Formulation and evaluation of oral floating tablets of Atenolol using Okra gum

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ABSTRACT

The main aim of this study was to optimize and evaluate the floating tablets of atenolol that prolongs the gastric residence time. Semi-synthetic polymer, HPMC K100M and natural polymer i.e., okra gum were used as release retarding agents by its swelling nature. Sodium bicarbonate was used as a gas-generating agent, Atenolol were prepared by direct compression method. The prepared tablets were evaluated for physicochemical parameters and found to be within range viz. hardness, swelling index, floating capacity, thickness, and weight variation. Further, tablets were evaluated for in vitro release characteristics for 8 hrs. The concentration of okra gum with a gas-generating agent was optimized to get the sustained release of atenolol for 8hrs, drug release from all the formulations followed first order kinetics and higuchi’s mechanism. The optimized (F6) formulation has better release rate. Based on the diffusion exponent \( n \) value, the drug release was found to be diffusion controlled.

Key words: Atenolol, HPMC, Okra gum, floating tablets.

INTRODUCTION

Oral delivery is the preferred route for drug administration because it is more natural and less invasive than other traditional routes, such as intravenous and intramuscular injection. To achieve maximum bio-availability various techniques are designed in which gastro retentive dosage forms is one among them. The system may be floating; swelling; inflation; adhesion; high-density systems and low density systems that increase the gastric residence time[1]. Gastric retention is useful for those drugs which are (i) act locally; (ii) have a narrow absorption window in the small intestinal region; (iii) unstable in the intestinal environment; and (iv) low solubility at high pH 4 environment[2]. The major causes of the low oral bioavailability of macromolecular drugs are generally luminal enzymatic hydrolysis and low membrane permeability.
Gastric emptying occurs during fasting as well as fed states. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into 4 phases.[3][4]

Classification of Gastro Retentive Drug Delivery System [5-9]
1. Floating drug delivery system.
2. Sinking system.
3. Bioadhesive system.
4. Swelling and expanding system.
5. Magnetically controlled gastric residence system.

Various factors effecting GRDDS[10] they are Density, Size, Caloric content, Gender, Posture, Concomitant drug administration.

Floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the non floating units, which lie in the antrum region and are propelled by the peristaltic waves[11]. High density systems whose action is based on their dipping to the bottom of the stomach[12]. Floating is achieved by low density materials, floating system based on polymer swelling mechanism is termed to Non Effervescent FDDS[13] and Effervescent FDDS[14] is known to be utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., Chitosan and natural gum, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid. Technique to rendered drug floating generation of CO₂ via chemical reaction between sodium bicarbonate and hydrochloric acid of gastric juice thereby entrapping gas into swellable polymer this ensures drug to prolong. Floating drug delivery shows the application [15] on Sustained drug delivery, Site specific drug delivery, Pharmacokinetic advantages.

MATERIALS AND METHODS

Materials:
Atenolol was obtained as gift sample (International health care LTD, Vijayawada, Andhra Pradesh, India). Other chemicals and polymers such as hydroxypropyl methylcellulose (HPMC K 100 M) (M/S Seeko biotech. Vijayawada, India), Magnesium stearate magnesium stearate (Qualigens fine chemicals, Mumbai, India)

Sodium bicarbonate & Talc (Molychem, Mumbai), Micro crystalline cellulose (MCC) (rolex chemical industries), Okra gum (okra seeds, market).

Preparation of Atenolol floating tablets
Effervescent type floating tablets were prepared by direct compression technique by employing the rate controlling polymer like, Hydroxyporpylmethylcellulose (HPMC) and okra gum is used as hydrophilic swellable gum. The composition of the tablets was presented in table no.1. The components were blended according to their ascending order of weight and finally with lubricants like magnesium stearate & talc. By blending it for 15 to 20 min. Direct compression
was done by using a Cadmach 16 station tablet machine with & dies flat face punches & dies (12 mm in diameter).

### Table 1 Composition of different Atenolol floating tablets

<table>
<thead>
<tr>
<th>Ingredients (mg/tablet)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>HPMC K 100 M</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Natural gum</td>
<td>20</td>
<td>60</td>
<td>140</td>
<td>220</td>
<td>300</td>
<td>380</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>MCC</td>
<td>426</td>
<td>386</td>
<td>306</td>
<td>226</td>
<td>146</td>
<td>66</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Talc</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Abelmoschus Esculentus Pod Mucilage (OKRA GUM)[16]:
The fresh Abelmoschus esculentus fruits will be collected and washed with water. The fruits will be crushed and soaked in water for 5-6 hours, boiled for 30 minutes and left to stand for 1 hour to allow complete release of the mucilage into the water. The mucilage will be extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three Times the volume of filtrate) will be added to precipitate the mucilage The mucilage will be separated, dried in an oven at 40°C collected, passed through a # 80 sieve and will be store in a desecrator.

Pre-Compression Parameters and Characterization of Powders
The flow properties of powders (before compression) were characterized in terms of, bulk density[17], Hausner’s ratio[17], angle of repose[18], Carr’s index[19].

Evaluation of Physical Properties of Tablets
The formulated tablets were evaluated by various parameters. Like Thickness[20], hardness, Weight variation, friability[21], Floating characteristics[22] (Floating lag time, Floating time), Swelling index[23], Drug content[24].

**In Vitro Dissolution Studies**
Dissolution rate was studied using USP type-II dissolution apparatus, in 900ml of 0.1 N HCl at 37± 0.5 °C at 100 rpm. Aliquot of dissolution medium was withdrawn at regular time intervals (30min) and the same volume of pre warmed fresh dissolution medium was replaced. The samples were filtered and drug content of Atenolol in each sample was analyzed after suitable by elico U.V Spectrophotometer at 255nm.

**In Vitro Drug Release Kinetic Studies**
Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order[25], first order[26], Higuchi square root[27], Korsmeyer- Peppas model[28].The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test.
Drug Polymer Compatibility studies
The pure drug and physical mixture of drug and polymers were subjected to IR spectroscopic study using FT-IR spectrophotometer (IRAffinity-1, Shimadzu). The spectra were scanned over the wave number range from 4000 – 400 cm$^{-1}$.

RESULTS AND DISCUSSION
The objective of the present study was to develop a gastro retentive drug delivery system of Atenolol with a view to increase the bioavailability as well as its complete utilization by sustaining the dose. For this purpose hydrophilic swellable polymer like okra gum was used as the key excipient. Among the various approaches involved in gastro retentive systems, effervescent floating drug delivery system were selected in this investigation as they were easy to fabricate and produced buoyancy in the G.I.T and the absorption of the drug.

Studies on Micromeritics Properties for Atenolol Mixture:
The Atenolol powder mixtures obtained during the pre compression process were subjected to different parameters and the results were represented in the Table 1. From the results it was observed that the bulk density was found to be between 0.845gm/ml to 0.909gm/ml and the tapped density ranged between 0.86gm/ml to 0.956gm/ml, which make them floatable in the gastric fluid. The other micromeritic properties such as Carr’s index, Hausner’s ratio revealed no significant differences. Angle of repose was to be between 24.525to 25.913 indicating good flow properties.

Studies on Atenolol floating tablets:
The quality control tests adopted for the tablets were depicted in the table 2. The hardness of the floating tablets ranged between 4.1 to 5.7 kg/cm$^2$. The thickness of the tablets ranged between 5 to 5.5 mm. the percentage friability of the prepared tablets was well within the limits (<1%). There was no significant weight variation observed between average weight and individual weight.

All the formulations had desired floating lag time (<4min) and total floating time between 6-8 hrs was found to be the function of concentration of gum and type of disintegrating agent incorporated. This may be because of the fact that at lower concentrations, the gum has lesser ability to form as gel. This was mainly due to the evolution of CO$_2$ entrapped into the matrix of swollen polymer of the matrix and well protected by gel formation by the hydrated polymer resulting from interaction between the gas generating agent (sodium bicarbonate) and dissolution medium (0.1N HCl with pH 1.2) that leads to lowering the density and enabling the tablet to float. The swelling index results were depicted in table 2. It was observed that the swelling indexes were increased with increasing gum concentration of gum. Swelling was strong enough to avoid premature disintegration as well as burst effect and retards the release of drug for a layer period of time. For floating of tablet, there should be appropriate balance between swelling and water uptake.

Further results suggested that the drug release from the polymer was more by diffusion and less by erosion mechanism that correlates with results of release kinetics. The drug content in all the
formulations was within the range of 96.84 to 98.37% ensuring uniformity of drug content in the formulations.

Table: 2 Physicochemical characterization of Atenolol powder mixture

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Angle of Repose (θ)</th>
<th>Loose bulk Density (g/ml)</th>
<th>Tapped bulk Density (g/ml)</th>
<th>Compressibility Index (%)</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>24.52±0.011</td>
<td>0.83±0.011</td>
<td>0.90±0.010</td>
<td>7.78±0.010</td>
<td>1.084±0.041</td>
</tr>
<tr>
<td>F2</td>
<td>25.137±0.021</td>
<td>0.76±0.042</td>
<td>0.83±0.011</td>
<td>8.43±0.032</td>
<td>1.023±0.012</td>
</tr>
<tr>
<td>F3</td>
<td>22.127±0.02</td>
<td>0.90±0.021</td>
<td>1.0±0.021</td>
<td>10.0±0.041</td>
<td>1.111±0.011</td>
</tr>
<tr>
<td>F4</td>
<td>26.567±0.030</td>
<td>0.71±0.051</td>
<td>0.76±0.031</td>
<td>5.92±0.040</td>
<td>1.025±0.013</td>
</tr>
<tr>
<td>F5</td>
<td>24.343±0.022</td>
<td>0.62±0.043</td>
<td>0.66±0.041</td>
<td>6.30±0.011</td>
<td>1.126±0.048</td>
</tr>
<tr>
<td>F6</td>
<td>25.913±0.016</td>
<td>1.11±0.041</td>
<td>1.25±0.062</td>
<td>12.6±0.012</td>
<td>1.056±0.054</td>
</tr>
</tbody>
</table>

Table: 3 Physicochemical Evaluation of Atenolol Floating Tablet

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight Variation (%)</th>
<th>Hardness (mm)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Floating Lag time (min)</th>
<th>Floating Time (hr)</th>
<th>Swelling Index (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.75±0.01</td>
<td>4.5±0.03</td>
<td>5.0±0.01</td>
<td>0.75±0.04</td>
<td>0.9±0.11</td>
<td>6</td>
<td>71.67±0.01</td>
<td>96.84±0.01</td>
</tr>
<tr>
<td>F2</td>
<td>4.72±0.05</td>
<td>5.3±0.02</td>
<td>5.2±0.01</td>
<td>0.82±0.06</td>
<td>1.1±0.17</td>
<td>6</td>
<td>76.92±0.04</td>
<td>98.17±0.02</td>
</tr>
<tr>
<td>F3</td>
<td>4.71±0.05</td>
<td>5.5±0.02</td>
<td>5.3±0.02</td>
<td>0.85±0.07</td>
<td>1.7±0.22</td>
<td>&gt;8</td>
<td>80.47±0.05</td>
<td>97.97±0.01</td>
</tr>
<tr>
<td>F4</td>
<td>4.02±0.03</td>
<td>4.8±0.01</td>
<td>5.4±0.03</td>
<td>0.88±0.04</td>
<td>2.0±0.13</td>
<td>&gt;8</td>
<td>82.11±0.06</td>
<td>95.92±0.03</td>
</tr>
<tr>
<td>F5</td>
<td>2.46±0.03</td>
<td>5.5±0.01</td>
<td>5.5±0.01</td>
<td>0.87±0.07</td>
<td>2.8±0.32</td>
<td>&gt;8</td>
<td>85.45±0.07</td>
<td>98.37±0.02</td>
</tr>
<tr>
<td>F6</td>
<td>2.50±0.04</td>
<td>4.7±0.02</td>
<td>5.7±0.02</td>
<td>0.91±0.02</td>
<td>3.7±0.13</td>
<td>&gt;8</td>
<td>89.48±0.05</td>
<td>97.77±0.04</td>
</tr>
</tbody>
</table>

Table: 4 Dissolution Kinetics of Atenolol Floating Tablet Formulated With Various Concentration of Okra Gum

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Peppas</th>
<th>K value (mg/hr)</th>
<th>T 50 %</th>
<th>T 90 %</th>
<th>Slope (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.7851</td>
<td>0.9903</td>
<td>0.9779</td>
<td>0.9654</td>
<td>4.236</td>
<td>2.4</td>
<td>4.3</td>
<td>0.5750</td>
</tr>
<tr>
<td>F2</td>
<td>0.8539</td>
<td>0.9475</td>
<td>0.9887</td>
<td>0.9762</td>
<td>3.860</td>
<td>2.6</td>
<td>4.7</td>
<td>0.6337</td>
</tr>
<tr>
<td>F3</td>
<td>0.8194</td>
<td>0.9514</td>
<td>0.9912</td>
<td>0.9836</td>
<td>3.139</td>
<td>1.5</td>
<td>5.0</td>
<td>0.5746</td>
</tr>
<tr>
<td>F4</td>
<td>0.9240</td>
<td>0.9268</td>
<td>0.9876</td>
<td>0.9820</td>
<td>2.990</td>
<td>1.7</td>
<td>5.5</td>
<td>0.6762</td>
</tr>
<tr>
<td>F5</td>
<td>0.9308</td>
<td>0.9661</td>
<td>0.9904</td>
<td>0.9895</td>
<td>2.808</td>
<td>2.2</td>
<td>7.4</td>
<td>0.7238</td>
</tr>
<tr>
<td>F6</td>
<td>0.9589</td>
<td>0.9965</td>
<td>0.9976</td>
<td>0.9852</td>
<td>2.844</td>
<td>1.9</td>
<td>6.4</td>
<td>0.7544</td>
</tr>
</tbody>
</table>

Figure: 1  Dissolution Profiles of Atenolol Floating Tablets Formulated With Various Concentrations of Okra Gum &MCC
In vitro dissolution studies

Influence of concentration of okra gum on release rate of Atenolol:

To study the effect of okra gum on release rate of atenolol from the tablets, different concentrations of okra gum (20 to 380) were employed by kneading the other process variables versus concentration of other excipients, method of preparation and hardness were kept constant as shown in figure: 1. The drug release followed first order kinetics as the graph was drawn in between the log % of unreleased drug verses time were found to be linear. To ascertain the mechanism of drug release the data was subjected to Higuchi & korsmeyer peppas equation. Application of korsmeyer peppas equation to the data showed that the mechanism of drug release of atenolol from okra gum matrix is governed by predominant non-fickian diffusion (slope>0.5). It was also observed that the release rate was found to be influence of gum employed in the preparation of tablets (table: 4). Good correlation was observed in between the concentration of gum and release rate constant it may be attributed due to increased viscosity of dissolution media with the increment in concentration of okra gum.
Influence of concentration of Micro crystalline cellulose on release rate of Atenolol
To study the effect of MCC on release rate of atenolol from the tablets, different concentrations of MCC (66 to 426) were employed by kneading the other process variables verses concentration of other excipients, method of preparation and hardness were kept constant as shown in figure: 1. The drug release followed first order kinetics as the graph was drawn in between the log % of unreleased drug verses time were found to be linear. To ascertain the mechanism of drug release the data was subjected to Higuchi & korsmeyer-peppas equation. Application of korsmeyer-peppas equation to the data showed that the mechanism of drug release of atenolol from MCC matrix is governed by predominant non-fickian diffusion (slope>0.5). It was also observed that the release rate was found to be influenced by MCC employed in the preparation of tablets (table: 4). Good correlation was observed in between the concentration of MCC and release rate constant.

Drug Polymer Compatibility studies:
Compatibility study of drug and polymers were conducted by employing F.T.I.R Spectral studies. In this FTIR spectra of Atenolol, HPMC K-100M, Okra gum, the physical mixture of drug and excipients.

The figures were shown in figure: 2&3 The following characteristic peaks were observed with Atenolol 3355.60 cm⁻¹ Asymmetric Amines, 3172.94 cm⁻¹ Secondary amines, C-H Stretching 2964.09 cm⁻¹, 1638.64 cm⁻¹ and 1514.89 cm⁻¹ Aromatic ring, 1415.24 cm⁻¹ and 1334.09 cm⁻¹ Nitro compound. The results revealed no considerable changes in the IR peaks of Atenolol when mixed with polymer, such as HPMC, MCC, NaHCO₃, and Okra gum.

CONCLUSION
The present investigation focused on the improvement of the absorption and bioavailability of Atenolol along with sustained action. To meet the above criteria Gastro retentive effervescent floating tablets of Atenolol were formulated. With natural gum such as okra was selected as the key excipient.

The hydrophilic swellable gum selected was more reliable as they released the drug slowly, extending it over a long period of time. More over the high swelling capacity of this polymer helped in maintaining the buoyancy with the minimal utilization of gas generating agent such as sodium carbonate. Which if increased would make a marked impact on G.I.T. fluids by its alkaline nature. Alternating concentrations

REFERENCES