DEVELOPMENT AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY SYSTEM OF METOPROLOL SUCCINATE

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ABSTRACT
The present study deals with develop and evaluation a floating – pulsatile drug delivery system (FPDDS) of Metoprolol Succinate intended for chronopharmacotherapy of hypertension. The dry coated system consisting of drug containing core, coated with hydrophilic erodible polymer, which is responsible for a lag phase for pulsatile release, top cover buoyant layer, prepared with HPMC K4M and sodium bicarbonate, provides buoyancy to increase retention of the oral dosage form in the stomach. Metoprolol succinate is a cardioselective β1-adrenergic blocking agent used for mild to moderate hypertension. Generally in hypertension, the risk of getting heart attacks is just before the walking hours of the patient i.e, early in the morning and therefore the need of antihypertensive is typically felt during morning hours. Hence, the main objective of present work to formulate FPDDS of Metoprolol succinate in ordered to achieve drug release after pre-determined lag phase. Developed formulations evaluated for their physical characteristics, drug content, in-vitro drug release studies, Floating behavior. Results showed that a certain lag time before drug release due to the erosion of the hydrophilic erodible polymer. The lag time clearly depends on the type and amount of hydrophilic polymer which was applied on the inner cores. Floating time and floating lag time was controlled by quantity and composition of buoyant layer.

KEYWORDS: Metoprolol Succinate, Pulsatile release, Floating pulsatile tablet, HPMC, Chronopharmacology and Anti Hypertensive.
INTRODUCTION
Conventional dosage forms, particularly drugs having a short biological half life needs frequent daily administration resulting in wide fluctuations in peak and trough steady-state drug levels.[1] In recent times, due to the advances in the pharmaceutical formulation technologies, the pharmaceutical research is shifted towards the development of more efficacious, novel drug delivery systems using already existing molecules rather than going for new drug discovery program. These new delivery systems offer therapeutic benefits such as optimum biological response, prolonged efficacy, reduced toxicity as well as dose reduction.[2, 3]

In the last few decades, pulsatile release systems have evoked immense interest for chronopharmacological needs or to target a drug to a specific site in the gastrointestinal tract (GIT), after a predetermined off-release period.[4] Circadian rhythms in the onset and extent of disease symptoms were observed for several diseases, including bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer disease, and hypertension.[5] Many diseases and body functions are reported to depend on circadian rhythms.[6]

Pulsatile release of antibiotics is desirable in controlling the evolution of the bacterial resistance. This release pattern is highly useful in vaccine delivery; initial burst followed by delayed release pulses can mimic an initial and boost injection, respectively.[7, 8] There is a need for chronopharmacological adaptation mode of treatment of pain in patients suffering from postoperative pain. The analgesia requirements followed a diurnal rhythm with peaks at 9 A.M. and 8 P.M.[9] The incidence of asthmatic attacks increased during the early morning hours with a maximum at 4 A.M.[10] Many drugs were studied with respect to their pharmacokinetics and chronopharmacology, including analgesics, anticancer, antibiotics, psychoactive drugs, local anesthetics, antiasthmatics, anticonvulsants and betablockers.[11]

MATERIALS AND METHODS
Materials
Metoprolol Succinate (MS) sample was gifted by Shreeji pharma International, Vadodara. HPMC E 5, HPMC E 15, HPMC E 50 were obtained from Nova Polychem, New delhi. Crosspovidone, Spray dried Mannitol, Magnesium Stearate and Talc were purchased from commercial supplier. All the ingredients are used in the formulation as such without any further processing.
Methods

Preparation of core tablets
The composition of the tablets is given in Table-1. The core tablets containing MS were prepared by weighing the drug, Crosspovidone and mixing with spray dried mannitol. Each blend has been lubricated with Magnesium stearate and talc and Compressed using 6 mm flat-faced punches using rotary tablet machine (Rimek minipress, 10 stations).

Table-1: Composition of Core tablets.

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol succinate</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Perlitol (mannitol SD 200)</td>
<td>30.8</td>
<td>29.8</td>
<td>27.8</td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>3</td>
<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Talc</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Table-2: Composition of Pulsatile Release Tablet

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Tablet</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>HPMC E5</td>
<td>250</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC E 15</td>
<td>-</td>
<td>250</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC E 50</td>
<td>-</td>
<td>-</td>
<td>250</td>
<td>150</td>
<td>200</td>
</tr>
</tbody>
</table>

Preparation of pulsatile release tablets (PRT)
The core tablets containing MS were compression-coated with 250 mg low-viscosity polymers HPMC E5, E15 and E50 in two steps. The first 100-mg coatings were filled into the die, followed by core tablet in the center of die (8 mm), and slightly pressed to fix the coatings around and under the core, and then the rest of the coatings were filled and compressed. So PRT dry-coated with 250 mg Methocel E50 was prepared.

Preparation of Floating pulsatile release tablets
FPRT was designed to comprise PRT and a top cover buoyant layer included powder of 80% (w/w) HPMC K4M and 20% (w/w) NaHCO3 which passed through a 210-µm sieve to obtain a well-dispersed mixture and followed by the addition of 1% (w/w) magnesium stearate. The 100-mg buoyant powder was filled into the die (10 mm), followed by PRT in center of the die, covered with remaining 100 mg of buoyant powder and then compressed.
Evaluation of Pre-compression Blend

Angle of Repose
The angle of repose of granules was determined by the funnel-method. The powder mixture was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.\[12\]

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

Where, \(h\) and \(r\) are the height and radius of the powder cone, \(\theta\) is the angle of repose.

Compressibility Index (Carr’s Index)
Carr’s index (CI) is an important measure that can be obtained from the bulk and tapped densities. An accurately weighed quantity of the granules/powder (W) was carefully poured into the graduated cylinder. The Bulk volume (\(V_0\)) and tapped volume (\(V_t\)) after 100 tabs using the tap density tester (USP) was measured. In theory, the less compressible a material the more flowable it is.\[12\]

\[CI = (TD-BD) \times 100/TD\]

Where, TD is the tapped density and BD is the bulk density.

Hausner’s Ratio\[12\]
It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr’s index.

Evaluation of Matrix Tablets\[13\]

Weight Variation Test
To study weight variation individual weights (\(W_I\)) of 20 tablets from each formulation were noted using electronic balance. Their average weight (\(W_A\)) was calculated. Percent weight variation with standard deviation was calculated.

Thickness
Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using vernier caliper. Average thickness and standard deviation values were calculated.
Hardness
Tablet hardness was measured by using Monsanto hardness tester. From each batch three tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test
Accurately weighed ten tablets were placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss as follows

\[
\% \text{ Friability} = \frac{(W_1 - W_2) \times 100}{W_1}
\]

Where, \( W_1 \) = Initial weight of the 20 tablets. \( W_2 \) = Final weight of the 20 tablets after testing.

Drug Content
Powdered formulation equivalent to about 100 mg of MS was transferred to a 100 ml volumetric flask containing 100 ml of methanol. It was shaken by mechanical means for 15 min. Then it was filtered through a 0.45 µm filter paper and diluted to 10 ml with simulated intestinal fluid without enzymes and absorbance was measured against blank at 222 nm.

In-Vitro Drug Release Characteristics
For core tablets
The dissolution testing of core tablet was carried out using a USP Type II dissolution apparatus at 37±0.5°C in 900 ml simulated intestinal fluid without enzymes (SIF) with mixing speed of 50 rpm (n=3).

For pulsatile release tablets
For pulsatile tablets two sets dissolution studies were carried out using USP Type I dissolution apparatus. Volume of dissolution medium (900 ml), stirring speed (100 rpm) and temperature of medium (37±0.2°C) were kept same for all dissolution studies (n=3).

In one set of dissolution studies, simulated gastric fluid without enzymes (SGF) was used as dissolution medium and dissolutions were performed for 5.45h. The second set of dissolution studies were performed using SGF for time period equivalent to erosion time which varied for each formulation and then subsequently in SIF without enzyme till complete release of drug.
For Floating- pulsatile release tablets
For Floating- Pulsatile tablets two sets dissolution studies were carried out using USP Type I dissolution test apparatus. Volume of dissolution medium (900 ml), stirring speed (100 rpm) and temperature of medium (37±0.2°C) were kept same for all dissolution studies (n=3). The dissolution studies were performed using SGF for time period equivalent to erosion time and then subsequently in SIF till complete release of drug. At appropriate time intervals, 5 ml of the solution was withdrawn, filtered through 0.45 µm filter paper, and assayed by a UV spectrophotometer at 222 nm, while an equal volume of fresh dissolution medium was added into the apparatus.

Buoyancy studies
Floating lag time and floating time of FPRT was studied by placing them in 900 ml containers SGF without enzyme. The Floating Lag Time (FLT), time period between placing FPRT in the medium and buoyancy begins and Total Floating Time of FPRT were determined by visual observation.

Drug-Excipient compatibility studies
FTIR Studies
Infrared spectra were taken by using KBr pellet technique using a Bruker Alpha FT-IR Spectrophotometer in the frequency region of 500 to 4000 cm⁻¹. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients or formulation) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrums of samples were analyzed for drug excipient compatibility.

Fig. 1: FTIR spectra of a) Metoprolol succinate b) Core tablet mixture(C-3) c) Drug-polymer mixture.
FTIR spectrum of MS is characterized by the absorption of –COOH group at 1612.5 cm\(^{-1}\), -OH stretching absorption at 3061.0 cm\(^{-1}\) and –NH deformation at 1375.5 cm\(^{-1}\). No drug-polymer interaction was observed in the FT-IR spectra of the powder mixture of optimized formulation since the absorption peaks of the drug still could be detected in the mixture.

DSC Studies
The DSC measurements were performed on a differential scanning calorimeter (Mettler DSC 823e, Mettler-Toledo, Germany) with a thermal analyzer. Under nitrogen flow of 25 ml/min, approximately 2 mg of MS and formulations were placed in a sealed aluminum pan, and heated at a scanning rate of 5°C/min. An empty aluminium pan was used as reference.

![DSC thermograms](image)

Fig. 2: DSC thermograms of a) Metoprolol succinate alone, b) core tablet mixture (C3) c) Drug- polymer (HPMC E 50) mixture

The thermal curve of MS showed a melting endothermic peak at 140°C. The drug availed in core tablet mixture shown the clear sharp peak characteristic for MS at 149.6°C and the drug shows melting peak at 132.4°C when mixed with buoyant polymer. There was no considerable change in the endothermic values of MS when mixed with excipients.

RESULT AND DISCUSSION
Characterization of Powder blends
The powder blend of all formulations were characterized with respect to angle of repose (\(\theta\)), bulk density, tapped density, Carr’s index, and drug content (Table-3). Angle of repose was
less than 35° and Carr’s index values were less than 25 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner’s ratio was found to be less than 1.25 for all the batches indicating the powder blend has good flow properties.

Table-3: Physical evaluation of powder blend

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of Repose (θ)*</th>
<th>Bulk density (gm/cc)</th>
<th>Tapped density (gm/cc)</th>
<th>Carr's index*</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>26.12±1.13</td>
<td>0.311</td>
<td>0.365</td>
<td>14.79±1.12</td>
<td>1.17</td>
</tr>
<tr>
<td>C2</td>
<td>28.39±1.21</td>
<td>0.329</td>
<td>0.383</td>
<td>14.12±1.2</td>
<td>1.16</td>
</tr>
<tr>
<td>C3</td>
<td>25.79±1.29</td>
<td>0.321</td>
<td>0.342</td>
<td>20.15±1.3</td>
<td>1.06</td>
</tr>
<tr>
<td>P1</td>
<td>30.23±1.23</td>
<td>0.332</td>
<td>0.345</td>
<td>23.33±1.08</td>
<td>1.03</td>
</tr>
<tr>
<td>P2</td>
<td>31.12 ±1.13</td>
<td>0.312</td>
<td>0.376</td>
<td>24.09±1.05</td>
<td>1.20</td>
</tr>
<tr>
<td>P3</td>
<td>29.13±1.26</td>
<td>0.342</td>
<td>0.389</td>
<td>24.17±1.2</td>
<td>1.13</td>
</tr>
<tr>
<td>P4</td>
<td>32.72±1.23</td>
<td>0.319</td>
<td>0.406</td>
<td>21.43±1.03</td>
<td>1.27</td>
</tr>
<tr>
<td>P5</td>
<td>33.12±1.84</td>
<td>0.365</td>
<td>0.461</td>
<td>20.82±1.04</td>
<td>1.26</td>
</tr>
<tr>
<td>FP1</td>
<td>28.12±1.13</td>
<td>0.344</td>
<td>0.378</td>
<td>23.21±1.21</td>
<td>1.09</td>
</tr>
<tr>
<td>FP2</td>
<td>29.13±1.26</td>
<td>0.332</td>
<td>0.422</td>
<td>21.33±1.3</td>
<td>1.27</td>
</tr>
<tr>
<td>FP3</td>
<td>31.61±1.91</td>
<td>0.315</td>
<td>0.398</td>
<td>20.65±1.03</td>
<td>1.26</td>
</tr>
<tr>
<td>FP4</td>
<td>25.72±1.23</td>
<td>0.312</td>
<td>0.341</td>
<td>22.19±1.29</td>
<td>1.09</td>
</tr>
<tr>
<td>FP5</td>
<td>27.23±1.4</td>
<td>0.316</td>
<td>0.397</td>
<td>20.4±1.01</td>
<td>1.25</td>
</tr>
</tbody>
</table>

* All values represent mean ± Standard Deviation (SD), n=3

Physical Evaluation of tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table-4. All the tablets of different batches have complied with the official requirements of uniformity of weight as their weights varied within the limits.

Table-4: Physical Evaluation of prepared tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness Kg/cm**</th>
<th>Friability (%)**</th>
<th>weight variation (mg) ***</th>
<th>Thickness (mm)*</th>
<th>Drug content (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>2.3±0.6</td>
<td>0.43±0.1</td>
<td>59.2±0.7</td>
<td>2.25±0.5</td>
<td>99.1±0.8</td>
</tr>
<tr>
<td>C2</td>
<td>2.4±0.8</td>
<td>0.38±0.04</td>
<td>61.5±1.9</td>
<td>2.4±0.7</td>
<td>102.8±0.2</td>
</tr>
<tr>
<td>C3</td>
<td>2.5±0.5</td>
<td>0.34±0.07</td>
<td>59.8±1.6</td>
<td>2.5±0.9</td>
<td>98.1±1.2</td>
</tr>
<tr>
<td>P1</td>
<td>5.3±0.8</td>
<td>0.28±0.06</td>
<td>310±0.9</td>
<td>4.2±0.8</td>
<td>101.2±0.8</td>
</tr>
<tr>
<td>P2</td>
<td>5.6±0.2</td>
<td>0.40±0.08</td>
<td>308.9±2.1</td>
<td>4.1±0.9</td>
<td>100.8±0.4</td>
</tr>
<tr>
<td>P3</td>
<td>6.1±0.5</td>
<td>0.31±0.04</td>
<td>309.4±1.5</td>
<td>4.3±0.8</td>
<td>97.5±0.9</td>
</tr>
<tr>
<td>P4</td>
<td>5.5±0.7</td>
<td>0.27±0.2</td>
<td>209.5±1.9</td>
<td>3.5±0.5</td>
<td>98.6±1.9</td>
</tr>
<tr>
<td>P5</td>
<td>5.9±0.4</td>
<td>0.25±0.06</td>
<td>259.9±1.2</td>
<td>3.1±0.4</td>
<td>100.4±0.9</td>
</tr>
</tbody>
</table>

* All values represent mean ± Standard Deviation (SD), n=3

** All values represent mean ± Standard Deviation (SD), n=6

*** All values represent mean ± Standard Deviation (SD), n=20
The hardness of the tablets ranged from 2.3 to 6.1 kg/cm² and the friability values were less than 0.43% w/w, indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.25 to 4.3 mm. The drug content of all formulations was found to be in the range of 97.5 to 102.8% w/w. Thus, all the physical attributes of the prepared tablets were found be practically within control.

**In-Vitro Drug Release Studies**

**For Rapid releasing tablets (RRT)**

The release of drug depends on the nature and concentration of super disintegrating agent used in the core tablet formulation. Crosspovidone is a water insoluble, exhibiting high capillary activity and prominent hydration capacity with little tendency to gel formation. The formulation C-1 containing 5% CPVP disintegrated in 4 min, C-2 (7.5% CPVP) in 2 min and C-3 (10% CPVP) within fraction of seconds. The formulation C-3 showed 88.14±1.21% release in 60 min and found to be suitable for use in pulsatile release tablets.

![In-vitro release profiles of rapid release (Metoprolol Succinate) Tablets.](image)

**For pulsatile release tablets**

The in vitro release profiles of MS from HPMC-coated system were provided in Fig 4. The various type of HPMC (E5, E15, and E50) added in the formulation P1, P2, P3 respectively shows significant variation in lag time of Drug release from inner core. The Lag time in drug release was found to be 3 h and 5.45 h for the formulation P1 and P2 respectively. The formulation P3, coated with HPMC E 50 has the highest lag time in drug release around 7.3 h is further designed with change in weight (150, 200, 250 mg P4, P5, P3 respectively) of coating layers with HPMC E50. The in vitro drug release of the formulation P3, P4 and P5 were shown in Fig 5.
As the coated tablet was placed in the aqueous medium, initial swelling was observed that underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually started to erode up to a limiting thickness. After this stage, the shell was ruptured due to the pressure built up by the swelling of the core tablet. All of this process corresponded to a lag time capable of exhibiting a pulsatile release of the drug.

The delay in duration clearly depended on the kind and amount of hydrophilic polymer which was applied on the pulsatile layer. The in vitro drug release lag time for the formulation P4 coated with 150 mg HPMC E50 was 3.15 h and the maximum drug release of the same formulation was found to be 86.34±1.6%w/w. The formulation F5 coated with 200 mg of HPMC E50 had shown Drug release lag time of 6 h with maximum drug release of 84.25±1.63%w/w which is optimized value needed for pulsatile tablet to release Metaprolol Succinate. Further in the development of Floating Pulsatile Tablet the addition of HPMC K4M and sodium bicarbonate didn’t have much effect on the in vitro drug release lag time but, the formulation acquired floating nature so that the gastric retention of the dosage form may be succeeded.

Fig. 4: In-vitro release profiles of Metoprolol Succinate from the pulsatile Release tablet (PRT) coated with 250-mg different kinds of HPMC.

Fig. 5: In-vitro release profiles of Metoprolol Succinate from the pulsatile Release tablet (PRT) coated with different amount of methocel E50.
Buoyancy studies

When the system was immersed in a simulated gastric fluid at 37±0.5°C, it sank at once in the solution and formed a swollen tablet with a density much lower than 1 g/ml. The reaction was due to carbon dioxide generated by neutralization in the buoyant layer with the solution. These systems (Tab. FP1, FP2 and FP3) have acceptable FLT and remained floating over a period of 12 h. The highest FLT was observed to be about 2–3 min for FP3 because of absence of sodium bicarbonate in the buoyant layer. The TFT for FP1 was no more than 3 h probably because of higher amount of sodium bicarbonate replaced HPMC K4M in the buoyant layer. It is worth mentioning here that sodium bicarbonate, in addition to imparting buoyancy to the novel formulation, provided the initial alkaline microenvironment for polymers to gel. Moreover, the release of CO$_2$ helps to accelerate the hydration of the floating layer.

Fig. 6: In-vitro Release Data of Metoprolol Succinate from floating pulsatile Release tablets (FPRT).

Fig. 7: Monographical changes of Pulsatile release tablets during dissolution study.
Table-5: Floating ability of Various Formulations of the Floating–Pulsatile Release Tablet (FPRT).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Floating Onset Time (min)</th>
<th>Floating Duration (h)</th>
<th>Integrity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP1</td>
<td>&lt;1</td>
<td>&lt;3</td>
<td>Broken</td>
</tr>
<tr>
<td>FP2</td>
<td>2-3</td>
<td>&gt;12</td>
<td>Intact</td>
</tr>
<tr>
<td>FP3</td>
<td>&lt;1</td>
<td>&gt;12</td>
<td>Intact</td>
</tr>
</tbody>
</table>

Fig. 8: Time dependent Morphological Changes in FPT while floating on Simulated Gastric Medium.

CONCLUSION
Prepared floating-pulsatile release tablets containing the floating material, such as HPMC K4M and NaHCO₃ (80:20), achieved a satisfactory buoyant force in vitro, whereas the floating lag time was less than 1 min and the floating time was more than 12 h. Drug releasing mechanism of FPRT is based on the interaction between hydrophilic polymeric coating and the aqueous gastrointestinal fluids. The in vitro release profiles of MS from FPRT prepared using HPMC E50 (200mg) as retarding polymer are characterized by a predetermined lag phase, the lag time which depends on the kind and amount of the polymeric layer applied on the cores. The developed system offers a simple and novel technique for pulse release of drugs in stomach or upper part of small intestine.

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