Formulation and Evaluation of Pulsatile Drug Delivery System of Atenolol

Sudipta Das*, Baishali Ghosh, Surita Basu
Department of Pharmacetics, Netaji Subhas Chandra Bose Institute of Pharmacy, Nadia, West Bengal, India

*Corresponding Author: sudiptapharmacy6@gmail.com

Abstract: The objective of the present study was formulation and evaluation of pulsatile release tablets of Atenolol. A tablet system consisting of cores which was coated with layers of swelling and rupturable coatings. Cores containing Atenolol as model drug were prepared by direct compression with appropriate ratios of lactose and microcrystalline cellulose and then coated sequentially with different ratios of an inner swelling layer containing HPMC and an outer rupturable layer of Ethyl Cellulose. The effect of level of swelling layer and rupturable coating was investigated. The different formulation press coated by using different weight ratios of Hydroxy Propyl Methyl Cellulose (HPMC) / Ethyl Cellulose (EC) / both HPMC and EC. The optimum result was achieved in formulation containing HPMC: EC weight ratios. The F3 batch achieved a highest burst release after the lag time which is applicable pulsatile drug delivery system of Atenolol.

INTRODUCTION
Oral drug delivery system is the fast growing, largest and the oldest segment of the total drug delivery market. Over the past two decades, the pharmaceutical market has been demonstrating increased prefer ability for controlled and targeted drug delivery system. Such system has been focused on constant, variable; sustain drug release delivery system targeting the therapeutic agent to specific site/organ (Sadaphal et.al, 2011). Studies have revealed that disease has a predictable cyclic rhythm and that the timing of medication regimen can improve the outcome of a desired effect. This condition demands release of drug as a “pulse” after a lag time and has to be designed in such a way that a complete and rapid drug release should follow lag time. Such systems are called pulsatile drug delivery system (Survase et.al, 2007).

Conventional controlled release drug delivery systems are based on single- or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time.(Zhang et.al,2000).However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastrointestinal tract or for drugs with an extensive first pass metabolism, e.g. B-blockers or for drugs, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special pharmacokinetic features designed according to the circadian rhythm of human.( Doelker et.al,1996; Lemmer et. al,1999).

A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release at specific time and specific site. Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro-intestinal tract such as pH or enzymes. Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating. Time controlled drug delivery system based on chronotherapy or chronopharmacology have been investigated together with release rate controlled system for the treatment of diseases such as ischemic heart disease, asthma and arthritis. Drug for treatment of such diseases should be administered so as to maintain a therapeutic blood level only at the required time at the required time, and hence the drug release behavior should be controlled by rate. For this purpose various system and sigmoidal release system have been developed using various techniques and functional polymers or additives (Krogel et.al, 1999).

In the present investigation, the barrier can dissolve, erode or rupture during/after a certain lag time, after which the drug is released rapidly from the inner reservoir core.( Hata et.al,1994; Gazzaniga et.al,1994). The rupturing of the barriers...
are induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipients or swelling agents(Sangalli et.al,2001).This study focused on the development of pulsatile release tablets as a per oral,time-controlled, single-unit dosage form. The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating.

This system is developing time dependent rupturable and erodible type press coated pulsatile colon targeted drug delivery using combination of hydrophilic and hydrophobic polymer. Hydroxypropyl Methylcellulose (HPMC) is a well known water-soluble polymer that has long been used as a rate controlling membrane in medication dosage forms to regulate drug release. HPMC has an ability to swell upon gelification once in contact with water. The gel becomes a viscous layer around a core, acting as a protective barrier to both the influx of water and the efflux of the drug in solution (Kii et. al,2003). HPMC has a swelling, viscous property of gelation and an erosion property which might delay the drug release because of lengthening of the drug diffusion pathway and drug release rate. This hydrophilic polymer is responsible for rupturing the outer coat. Hydrophilic polymer (HPMC) alone for controlling the drug release of highly water soluble drugs like atenolol is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer. Use of hydrophobic polymers such as Ethyl cellulose with HPMC will retard the drug release. So, in the present investigation, an attempt has been to formulate time controlled pulsatile release tablets of atenolol using hydrophilic polymer (HPMC) in combination with hydrophobic polymer (EC). Ethylcellulose (EC) is a semipermeable in nature, although it is naturally insoluble in water, has been used as a rate-controlling membrane to regulate drug release. EC has been directly compressed to form compact film in which plastic deformation is the predominant consolidation mechanism (Liberman et.al,1990). Ethyl cellulose exhibiting a porous structure, it controls the diffusion of the water inside the coating layer of HPMC, kept integrity of swellable layer of HPMC and the retard the drug release. When the barrier layer containing HPMC along with ethyl cellulose was exposed to dissolution media, the HPMC particles swell and erode which is responsible for breakdown of outer coating, a process which was retarded to varying degrees depending upon the quantity of EC present demonstrating that manipulation of both components controls the erosion rate.( Rubinstein et.al,1997)

Advantages of pulsatile drug delivery are extended day time or night time activity, reduced side effects, reduce dosage frequency, reduction in dose size, improved patient compliance, lower daily cost to patient, drug adapts to suit circadian rhythms of body functions or diseases, drug targeting to specific site like colon, protection of mucosa from irritating drugs, drug loss is prevented by extensive first pass metabolism etc. Disadvantages of pulsatile drug delivery system are lack of manufacturing reproducibility and efficacy, larger number of variables, multiple formulation steps, higher cost of production, need of advanced technology, trained/skilled person needed for manufacturing. Necessities of PDDS includes first pass metabolism, biological tolerance, special chronopharmacological needs, local therapeutic need, gastric irritation or drug instability in gastric fluid.

MATERIALS AND METHODS

MATERIALS

Atenolol, Sodium Starch Glycolate, Microcrystalline Cellulose, Magnesium Stearate and Talc were purchased from Yarrow Chem Pvt. Ltd. All chemicals and reagents used were of analytical grade.

METHODS

PREPARATION OF ATENOLOL CORE TABLETS: (Keraliya et.al,2014)

The core tablets of Atenolol were prepared by direct compression method. An accurately weighed quantity of Atenolol, Microcrystalline Cellulose, Sodium Starch Glycolate, Talc (2% w/w) and Magnesium stearate (1% w/w) were passed through sieve no. 24 and mixed by triturating in a mortar and pestle for 10 minutes. The resultant powder mixture were compressed into tablets (average weight = 170 mg) by concave punch using tablet punch machine.

PREPARATION OF PRESS COATED TABLETS: (Keraliya et.al,2014)

The core tablets were compressed coated with 340 mg of coating material containing different weight ratios (w/w) of HPMC / EC / HPMC: EC. The weight ratio of HPMC and EC were used for the compression coating. Weighed amount of coating material, 1% magnesium stearate and 2% talc were passed through sieve no. 24 separately and blended using mortar and pestle for 10 minutes. 170 mg weight of the coating material first placed into the die cavity. Then, the core tablet was carefully placed on it manually at the center of the die. The remaining 170mg of the coating material was added into the die and the coating material was then compressed around the core tablet using concave punch using tablet punch machine.
Table 1: Composition of Pulsatile drug delivery of Atenolol tablets (mg).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
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<tbody>
<tr>
<td>Atenol</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>145</td>
<td>145</td>
<td>145</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Composition of core tablets**

<table>
<thead>
<tr>
<th>Composition of press coated tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC</td>
</tr>
<tr>
<td>337</td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Total Weight</td>
</tr>
<tr>
<td>510</td>
</tr>
</tbody>
</table>

**Evaluation of tablets:**

**WEIGHT VARIATION:** (Fukui et al., 2000)

Twenty tablets were randomly selected from each batch individually. The average weight and standard deviation was calculated.

**THICKNESS:** (Fukui et al., 2000)

Three tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of Vernier caliper. The average thickness was calculated.

**HARDNESS:** (Prasad et al., 1998; Jain et al., 2007)

Hardness was measured using Monsanto tablet hardness tester. The hardness of five tablets in each batch was measured and the average hardness was calculated in terms of kg/cm^2.

**FRIABILITY:** (Das et al., 2015; Mandal et al., 2019; Das et al., 2013)

Friability of the tablet determined using Roche friabilator. Pre-weighted sample of tablets were placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The % friability (F) was calculated using following formula:

\[
F = \left( \frac{W1-W2}{W1} \right) \times 100
\]

**SWELLING INDEX:** (Yeole et al., 2006)

One tablet from each press coated formulation was randomly selected, weighed individually (W1) and placed separately in petridishes containing 20 ml of phosphate buffer pH 7.4. After 6 hour, the tablets are carefully removed from petridishes and excess water was removed using filter paper. The swollen tablets were reweighed (W2) and swelling index of each tablet was calculated using the following equation and expressed in percentage.

\[
\text{Swelling Index} = \frac{(W2-W1)}{W1} \times 100
\]

**In-Vitro Release Study:** (Sungthongjeen et al., 2004)

*In vitro* drug release studies were carried out using USP Type II dissolution apparatus in a 900 ml of dissolution media at a temperature of 37±0.5°C. Two dissolution media with pH 1.2 and 6.8 sequentially used. Initially dissolution study was performed using 0.1 N HCl (pH 1.2) as dissolution medium for 2 hour. There was no release of drug. This is the lag time of the press coated atenolol tablet. After 2 hour the dissolution medium was removed and replaced with phosphate buffer pH 6.8 and dissolution study was done for 3 hours. At regular time interval 5 ml sample was withdrawn and same amount replaced by fresh medium. Samples were suitably diluted and filtered. Drug amount released was analyzed spectrophotometrically by UV spectrometer at the wavelength of 278 nm.

**RESULT AND DISCUSSION**

Swelling study of press coated tablets indicate that combination of EC and HPMC, when used have better capacity to protect the drug from being released in the upper parts of the GIT than HPMC alone compression coated tablet. This may be due to HPMC is more hydrophilic as swelling index is better for HPMC. F1 batch having high amount of HPMC (having HPMC alone) was showed high percentage of swelling (82.96%). HPMC alone released the drug relatively at higher rate than combination of EC and HPMC because it formed weak swellable layer, which could rupture easily upon exposure to the dissolution medium. While F2 batch having EC alone could not maintain the integrity, and it divided into two equal half and negligible sign of swelling (29.34%). Batch F3 showed that as the amount of EC and HPMC are equal in the mixture of HPMC and EC mixture, %swelling of tablet(63.46%) decreases because of EC retards the swelling of the formulation F3 than the formulation F1. EC retard the hydration of HPMC and maintain the integrity of swellable layer of HPMC.

In time controlled press coated tablets, drug containing core compressed with the outer barrier of HPMC, it prevents the rapid drug release from core tablets. The drug will not be released unless the coat is broken. When the dissolution medium reaches the core after eroding or rupturing the outer barrier layer rapid drug release was observed.
Table 3: Evaluation of tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight Variation (mg) N= 20</th>
<th>Hardness(Kg/cm²) N= 6</th>
<th>Thickness(mm) N=4</th>
<th>Friability (%) N=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>168.24±4.23</td>
<td>5.02±0.25</td>
<td>2.99±0.02</td>
<td>0.26</td>
</tr>
<tr>
<td>F1</td>
<td>498±4.32</td>
<td>6.05±0.33</td>
<td>6.02±0.054</td>
<td>0.42</td>
</tr>
<tr>
<td>F2</td>
<td>508±3.24</td>
<td>6.79±0.38</td>
<td>6.04±0.049</td>
<td>0.38</td>
</tr>
<tr>
<td>F3</td>
<td>506±4.55</td>
<td>7.75±0.35</td>
<td>5.78±0.063</td>
<td>0.59</td>
</tr>
</tbody>
</table>

* All value are express as Mean±(t x SEM), n=3

The release profile of compression coated tablet exhibited lag time followed by burst release, in which the outer shell breaks into two halves. Press coated tablet (F1 to F3formulations) showed distinct lag time. When HPMC was used alone (F1), it formed mechanically weak swellable layer, which could rupture easily upon exposure to the dissolution medium and resulting development of internal pressure within tablet core and drug release was initiated. Hydrophilic polymer (HPMC) alone for controlling the drug release of highly water soluble drugs like atenolol is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer.

With ethyl cellulose alone (F2), showed lowest drug release as compared to any weight ratio of mixture of HPMC and EC. EC has no swelling property and is hydrophobic and cracking of tablet occurs as it has no push effect like HPMC. EC exhibiting a porous structure, the porosity is proportional to the proportion of ethyl cellulose. Ethyl cellulose is semi-permeable in nature, although it is naturally insoluble in water, controls the passage of water inside the core, core swells and ruptures the EC coat. Water penetrates faster the coating layer of the core tablet when used alone. After hydration of core, the drug was released.

When ethyl cellulose was used in combination with HPMC, it causes synchronization between swelling and erosion of the polymer in maintaining a constant gel formation for a longer period of time. Upon contact with dissolution medium HPMC hydrated and formed compact with ethyl cellulose. The hydrophobicity of ethyl cellulose retards the hydration of HPMC. Therefore the dissolution medium did not penetrate the outer coating layer, but the coating eroded slowly. The active erosion rate of outer barrier layer depends upon the composition of the formulation which determines the lag time of press coated tablet.

The combination of HPMC and EC showed the synergistic effect on lag time. The finding indicates that the lag time of press coated tablet can be modulated from 4 hours to 6 hours. System was found to be satisfactory in terms of release of the drug after the predetermined lag time. This is shown by the formulation F3 (HPMC: EC). Thus the dosing form can betaken at bed time, so that the content will be release in the morning hours, i.e. at the time when the symptom is more progressive. The release study of different batches of press coated Atenolol tablets were shown in Fig 1. The release was rapid after the completion of lag time. Lag time can be controlled by adjusting the mixture containing different weight ratio of HPMC and EC.

CONCLUSION

The promising pulsatile drug release of atenolol is successfully achieved by press coating technique using combination of time dependent rupturable and erodible polymers. Ethyl Cellulose was chosen because of its rupturable behavior and HPMC was selected because of its swelling and erodible behavior. Atenolol press coated tablet was prepared using different weight ratios of HPMC and EC. The formulation F3 achieved a highest burst release after the lag time which is applicable pulsatile drug delivery system of atenolol. Though long term stability study is required for future development of these formulations.
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CONFLICTS OF INTEREST STATEMENT
There are no conflicts of interest

REFERENCES


