Formulation and evaluation of enalapril maleate sustained release matrix tablets

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ABSTRACT
The aim of the present research work was to develop and evaluate the sustained release matrix tablets of enalapril maleate. The tablet was formulated using HPMC KM and HPMC K15 M polymers by wet granulation method. In vitro drug release study was carried out in simulated gastric fluid (0.1 N HCl) for the first 2h and in phosphate buffer (pH 6.8) for the next 3h following USP apparatus II paddle method. An independent model method, Lin Ju and Liaw’s similarity factor ($f_2$) were used to compare various dissolution profiles. In order to describe the enalapril maleate release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell. The results indicated that the drug release characteristics from HPMC polymer matrices follow Higuchi square root time kinetics and the mechanism of drug release was both diffusion and erosion.

Key words: Oral dosage form, Controlled drug release, Half-life, HPMC KM, Release kinetics

1. INTRODUCTION
Oral dosage forms has long been the most popular and convenient route of drug delivery. Various types of modified release formulations have been developed to improve the patient compliance and also clinical efficacy of the drug. The sustained release oral dosage forms have been demonstrated to improve therapeutic efficacy by maintaining steady state drug plasma concentration.

Nonionic cellulose ethers and hydroxypropyl methyl cellulose (Hypermellose, HPMC) have been widely studied for their application in oral sustained release formulations [1]. Such hydrophilic polymers are most popular because of their flexibility to get a desirable drug release profile, cost effectiveness and broad regulatory acceptance [2]. HPMC has always been a first choice for formulation of hydrophilic matrix systems, because of providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods [3]. HPMC most widely used as the gel forming agent in the formulations of solid, liquid, semisolid and controlled release dosage forms. The adjustment of the polymer concentration, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates [4].

Drug release from dosage form like tablets capsules, and granules shows complex interaction between mechanisms like wetting, capillary penetration, swelling, disintegration diffusion, dissolution, erosion etc. These processes are mainly depends on type, quantity and properties of the drug and excipients as well as manufacturing processes. Polymer dissolution, erosion in solvent is an important area in drug delivery system, which allows for optimization of design and processing of drug dosage form as well as selection of suitable excipients. The ideal drug delivery system is one which provides the drug only when and where required and in minimum dose is required to give the desired therapeutic.

When the dosage form introduced into the solvent, swelling occur allowing increased mobility of drug and it diffuses out of polymer in the surrounding fluid. Various mathematical models can be applied to the dissolution profile...
to describe the mechanism and kinetics of dissolution process, whereas, it is quite difficult to create mathematical equations due to different dissolution curves shows very different shapes.

The hypertensive patients are more prone to morning surge in blood pressure and hypertensive attacks during morning hours between 5 a.m. to 9 a.m. The development sustained release tablets of enalapril are expected to avoid acute overdose, and to prevent morning hypertension [5]. The other advantages of sustained release dosage forms are patient compliance, reduction of local and systemic side effects, minimization of peaks and valleys in drug blood levels [6].

Enalapril, an orally-active, long-acting, nonsulphydryl angiotensin-converting enzyme (ACE) inhibitor, is extensively hydrolyzed in vivo to enalapril at its bioactive form. Bio activation probably occurs in the liver. Metabolism beyond activation to enalapril is not observed in man. Administration with food does not affect the bioavailability of enalapril; excretion of enalapril and enalapril at is primarily renal. Enalapril reduces blood pressure in hypertensive patients by decreasing systemic vascular resistance. The blood pressure reduction is not accompanied by an increase in heart rate. Furthermore, cardiac output is slightly increased and cardiovascular reflexes are not impaired [7].

In the present work, enalapril maleate sustained release matrix system has been developed using HPMC KM and HPMC K15 M polymers by wet granulation method. In order to compare the dissolution profiles, Lin Ju and Liaw’s similarity factor ($f_2$) was used. In order to describe the release kinetics and the mechanism of drug release, dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell.

2. MATERIALS AND METHODS

2.1. Chemicals and reagents

Enalapril maleate was a gift sample from Cadila Pharmaceuticals, Ahmedabad. All other chemicals used were of analytical reagent grades.

2.2 Preparation of tablets

Different tablets formulations were prepared by wet granulation technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly, and sufficient quantity of isopropyl alcohol and methylene dichloride was added slowly as granulating fluid. Dummy granules were added to improve flow property of granules. The granules were passed through 22/44 mesh and dried at room temperature for 12h. Magnesium stearate was added as lubricant. Lactose was used as diluents, Starch paste is used as binder for granules. Finally were subjected to compression. Prior to compression, the granules were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 20mg of enalapril maleate (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Enalapril maleate (mg)</th>
<th>HPMC K4M (mg)</th>
<th>HPMC K15M (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>20</td>
<td>--</td>
<td>15</td>
</tr>
<tr>
<td>F2</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>F3</td>
<td>20</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>F4</td>
<td>20</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>F5</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>F6</td>
<td>20</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>F7</td>
<td>20</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>F8</td>
<td>20</td>
<td>15</td>
<td>17.5</td>
</tr>
<tr>
<td>F9</td>
<td>20</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>F10</td>
<td>20</td>
<td>10</td>
<td>12.5</td>
</tr>
<tr>
<td>F11</td>
<td>20</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

2.3. Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in funnel. 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 from the funnel on the surface. The diameter and height of the heap formed from the granules were measured. The angle of repose was calculated using following formula [8]:

\[ \tan \Theta = \frac{h}{r} \]

Where, “h” is height of the heap and “r” is the radius of the heap of granules.

2.4. Carr’s compressibility index

The Carr’s compressibility Index was calculated from Bulk density and tapped density of the granules. A quantity of 2g of granules from each formulation, filled into a 10mL of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the granules. The bulk density and tapped density were calculated by using the bulk volume and tapped volume. Carr’s compressibility index was calculated by using following formula [9]:

\[ \text{Carr’s compressibility index (\%)} = \frac{[(\text{Tapped density-Bulk density}) \times 100]}{\text{Tapped density}} \]

2.5. Evaluation of tablets

The weight of tablets was evaluated on 20 tablets using an electronic balance. The flow properties were measured by Carr’s compressibility index, Friability was determined using
6 tablets in Roche friability tester at 25rpm. Hardness of the tablets was evaluated using an ERWEKA hardness tester (Erweka GmbH, Germany). The hardness of all the formulation was between 4-6kg/cm².

2.6. In vitro dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50rpm. Dissolution mediums used were 900mL of 1.0N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for 2h and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by HPLC. The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.

2.7. Dependent-model method (Data analysis)

In order to describe the enalapril maleate release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analysed by release kinetic theories [10-14].

To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as cumulative amount of drug release vs. time (Eqn.3), first order as log cumulative percentage of drug remaining vs. time (Eqn.4), Higuchi model as cumulative percent drug release vs. square root of time (Eqn.5), Hixon-Crowell cube root law as cube root of percent drug remaining vs time (Eqn.6). To describe the release behavior from the polymeric systems, data were fitted according to well known exponential Korsmeyer – Peppas equation as log cumulative percent drug release vs log of time equation (Eqn.7).

(i) Zero order kinetics

\[ Q_t = Q_0 t \]  

Where,

\( Q_0 \) = the initial concentration of drug
\( t \) = release time

(ii) First order kinetics

\[ \log Q = \log Q_0 + kt \]  

Where,

\( Q_0 \) = initial amount of drug in tablets
\( k \) = Release rate constant
\( t \) =release time

(iii) Higuchi kinetics

\[ Q = kt^{1/2} \]  

Where,

\( k \) = Release rate constant
\( t \) =release time, Hence the release rate is proportional to the reciprocal of the square root of time.

(iv) Hixon Crowell cube root law

\[ Q^{1/3} = Q_0^{1/3} - Q_t^{1/3} = K HC t \]  

Where,

\( K_H C \) = rate constant for Hixon Crowell.

(v) Korsmeyer-Peppas

First 60% in vitro release data was fitted in equation of Korsmeyer et al. to determine the release behavior from controlled release polymer matrix system. The equation is also called as power law,

\[ M_t / M_\infty = K t^n \]  

Where,

\( M_t / M_\infty \) = fraction solute release
\( n \) = diffusional exponent incorporating structural and geometric characteristics of the polymer system
\( t \) = release time

The magnitude of the release exponent “n” indicates the release mechanism (i.e. Fickian diffusion, Non Fickian, supercase II release). For matrix tablets, values of n of near 0.5 indicates Fickian diffusion controlled drug release, and an n value of near 1.0 indicates erosion or relaxational control (case II relaxational release transport, non Fickian, zero order release) [15-16]. Values of n between 0.5 and 1 regarded as an indicator of both diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism [17]. The values of n and k are inversely related. A very high k values may suggest a burst drug release from the matrix [18,19].

2.8. Independent-model method (Data analysis)

The dissolution profile was statistically analyzed by using dissolution similarity factor (f₂), which was calculated by the following formula:

\[ f_2 = 50 \times \log \{ [1 / (1 + (\Sigma (R_i - T_i)^2) / n)]^{1/2} \times 100 \} \]  

Where,

\( n \) =Number of dissolution time points.st that
\( R_i \) =Reference dissolution value at time t

\( T_t \) = Test dissolution value at time \( t \)

In vitro release profile of test formulation was compared with the desired theoretical dissolution profile. The \( f_2 \) value between 50-100 ensures sameness and equivalence between two dissolution profiles.

3. RESULTS AND DISCUSSION

3.1. Physical characteristics of granules and tablets

The granules of different formulations were evaluated for angle of repose, Carr’s compressibility index etc (Table 2). The results of Angle of repose and Carr’s compressibility Index (%) ranged from 22-27 and 16-24, respectively. Which showed that granules from all the formulations having good flow property. The hardness and percentage friability ranged from 4-6kg/cm\(^2\) and 0.64-0.81% respectively.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Friability (%)</th>
<th>Angle of repose</th>
<th>Carr’s index</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.64</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>F2</td>
<td>0.72</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>F3</td>
<td>0.69</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>F4</td>
<td>0.67</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>F5</td>
<td>0.71</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>F6</td>
<td>0.63</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>F7</td>
<td>0.69</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>F8</td>
<td>0.66</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>F9</td>
<td>0.73</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>F10</td>
<td>0.63</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>F11</td>
<td>0.62</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>

3.2. In vitro dissolution studies

Enalapril maleate sustained release tablets were prepared by using HPMC polymers. The release profiles of enalapril maleate sustained release tablets were plotted as Fig.1-5. The release rate of enalapril maleate mainly controlled by the hydration and swelling properties of HPMC which forms a gel layer that controls the water penetration and drug diffusion. The effect of polymer concentration on drug release could be clearly seen from the variation of the dissolution profiles. It was found that drug release from F1 and F2 composed of HPMC single polymer was no longer than 2.5h, and significantly higher drug release rate than other formulation which were prepared by using combination of HPMC K4M and HPMC K15 M. Formulations F3 to F11 shows different release rate profile up to 5h period. Formulation F3 and F8 shows less than 70% drug release in 2h. However other formulation shows more than 80% of drug release within first 2h, which is due to higher amount of drug release retarding polymers. The release rate decreased significantly and the drug release prolonged as the polymer concentration was increased. The release profiles were compared with target release profiles. The release profiles of F1, F2, F3, F4, F5, F6, F7, and F8 were found to be out of the target release profile during first 1h. The drug release was comparatively slower than the target profile. This might be due to use of higher proportion of HPMCK4M to HPMCK15M polymers. However F9 and F10 showed the proper dissolution profiles which were required for target release profile of enalapril maleate for 5h.

![Fig.1. Zero order release plot for enalapril maleate matrix tablets](image1)

![Fig.2. First order release plot for enalapril maleate matrix tablets](image2)

![Fig.3. Higuchi release plot for enalapril maleate matrix tablets](image3)
The hydration rate of HPMC depends on the nature of the substituent like hydroxypropyl group contents. HPMC K4M and HPMC K15M are having viscosity 4000cps and 15000cps respectively, which forms a strong viscous gel in contact with aqueous media, which controls the release rate of enalapril maleate. For formulation F3, F4, F8 containing highest amount of polymer shows more controlled release of drug in both pH 1.2 and distilled water. This may be owing to a more rigid complex formed by presence of higher proportion of HPMC K4M and HPMC K15M which helped in retaining the drug in matrix and did not allow rapid diffusion of drug from matrix.

The rate and amount of drug release were decreased with increasing the amount of HPMC polymers. This polymers ability to retard the drug release rate is depends on its viscosity. The increase in polymer content decreases the total porosity therefore drug release extended for prolonged period because decreased porosity have lower lateral area. The release rate decreased significantly and drug release retarded as the polymer proportion was increased.

The drug release became sustained with increasing HPMC concentration because of poorer wetability, slower hydration and formation of gelatinous layer. Another important factor is viscosity of the polymers which is higher as the molecular weight polymer increases. If the viscosity of the polymer increases the gel layer viscosity also increases so that the gel layer becomes resistant to diffusion and erosion. The release rate therefore decreases. Different levels of methyl and hydroxypropoxy substitution resulted in intrinsically different hydration rates, which affected the performance of the polymer in the initial stages of tablet hydration.

When glassy polymer comes into contact with water or any other medium with which it is thermodynamically compatible, the solvent penetrates into the free spaces on the surface between macromolecular chains. When enough solvent has entered into the matrix, the glass transition temperature of the polymer drops to the level of the experimental temperature (which is usually 37°C). The presence of solvent in the glassy polymer causes stresses, which are then accommodated by an increase in the radius of the gyration and end to end distance of the polymer molecules. i.e., the polymer chains get solvated. The solvent molecules move into the glassy polymer matrix. The thickness of the swollen or rubbery region increases with time in the opposite direction. This phenomenon is a characteristic for that particular polymer/solvent system.

3.3. Influence of ionic strengths on drug release

The release rate of drug is known to be affected by changing the pH of dissolution medium although HPMC hydration and gel formation is not affected by changes in pH. Bravo et al [20], studied the effect of pH on diclofenac sodium release from HPMC matrices. Study showed the release rate of diclofenac sodium was extremely slow in acidic pH, since after 2h only 1% of drug was released and showed faster drug dissolution rates at pH 6.8.

Various attempts have been made to quantify the influence of the solution containing phosphate and chloride ions at different ionic strengths on dissolution rates from HPMC SR tablets. In this study effect of phosphate buffer on drug release from HPMC matrices have been studied. No significant changes in drug dissolution in buffer compared to water medium observed for enalapril maleate.

3.4. Release kinetics

The best fit with higher correlation coefficient was found with Higuchi model which indicates that the amount of drug release is proportional to the square root of total amount of drug in tablet and solubility of drug in polymer matrix and time. (Fig.3) The rate of release can be altered by increase or decrease in the drug solubility and concentration of drug in matrix system. The drug release mechanism based upon entrance of the surrounding medium into a polymer matrix where it dissolves and leaches out the soluble drug, leaving a shell of polymer and empty pores. Depletion zone moves to the centre of the tablet as the drug released. Since the boundary between the drug matrix and the drug depleted...
matrix recedes with time and the thickness of the empty matrix through which drug diffuses also increases with time. As the drug passes out of a homogeneous matrix, the boundary of the drug moves to the inside by an infinitesimal distance.

Table 3
Release kinetics of enalapril maleate sustained release tablet formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Hixon Crowell</th>
<th>Higuchi</th>
<th>Korsmeyer Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.803</td>
<td>0.962</td>
<td>0.549</td>
<td>0.957</td>
<td>0.988</td>
</tr>
<tr>
<td>F2</td>
<td>0.633</td>
<td>0.887</td>
<td>0.460</td>
<td>0.992</td>
<td>0.983</td>
</tr>
<tr>
<td>F3</td>
<td>0.895</td>
<td>0.979</td>
<td>0.583</td>
<td>0.976</td>
<td>0.994</td>
</tr>
<tr>
<td>F4</td>
<td>0.861</td>
<td>0.972</td>
<td>0.550</td>
<td>0.969</td>
<td>0.983</td>
</tr>
<tr>
<td>F5</td>
<td>0.835</td>
<td>0.969</td>
<td>0.478</td>
<td>0.969</td>
<td>0.989</td>
</tr>
<tr>
<td>F6</td>
<td>0.82</td>
<td>0.953</td>
<td>0.525</td>
<td>0.930</td>
<td>0.834</td>
</tr>
<tr>
<td>F7</td>
<td>0.798</td>
<td>0.947</td>
<td>0.583</td>
<td>0.986</td>
<td>0.976</td>
</tr>
<tr>
<td>F8</td>
<td>0.900</td>
<td>0.967</td>
<td>0.593</td>
<td>0.974</td>
<td>0.966</td>
</tr>
<tr>
<td>F9</td>
<td>0.800</td>
<td>0.964</td>
<td>0.484</td>
<td>0.984</td>
<td>0.995</td>
</tr>
<tr>
<td>F10</td>
<td>0.796</td>
<td>0.961</td>
<td>0.478</td>
<td>0.986</td>
<td>0.987</td>
</tr>
<tr>
<td>F11</td>
<td>0.842</td>
<td>0.970</td>
<td>0.549</td>
<td>0.989</td>
<td>0.987</td>
</tr>
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</table>

4. CONCLUSIONS

The sustained release tablets of enalapril maleate were prepared successfully using HPMC polymer of different viscosity. According to in vitro release studies, the release rate was decreased with increasing viscosity and amount of polymer. The results of the study clearly demonstrated that HPMC matrix tablet formulation is an effective and promising drug delivery system for once daily administration of enalapril maleate.

The analysis of the release profiles in the light of distinct kinetic models (zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell) led to the conclusion that, the drug release characteristics from HPMC polymer matrices follows Higuchi square root time kinetics and the mechanism of drug release was both diffusion and erosion.

REFERENCES