity of the polymer, content of polymer and solubility of the drug.

When 20% HPMC was used as matrix forming agent in the tablet for dissolution study, the percentage release was 34.88% in the first 0.5 hour of the test and 65.15% after 12 hours. While with formulation containing 30% HPMC, the release was 22.55% in the first 0.5 hour and 66.46% after 12 hours. Likewise, in formulation containing 40% HPMC, the drug release was 17.01% in the first 0.5 hour and 71.12% after 12 hours. From the formulation containing 50% HPMC, the release was 8.61% in the first 0.5 hour and 61.26% after 12 hours.

When the obtained dissolution data were fitted into the zero-order kinetic equation (Cumulative amount of drug released versus time), it is evident from Figure 4 and Table 3 that the plots were curvilinear for all formulations and the regression values were small, suggesting that the release kinetic did not follow the zero-order.

On the other hand, the dissolution results obtained were found to fit well with the first-order kinetic equation (Log cumulative percentage of drug remaining versus time). It is clearly evident from Figure 3 as well as the regression parameters illustrated in Table 3 that a high correlation coefficient was obtained with all the $r^2$ values close to unity. Also, these $r^2$ values of first-order kinetic equation (0.6805 to 0.9595) were higher than those obtained for zero-order kinetics equation (0.5904 to 0.8929) for all formulations. These data suggest strongly a diffusion drug release mechanism from the matrix tablets. First-order release describes the release from matrix tablet where dissolution rate is dependent on the concentration of the dissolving species. The release of the drug from the hydrophilic matrix was slowed down as the concentration of polymer increased as indicated by the first-order release rate constant values.
Furthermore, to determine whether the erosion was also involved in the drug release from the matrix tablet formulations, the dissolution data of drug release profiles were fitted to Hixson-Crowell cube root law (Cube root of cumulative percentage of drug remaining versus time). The $r^2$ values were high (0.6514 to 0.9401) indicating that a linear relationship was obtained for all formulations, implying erosion might have also occurred in the release of drug from the matrix tablet. So, the release of the drug from all formulations may be attributed to both diffusion and erosion mechanisms though diffusion might be dominating the release in the initial hours.

Table 3 Kinetics data of Diclofenac sodium release from different concentrations of HPMC (K15M) formulations. Mean, N = 3

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero-order $r^2$</th>
<th>K0</th>
<th>First-order $r^2$</th>
<th>K1</th>
<th>Higuchi $r^2$</th>
<th>KH</th>
<th>Hixson-Crowell $r^2$</th>
<th>KC</th>
<th>Korsmeyer-Peppas $r^2$</th>
<th>n</th>
<th>Similarity factor ($f^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>0.892</td>
<td>13.283</td>
<td>0.959</td>
<td>4.482</td>
<td>0.991</td>
<td>0.153</td>
<td>0.940</td>
<td>4.442</td>
<td>0.986</td>
<td>0.558</td>
<td>-</td>
</tr>
<tr>
<td>F1 20%</td>
<td>0.590</td>
<td>28.759</td>
<td>0.680</td>
<td>4.242</td>
<td>0.825</td>
<td>16.611</td>
<td>0.651</td>
<td>4.123</td>
<td>0.913</td>
<td>0.258</td>
<td>43.21</td>
</tr>
<tr>
<td>F2 30%</td>
<td>0.758</td>
<td>20.532</td>
<td>0.838</td>
<td>4.370</td>
<td>0.939</td>
<td>7.632</td>
<td>0.813</td>
<td>4.293</td>
<td>0.946</td>
<td>0.418</td>
<td>59.19</td>
</tr>
<tr>
<td>F3 40%</td>
<td>0.874</td>
<td>14.908</td>
<td>0.944</td>
<td>4.458</td>
<td>0.988</td>
<td>1.719</td>
<td>0.923</td>
<td>4.410</td>
<td>0.989</td>
<td>0.502</td>
<td>88.30</td>
</tr>
<tr>
<td>F4 50%</td>
<td>0.921</td>
<td>8.544</td>
<td>0.967</td>
<td>4.530</td>
<td>0.993</td>
<td>2.688</td>
<td>0.953</td>
<td>4.517</td>
<td>0.990</td>
<td>0.662</td>
<td>49.58</td>
</tr>
</tbody>
</table>

Where, $r^2$ is the regression coefficient, $K_0$ is the zero-order release rate constant, $K_1$ is the first-order release rate constant, $K_H$ is the Higuchi rate constant, $K_C$ is the cube root law release constant, and $n$ is the release or, slope exponent.

Figure 5 Zero order and first order kinetic plots of Diclofenac sodium release from marketed reference product Voltaren® SR 100 (a&c) and Formulation 3 (b&d), respectively, Mean, N=3
Figure 6 Higuchi kinetic plots of Diclofenac sodium release from marketed reference product Voltaren® SR 100 (a) and Formulation 3 (b), respectively. Mean, N=3

Figure 7 Hixson-Crowell kinetic plots of Diclofenac sodium release from marketed reference product Voltaren® SR 100 (a) and Formulation 3 (b), respectively. Mean, N=3

Figure 8 Korsmeyer-Peppas kinetic plots of Diclofenac sodium release from marketed reference product Voltaren® SR 100 (a) and Formulation 3 (b), respectively, Mean, N=3
The dissolution data of drug release profiles were further fitted into Korsmeyer-Peppas equation (Log cumulative percentage of drug released versus log time). This analysis was conducted to further confirm that both diffusion and erosion mechanism were involved in releasing the drug from the matrix tablets by calculating the values of drug release exponent (n). In this context, when the n value is equal or less than 0.45 (n ≤ 0.45), it indicates that Fickian diffusion is the mechanism (Case I diffusion) of drug release where the relative relaxation time of the polymer is much shorter than the characteristic diffusion time of water transport which is controlled by concentration gradient. When, the n value is between 0.45 to 0.89, it indicates non-Fickian type of release (Anomalous transport) which refers to a combination of both diffusion and erosion drug release mechanisms\textsuperscript{15}. On the other hand, when n value is equal or greater than 0.89 (n ≥ 0.89), it indicates an erosion mechanism which is referred to as Case II Transport explains what is relaxation of polymeric controlled. In general, the diffusional exponent n value is smaller for drug release primarily by diffusion mechanism and greater for drug release primarily by erosion mechanism\textsuperscript{16}. From the results showed in Table 3, it can be observed that the all formulations had good correlation values (0.9139 to 0.9865), with slope exponent (n) values ranging between 0.2588 to 0.6625, indicating that the release of drug from all the matrix tablet formulations followed non-Fickian type of release (Anomalous transport). Such release characteristic could be attributed to the increase in strong entanglement bonds between the polymer particles which resisted the erosion by the dissolution medium in the initial hours of drug release.

The results from the present study showed that the drug release pattern of Diclofenac sodium from the different concentration of hydrophilic polymer HPMC (K15M) followed first-order release kinetics.

The similarity factor (f\textsubscript{2}) of formulation F1 when compared to Voltaren\textsuperscript{®} SR 100 was 43.21, similarly, the f\textsubscript{2} value for formulations F2, F3, and F4 were 59.19, 88.30, and 49.58% respectively. From the results tabulated in Table 3 it can be observed that the f\textsubscript{2} values for F1 and F4 was less than 50%, indicating that the dissolution profiles were not similar to that of Voltaren\textsuperscript{®} SR 100 while formulations F2 and F3 are similar to the reference product since the f\textsubscript{2} values were more than 50%.

4 Conclusions

Out of all the formulations studies, matrix tablets containing 40% HPMC (K15M) showed comparable dissolution profile and kinetics to that of the reference product, Voltaren\textsuperscript{®} SR 100.

The f\textsubscript{2} value between reference product and test formulation matrix with 40% HPMC (K15M) was 88.30% and hence it was selected for further investigation. The hydrophilic polymer, 40% HPMC (K15M) could be successfully employed in the formulation of hydrophilic matrix tablets where the drug release was governed with diffusion mechanisms as per Higuchi equation.

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6 References


