FORMULATION AND IN VITRO CHARACTERIZATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM OF METOPROLOL TARTRATE USING HYDROXYPROPYL CELLULOSE

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Abstract
Drugs that are used to treat cardiovascular diseases are suitable candidates for achieving chronological delivery owing to the circadian rhythm in physiological and pathological conditions such that a therapeutic plasma concentration of drug must be attained at a point in circadian cycle when symptoms of disease are intense. Aforementioned concept was exploited to design compression coated core tablet formulation of an important cardiovascular drug metoprolol tartrate (selective β1 blocker). It was purported to obtain a lag time of 6 h in onset of drug release in vitro followed by sustained drug release over a period of 12 h. This was achieved through dissolution-guided optimization of different grades of hydroxypropyl cellulose (HPC) polymer concentrations in the outer coat of tablets such that the optimized formulation contained HPC-L and HPC-M in ratio of 1:2. The optimized formulation produced a lag phase of 6 h followed by a complete release of 99.02±0.82% in 12 h. Core erosion ratio was greater than 55% thereby showing steady release of the drug after the lag time until complete dissolution. Dissolution studies of compression coated tablets were also performed at different pH and rotation speed of paddle in order to assess their influence. The present system of MT exhibited pH independent behaviour. The present study demonstrated that metoprolol tartrate compression coated core tablets could be successfully formulated as a Chronopharmaceutical delivery system yielding timed-drug release over a period of 6-12 h and may perhaps be useful for effective management of hypertension and other related disorders.

Key Words: Time-delayed release system, Circadian rhythm, Lag time, Core erosion ratio
pressure during sleep might predispose elderly hypertensive patients to ischaemic cerebrovascular disease. Conventional drug delivery systems seem inappropriate to address such medical needs by way of administering drugs as there is a sharp rise in BP during early hours (04:00-10:00). However, if these drugs are delivered as sustained release formulations that release the drug in constant manner over a period of time (12 or 24 h), likelihood of excessive reduction in blood pressure during the night time. Hence, it would be appropriate to control the disease before it intensifies and overcome the excessive reduction in blood pressure during night time. Therefore, there is a necessity to design a chronopharmaceutical system of antihypertensive drugs so that their administration at bed time would warrant release of therapeutic level of the drug during early morning. Chronopharmaceutical formulations are synonymous with time-delayed-release dosage forms that have onset of release after a pre-programmed time interval.

Such therapeutic needs could be met by designing compression coated or press coated core tablet formulations consisting of core containing the drug and surrounded by polymers that either dissolve or erode to produce a desired release profile. In the past this technique has been applied to many drugs requiring modification of drug release, though the technique has advantage in terms of minimal requirement of coating solvents or coating equipments, the requirement for reliable and reproducible central position of core tablet within press coated tablet is a major drawback. Nevertheless many timed release tablets have been developed in recent years by press coating technique using various polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxy propyl cellulose (HPC), polyethylene oxide (PEO), polyethylene glycol (PEG), low substituted hydroxypropyl cellulose (L-HPC) and sodium alginate.

Since β blockers specifically block the sympathetic drive, they may be particularly effective for suppressing the morning blood pressure surge which occurs when sympathetic activity exceeds parasympathetic activity in the course of the circadian rhythm of autonomic regulation. Beta receptor blocking agents such as metoprolol reduce ischaemic events during day time hours and are also of therapeutic value in the morning hours. MT which is therapeutically indicated in conditions such as hypertension, angina was chosen as model drug in the present study. It belongs to BCS class I, has a high solubility-high permeability pattern throughout the GI tract, half life of 3-7 h and plasma protein binding of 12%.

The purpose of this study was to prepare chronopharmaceutical drug delivery system of MT by preparing compression coated core tablets that would provide desired lag time of about 6 h followed by a sustained release up to a period of 12 h. Apart from in vitro dissolution test, in vitro core erosion test, effect of rotation speed and effect of pH of dissolution media have also been carried out to understand the behaviour of this system in different environments. Selection and optimization of polymers was done on the basis of release profile in vitro with respect to both lag time interval and constant release in therapeutic concentration up to 12 h.

Materials and methods

Materials

Metoprolol Tartrate was obtained as gift sample from Astra Zeneca, Bangalore (India), Hydroxypropyl cellulose (HPC) was obtained as gift sample from Colorcon Asia Pvt. Limited, Mumbai (India). All the excipients were of high quality and from reliable sources. Other reagents used were of analytical grade.

Preparation of core part of the press coated tablet

Nine press coated tablet formulations (TMP1-TMP9) were designed as per the composition given in Table 1. Core was first prepared by dry mixing weighed amount of MT, lactose, and HPMC (50 cp) by screening through sieve no. 10. The powder mixture obtained was then subjected to wet granulation using isopropyl alcohol as granulating vehicle with methocel E4M acting as a binder. The granules obtained by passing the wet mass through sieve no. 8 were compressed after air drying at room temperature and addition of suitable amount of talc and magnesium stearate as glidant and lubricant respectively. The blend was compressed into tablets using single punch tablet machine with 8 mm round and flat faced punches.

Preparation of press coated core tablet

Prior to preparing complete press coated tablets, the coat was prepared by dry mixing weighed amount of HPC-L and HPC-M screened through sieve no.10. The powder mixture obtained was used to prepare
the press coated tablets by placing the earlier prepared core tablet in the centre of die cavity with coat powder carefully placed in equal proportions both above and below the core tablet. The contents were then compressed using 11 mm round, flat faced punches using a single press tabletting machine.

Physical Evaluation of tablets
Drug content of all the press coated tablets was determined as per procedure mentioned in Indian Pharmacopoeia, 2007. Twenty tablets were randomly selected, powdered and 50 mg equivalent weight of drug was taken and suitable dilutions were prepared using ethanol (95%). Absorbance of the resulting solution was measured at 272 nm using UV spectrophotometer (Shimadzu 1601, Japan). The drug content was calculated from the regression plot of MT in the same solvent. The weight variation test on tablets was performed by randomly selecting 20 tablets. Hardness of tablets was measured using Monsanto hardness tester. The thickness of the tablet was measured by vernier caliper. Friability of tablets was tested by Roche friabilator.

In vitro core erosion test
In vitro core erosion test was performed to find the extent of water penetration into the core part of the tablet. Six coated tablets having an initial weight \( W_{\text{ini}} \) were dipped in phosphate buffer, pH 6.8 for 3 h following which the gelated portion of each tablet was carefully removed to get the non-eroded residual core. This non-eroded residual core was then weighed \( W_{\text{core}} \) after drying at 40°C for 20 h. The core erosion ratio was calculated using the equation (1)\(^{22}\)

\[
\text{Core erosion test}\ (\%) = \left[ 1 - \left( \frac{W_{\text{core}}}{W_{\text{ini}}} \right) \right] \times 100 \quad (1)
\]

In vitro drug dissolution test
The USP type 2 (Paddle Type) apparatus (Labindia DS 8000, Mumbai, India) was used to determine the amount of MT released from compression coated core tablets (TMP1-TMP9). The paddle rotation speed and temperature was set to 50 rpm and 37 ± 0.5°C. The dissolution medium was 750 mL of the 0.1 N HCl, pH 1.2 for initial 2 h subsequent to which 250 mL of 0.2 M trisodium phosphate dodecahydrate was added to make phosphate buffer pH 6.8 for upto 12 h. Samples (10 mL) were withdrawn at time intervals of 2, 4, 6, 8, 10, 12 h and sink conditions were maintained throughout the test. The amount of dissolved drug was determined by UV spectrophotometer at 272 nm using the calibration plot of MT prepared earlier in the same media. The lag time in the release of drug was obtained by extension of the linear portion of the release curve to time axis with drug release of less than 10%.\(^{23}\)

Effect of dissolution medium and rotation speed on release profile
Dissolution test of optimized formulation (TMP9) was carried out in different dissolution media as (a) 0.1 N HCl, pH 1.2 (b) Phosphate buffer, pH 6.8 and (c) Phosphate buffer, pH 7.4. Dissolution tests were also performed at varying rotation speed of 50, 75 and 100 rpm to evaluate the effects of rotating speed on lag period as well as release behaviour of drug.

Table 1 Composition of compression-coated core tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulations</th>
<th>TMP1</th>
<th>TMP2</th>
<th>TMP3</th>
<th>TMP4</th>
<th>TMP5</th>
<th>TMP6</th>
<th>TMP7</th>
<th>TMP8</th>
<th>TMP9</th>
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<td></td>
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<td>Metoprolol Tartrate</td>
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<td>50</td>
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<td>100</td>
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<td>HPC-M</td>
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<td>150</td>
<td>100</td>
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</tbody>
</table>

\*HPMC- Hydroxypropyl methylcellulose; HPC- Hydroxypropyl cellulose; cp- centipoise.
Effect of different viscosity grades of HPC
To understand the effect of different viscosity grades of HPC on release profile of the drug, dissolution test was performed as per the condition described under *in vitro* drug dissolution test. Two grades of HPC-L and HPC-M having viscosity of the order of 8.5 and 329 cp respectively were selected and tablets were prepared by varying the amount of polymer in the press coat while keeping the inner core part same with respect to both weight and composition (Table 1).

**Kinetics of drug dissolution**
The fitness of zero order, first order and Higuchi kinetics have been assessed by determining the regression coefficient of the curve between time and amount of drug released. Korsemeyer-Peppas model was also fitted to find out the mechanism involved in drug release from optimized formulation. The percentage cumulative release was plotted against time on log-log scale and linearity was confirmed from slope of curve using least square method.

**Results and discussion**

**Physical Evaluation of tablets**
The drug content was found to be in the range of 97.98-99.89% in all formulations. The average percentage weight deviation of all tablet formulation was in compliance with pharmacopoeial limits. The thickness of tablet was in range of 3.1 to 4.1 mm in all formulations. Hardness and friability of all formulations (6-8 kg and <1%, respectively) were found to be within the acceptable limits (Table 2).

**In vitro core erosion studies**
Core erosion was studied to find out the extent of water penetration into the compression coated tablets and to indicate the proportion of core part into which the water penetrates. The % core erosion ratios of all formulations (TMP1 to TMP 9) were 55.2, 60.5, 64.3, 62.4, 58.8, 63.3, 65.2, 59.2 and 63.5 respectively, all found to be greater than 55% thereby showing steady release of the drug after the lag time until complete dissolution. Therefore, tablet probably absorbs water during its transit through lumen thereby allowing the release of drug in colon in spite of lower amount of water available there for solubilising the drug. These results were found to be in consonance with previous studies by Sawada *et al* who also demonstrated that water soluble excipients like lactose monohydrate dissolve to enhance water penetration into the core part.

**In vitro drug dissolution test**
All the time controlled release formulations (TMP1-TMP9) were subjected to *in vitro* dissolution study. The tablets were rounded off due to erosion/dissolution of swollen polymer till the end of the complete dissolution. Through optimization of the proportions of HPC-L and HPC-M in the press coat, it was desired to achieve a lag period (<10% drug release) of 6 h in the release initially followed by constant release of drug upto 12 h. When HPC-L (300 mg) alone was used as a press coat polymer (TMP1), it provided only 2 h lag period with complete drug release in 6 h due to lower viscosity with high erosion of the polymer (Fig. 1). On contrary when HPC-M (300 mg) was used alone in the press coat (TMP2), it was unable to release the drug at all as swelling resulted into formation of thick gel like network. Hence, it may be attributed to increasing viscosity grades in press coat (TMP1, TMP2) which in turn delays the process of dissolution and/or erosion because the hydrogel layer remained longer on the surface of core tablet. The results are in concordance with the earlier study done by Nakano *et al*. 

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug content (%)</th>
<th>Weight variation (%)</th>
<th>Hardness (Kg)</th>
<th>Friability (%)</th>
<th>Thickness (mm)</th>
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</thead>
<tbody>
<tr>
<td>TMP1</td>
<td>98.34</td>
<td>3.22</td>
<td>6.5</td>
<td>0.41</td>
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<tr>
<td>TMP2</td>
<td>99.23</td>
<td>4.78</td>
<td>7.0</td>
<td>0.27</td>
<td>4.1</td>
</tr>
<tr>
<td>TMP3</td>
<td>98.67</td>
<td>3.56</td>
<td>7.5</td>
<td>0.33</td>
<td>3.1</td>
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<tr>
<td>TMP4</td>
<td>99.42</td>
<td>2.26</td>
<td>6.5</td>
<td>0.41</td>
<td>2.7</td>
</tr>
<tr>
<td>TMP5</td>
<td>99.12</td>
<td>4.15</td>
<td>7.5</td>
<td>0.39</td>
<td>3.4</td>
</tr>
<tr>
<td>TMP6</td>
<td>97.98</td>
<td>3.63</td>
<td>6.5</td>
<td>0.30</td>
<td>4.1</td>
</tr>
<tr>
<td>TMP7</td>
<td>99.89</td>
<td>2.54</td>
<td>7.0</td>
<td>0.43</td>
<td>3.7</td>
</tr>
<tr>
<td>TMP8</td>
<td>99.43</td>
<td>3.15</td>
<td>6.5</td>
<td>0.22</td>
<td>3.4</td>
</tr>
<tr>
<td>TMP9</td>
<td>99.25</td>
<td>3.08</td>
<td>7.0</td>
<td>0.28</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Therefore, the lag time as well as release of drug may be longer with increasing HPC viscosity because the dissolution or erosion rate of the polymer would be delayed as the molecular weight is increased. In the dissolution test of press coated tablets prepared with different amounts of HPC-M in the outer layer (TMP2, TMP3 and TMP4), the hydrogel layer observed on the surface of the outer coat was relatively thin compared to HPC-L (TMP1). Therefore, amount of HPC-M was decreased from an initial 150 mg in TMP3 to 100 mg in case of TMP4. The former showed a lag period of 8 h with only 31.63±5.43% drug release in 12 h, whereas latter exhibited no lag phase with complete drug release in 12 h because of inability of polymer to form enough coat on tablet. Increasing the amount of outer coat prolonged the lag time since the time required to complete the dissolution or erosion of the outer shell increased. Therefore, to adjust the lag time and provide sustained release, blend of HPC-L and HPC-M were utilized in the outer coat. However, higher proportion of HPC-L (200 mg) blended with HPC-M (100 mg) as in formulation TMP5, provided a lag period of only 2 h and a drug release of 28.43±1.63% after 12 h, an obvious indication of minor role of HPC-L in providing lag. Nevertheless, it was found that increasing the proportions of HPC-L in coat part from 50 to 100 mg along with 150 mg of HPC-M in the blend (TMP6, TMP7), increased the lag phase from 8 to 12 h with only 15.19±0.71 and 7.12±3.26% drug release at 12h. It was hence understood that HPC-M could impart strength to the polymeric coat. Further decreasing the weight of HPC-M upto 125 mg with 75 mg HPC-L resulted in decreased lag period upto 8 h and improved sustainability of drug (79.07±5.87% upto 12 h). Further decrease in HPC-M amount from 125 to100 mg with 50 mg HPC-L, provided desired lag period of 6 h and 99.02±0.82% drug release in 12 h (TMP9).

As the GIT varies in pH from 1.2 to 8.0 when tablet transits from stomach to colon, therefore it was imperative to understand the effect of pH of dissolution media on release pattern of drug. Three different dissolution media 0.1N HCl, pH 1.2, phosphate buffer, pH 6.8 and phosphate buffer, pH 7.4 for 12 h were used to obtain a 12 h release profile of MT under the conditions mentioned above. It was found that there was no considerable change in release pattern in all the dissolution media (Fig. 2). Therefore, it may be inferred that the performance of the present chronopharmaceutical system of MT is not influenced by simulated environment throughout the GIT.

To further understand how peristaltic motion of MT may affect the pattern of release from the formulations, in vitro test was performed at three different speeds of rotating paddle (50, 75 and 100 rpm). It was found that the lag time decreased by 2 hour in each case such that TMP9 showed lag time of 6, 4 and 2 h at rotation speed of 50, 75 and 100 rpm respectively. The time taken for overall release of drug also reduced with increasing paddle speed (Fig. 3). Such reduction in lag period with increasing rotating speed could be because of initial fast erosion and/or dissolution of outer polymeric layer as well as core part of tablet. These findings were found to be in good agreement with those of Matsuo et al\textsuperscript{23} and Fukui et al\textsuperscript{12} showing this type of release behaviour.

![Fig. 1. Drug release profile of different formulations (TMP1-TMP9). Mean ± Standard error (SE), n=3.](image)

![Fitness of Dissolution data](image)

**Fitness of Dissolution data**

The testing of fitness of data was carried out by estimating regression coefficient ($r^2$) for zero order, first order, Higuchi and Korsemeyer-Peppas models. The value of $K$ was found to be 8.1192, $-8.1192$, and 24.603 for zero order, first order and Higuchi models, respectively. While $r^2$ values were 0.792, 0.792, 0.5505, and 0.9855 for the zero order, first
order, Higuchi and Korsemeyer-Peppas models, respectively thereby indicating a better correlation from korsemeyer-Peppas model. Drug release from simple swellable systems may be described by the well known Korsemeyer kinetic equation:

\[
\frac{M_t}{M_{\infty}} = K t^n
\]

(2)

where \(M_t\) and \(M_{\infty}\) are the amounts of drug released at time \(t\) and the overall amount released, respectively, whereas \(K\) is a release rate constant and \(n\) is a release exponent indicative of the release mechanism. When \(n\) is 0.45, the diffusion phenomenon dominates and when \(n\) value reaches 0.89 and above, it may be characterized by case II relaxation release transport and super case II transport. Values of \(n\) between 0.45 and 0.89 can be regarded as an indicator of anomalous transport. However, \(n\) value in the present study (0.1578) failed to interpret the exact mechanism of release. Therefore, drug release might occur through a complex mechanism involving swelling of the hydrophilic polymer followed by erosion as well as diffusion through the hydrated polymeric network.

![Graph](image)

Fig. 3. Effect of rotation speed on in vitro release of TMP9. Mean ± Standard error (SE), \(n=3\).

**Conclusion**

Press-coated core tablets of hydrophilic drug metoprolol tartrate prepared by conventional pharmaceutical processes using different viscosity grades of hydrophilic polymer like HPC showed excellent time-delayed release of the drug by way of an optimal lag period in both acidic and basic environment followed by complete release in a controlled manner due to slow erosion and diffusion through the swollen polymer. Thus, chronopharmaceutical drug delivery system of metoprolol may be beneficial for alleviating the symptoms of hypertension and related cardiovascular diseases. The results are not only encouraging but they promise effective management of such diseases through this novel approach after suitable trials in animal models and human beings.

**Acknowledgements**

The authors acknowledge the directorate training and technical education (DTTE), Government of NCT of Delhi, New Delhi, for providing senior research fellowship to Mr SCD. The authors also acknowledge Astra Zeneca Ltd., Bangalore, India for providing MT as a gift sample.

**Declaration of Interest**

It is hereby declared that this paper does not have any conflict of interest. The authors alone are responsible for the content and writing of the paper.

**References**


