Formulation design and development of gastro retentive floating tablets of Atenolol

Damayanthi Dalu1*, Ganesh Kumar Y2

1 Department of Pharmacology, Pulla Reddy Institute of Pharmacy, Hyderabad, Telangana, India.
2 Department of Pharmaceutics, Brilliant Group of Institutions, Abdullapurmet, Hayathnagar, R.R Dist, Telangana, India.

ABSTRACT

Atenolol is a selective β1 receptor antagonist. Atenolol is employed in the therapy of angina pectoris and hypertension. Hence the current study is employed to design a floating delivery system of atenolol by swelling polymer through direct compression method. Fourier transform Infrared spectroscopy (FTIR) confirmed the absence of any drug/excipients interactions. The tablets were evaluated for hardness, thickness, friability and drug content and were subjected to a 12 h In vitro drug release studies (USP dissolution rate test apparatus II, 50 r/m, 37°C ± 0.5°C) using 0.1N hydrochloric acid. In this study, gastro retentive dosage form using HPMC-K100M, Guar gum was prepared to build up a prolonged release tablets, that could retain in the stomach for longer periods of time delivering drug to the site of action that is in the stomach. In-vitro dissolution studies of the formulation, concluded that the formulation F6 containing 87.5 mg of HPMC-K100M, 40mg of Sodium bicarbonate, 4mg of Mg. Stearate, 4mg of Talc and 39.5mg of micro crystalline cellulose is the superlative composition. Obtained results of the study concluded that floating tablets accomplishing HPMC-K100M, a hydrophilic polymer increases the GRT of the dissolution fluid in the stomach to deliver the drug in a prolonged manner. The concept of formulating floating tablets of model drug renders a suitable and practical approach in serving the needed objectives of gastro retentive floating tablets.

KEY WORDS: Atenolol, Direct compression, Floating Tablets, HPMC, Guar gum.

1. INTRODUCTION

Oral administration is the most expedient and preferred means of any drug delivery. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to accomplish enhanced therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.

Drugs that are easily absorbed from gastrointestinal tract and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained and controlled release formulations is an attempt to release the Drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract.[1-4]

2. MATERIALS AND METHODS

2.1. Materials:

Atenolol was obtained from Cipla Ltd, Mumbai, HPMC grades and Guar gum were received from Signet Chemical Corporation Pvt. Ltd, Mumbai, and other materials were purchased from Yarrow chem. products, Mumbai, India.

2.2. Methodology:

2.2.1. Preformulation Studies:

2.2.2. Standardization of Atenolol by UV-Visible Spectrophotometer: In 0.1 N Hcl Solution:

2.2.2.1. Preparation of stock solution:

*Corresponding author

Damayanthi Dalu

Department of Pharmacology.

Pulla Reddy Institute of Pharmacy,

Near dundigal, Airforce Academy,

Survey no: 167,168, Annaram (v), gummaddidala(m),

Dist: Sangareddy, Pincode: 502 313.

Hyderabad, Telangana, India.
two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in g/ml and is given by

\[ \text{Dt} = \frac{M}{Vt} \]

Where,
- \( M \) - Mass of powder,
- \( Vt \) - Tapped volume of the powder

\[ \text{Angle of Repose (} \theta \text{)}: \]

The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

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

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]

Where,
- \( \theta \) - Angle of repose.
- \( h \) - height in cms,
- \( r \) -radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

\[ \text{Carr’s index (or) } \% \text{ compressibility:} \]

It indicates powder flow properties. It is expressed in percentage and is given by

\[ I = \frac{\text{Dt} - \text{Db}}{\text{Dt}} \times 100 \]

Where, \( \text{Dt} \) is the tapped density of the powder and \( \text{Db} \) is the bulk density of the powder.

\[ \text{Hausner’s ratio:} \]

Hausner’s ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

\[ \text{Hausner’s ratio} = \frac{\text{Dt}}{\text{Db}} \]

Where, \( \text{Dt} \) is the tapped density, \( \text{Db} \) is the bulk density.

Lower hausner’s ratio (<1.25) indicates better flow properties than higher ones (>1.25).[5-9]

\[ \text{2.2.5. Preparation of Floating Tablet:} \]

Each floating tablet contains 200mg of Atenolol were prepared by direct compression method. Atenolol drug was assorted with necessary quantity of HPMC-K15M, HPMC-K100M, Guar gum, Sodium bicarbonate and MCC by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate and Talc in mortar and pestle for 2 min. The lubricated blend
was compressed into tablets using 8 mm flat-face round tooling on Pilot Press rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 3.5 to 4.5 kg/cm² with 4.0 mm of tablet thickness (Table 1).

Table 1: Composition of Atenolol Tablets

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tr>
<td>2</td>
<td>HPMC-K15M</td>
<td>37.5</td>
<td>62.5</td>
<td>87.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>HPMC-K100M</td>
<td></td>
<td></td>
<td></td>
<td>37.5</td>
<td>62.5</td>
<td>87.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Guar gum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37.5</td>
<td>62.5</td>
<td>87.5</td>
</tr>
<tr>
<td>5</td>
<td>Sodium bicarbonate</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
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<tr>
<td>6</td>
<td>Mg.Stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>7</td>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>MCC</td>
<td>89.5</td>
<td>64.5</td>
<td>39.5</td>
<td>89.5</td>
<td>64.5</td>
<td>39.5</td>
<td>89.5</td>
<td>64.5</td>
<td>39.5</td>
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<tr>
<td>Total weight</td>
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<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

2.2.6. Evaluation of tablets:
The weight of tablets was evaluated on 20 tablets using an electronic balance. Friability was determined using 6 tablets in Roche friability tester at 25 r/m. Hardness of the tablets was evaluated using a Monsanto hardness tester.[4,10]

2.2.7. In-vitro dissolution studies:
In-vitro drug release studies from the prepared Floating tablets were conducted using USP type II apparatus at 37°C at 50 r/m. Dissolution mediums used were 900ml of 0.1N HCl. The release rates from matrix tablets were conducted in HCl solution (pH 1.2). 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 Lab India UV/VIS spectrophotometer. 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.[11,12]

2.2.8. Data Analysis (Curve Fitting Analysis):
To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:
1. Cumulative percentage drug released Vs Time (In-vitro drug release plots)
2. Cumulative percentage drug released Vs Square root of time (Higuchi’s plots)
3. Log cumulative percentage drug remaining Vs Time (First order plots)
4. Log percentage drug released Vs Log time (Peppas plots)

Zero order:
\[ C = K_t \]
Where, \( K_o \) zero-order rate constant expressed in units of concentration/time \( t \)–Time (h).

First order:
\[ \log C = \log C_o - K t / 2.303 \]
Where, \( C_o \) - Initial concentration of drug, 
\( K \) - First order constant 
\( t \) – Time (h).

Higuchi:
\[ Q_t = K t^{1/2} \]
Where \( Q_t \) - Amount of the release drug in time t, 
\( K \) - kinetic constant and 
\( t \) - time (h)

Korsmeyer Peppas:
\[ M_t / M^n = K t \]
Where, 
\( M_t \) - Amount of the released drug at time t, 
\( M^n \) -Overall amount of the drug (whole dose) released after 12 h 
\( K \) - Diffusional characteristic of drug/polymer system constant 
\( n \) - Diffusional exponent that characterizes the mechanism of release of drug.

The value of \( n \) indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent \( n = 0.5 \), then the drug release mechanism is Fickian diffusion. If \( n < 0.5 \) the mechanism is quasi-Fickian diffusion, and \( 0.5 < n < 1.0 \), then it is non-Fickian or anomalous diffusion and when \( n = 1.0 \) mechanism is non Fickian case II diffusion, \( n > 1.0 \) mechanism is non Fickian super case II.[13,14]

3. RESULTS AND DISCUSSIONS
3.1. Preformulation characteristics:
Atenolol has the \( \lambda_{max} \) 223 nm. Standard graph of Atenolol in 0.1N HCl was plotted and the linearity range was 5-25 mcg/ml in the media and a good correlation was obtained with R² value of 0.999 (Table 2 & Figure 1).

Table 2: Standard graph of Atenolol in 0.1N HCl

<table>
<thead>
<tr>
<th>S. No</th>
<th>Concentration (mcg/ml)</th>
<th>Absorbance</th>
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<td>2</td>
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<tr>
<td>7</td>
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</table>
3.2. Drug Excipient Compatibility studies-FTIR:
Drug-Excipient compatibility studies by FTIR revealed no interaction between drug and the Excipients used in the formulation consequently performance compatibility (Figure 2, 3&4).

3.3. Physical characteristics of blends and tablets:
The blends of different formulations were evaluated for angle of repose, Bulk density, Tapped density, Carr’s compressibility index and Hausner’s ratio etc. The results of Angle of repose, Bulk density, Tapped density, Carr’s compressibility index and Hausner’s ratio ranged from 24.36 ± 0.11 to 28.49 ± 0.13, 0.421±0.02 to 0.512 ± 0.07, 0.498 ± 0.23 to 0.581 ± 0.39, 9.04 ± 0.45 to 14.09 ± 0.35 and 1.04 to 1.23 respectively which showed that blends from all the formulations having good flow property (Table 3). The Weight variation, Thickness, Hardness, Friability, Floating lag time and Floating duration ranged from 199± 0.02 to 201± 0.36mg, 3.4± 0.6 to 4.1± 0.9mm, 3.7± 0.6 to 5.1± 0.8Kg/cm², 0.47±0.54 to 0.86±0.53%, 60 to 180 minutes, 8to 12 h respectively. (Table 4)

3.4. In-vitro dissolution studies:
In-vitro dissolution studies of floated formulations (F1-F9) of Atenolol were carried out in 0.1 N HCl, by using USP dissolution apparatus Type-II at 50 r/m. Percentage drug release was calculated at different time intervals for 12 h.

Formulations (F1-F9) were containing drug to polymer ratios at different concentrations was prepared with different polymers such as HPMC-K15M, HPMC-K100M and Guar gum. Among all the formulation F6 is prepared with HPMC K100M in Drug: Polymer ratio of 1:3.5. F6 exhibited 98.35% of drug release within 12 h. Formulations F6 is found to be satisfactory with dissolution profile results. Hence this formulation was said to be optimized formulations (Table 5&6, Figure 5&6).
Table 5: Dissolution release profiles of Formulations (F1-F5)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
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<td>66.86</td>
<td>78.57</td>
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<td>12</td>
<td>88.36</td>
<td>82.25</td>
<td>90.98</td>
<td>89.36</td>
<td>91.12</td>
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Table 6: Dissolution release profiles of Formulations (F6-F9)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
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<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
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<td>98.35</td>
<td>88.24</td>
<td>92.35</td>
<td>93.32</td>
</tr>
</tbody>
</table>

3.5. Kinetics of In-vitro Drug Release:
The optimized composition F6 was subjected to graphical representation to assess the kinetics of drug release (Figure 7, 8, 9 & 10).

Figure 5: Dissolution profiles of Formulations F1-F5

Figure 6: Dissolution profiles of Formulations F6-F9.

Figure 7: Release Kinetics of optimized formulation F6 (Zero order)

Figure 8: Release Kinetics of optimized formulation F6 (First order)

Figure 9: Release Kinetics of optimized formulation F6 (Higuchi)

Figure 10: Release Kinetics of optimized formulation F6 (Peppas)
4. CONCLUSION
From the drug content and In-vitro dissolution studies of the formulations, it was concluded that the formulation F6 i.e. the formulation containing 87.5mg of HPMC-K100M, 40mg of NaHCO₃, 4mg of Magnesium stearate, 4mg of Talc and 39.5mg of MCC is the best formulation. The excellent total floating time of 12 h. As a consequence of this revision it may be concluded that the floating tablets by HPMC K100M are hydrophilic polymers enhance the GRT of the dissolution fluid in the stomach to deliver the drug in a sustained manner. The perception of formulating floating tablets of Model drug offers a suitable and practical approach in serving required objectives of gastro retentive floating tablets.

CONFLICT OF INTEREST
The authors have no conflict of interest

ABBREVIATIONS USED
HPMC: Hydroxy Propyl Methyl Cellulose; KBr: Potassium bromide; GRT: Gastro residence time; MCC: Micro Crystalline Cellulose; NAHCO₃: Sodium bicarbonate

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REFERENCES

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