Development and Evaluation of Gastroretentive Atenolol Tablets

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ABSTRACT

The low oral bioavailability of atenolol is primarily because of its poor absorption from the lower gastrointestinal tract. Gastroretentive dosage forms provide an opportunity to deliver the drug with absorption window in the proximal part of the GIT thereby increasing their bioavailability. The objective of this study was to develop a dosage form for atenolol with the objective of increasing the gastric residence and thereby its oral bioavailability. Different formulations of floating tablets of atenolol (AT1-AT10) were prepared by varying the composition of hydroxypropyl methyl cellulose (HPMC) K100, lactose and citric acid. The tablets were evaluated for various parameters like friability, weight variation, content variation, floating lag time, total buoyancy and in vitro dissolution. The physicochemical properties of the prepared formulations were found to possess adequate physical integrity. Formulation AT8 showed the lowest floating lag time with 14 h buoyancy. Drug release was found to be dependent on the concentration of HPMC K100 and lactose in the formulation. Further, the increase in amount of citric acid leads to increase in atenolol release rate while reduces the floating time. The findings revealed that the formulation AT8 retarded the atenolol release (~73% in 12 h) and followed zero order kinetics. The in vitro data observed here substantiate the potential of the prepared formulation to provide adequate drug release and buoyancy to improve the bioavailability of atenolol, which necessitate further in vivo studies.

Key words: Gastroretentive delivery; atenolol; floating delivery system, HPMC K 100

INTRODUCTION

Oral delivery of drug is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Approximately 50% of drug delivery systems in the market are oral dosage delivery system (Shivakumar et al., 2004; Ramarao et al., 2014). Oral sustained release dosage forms have retained prominence for the past 3 decades due to their clinical advantages in comparison with their immediate release forms (Hoffman, 1998). However, the conventional sustained release formulations are not suitable for drugs possessing narrow absorption window in the upper part of the gastrointestinal tract (GIT). These formulations are rapidly cleared from the upper GIT, resulting in the release of a significant fraction of the drug in non-absorbing distal segments of the GIT. This leads to a short absorption phase and poor bioavailability of several active pharmaceutical ingredients (Klausner et al., 2003a; Zhang et al., 2014). Many drugs, such as ciprofloxacin, ofloxacin, levodopa, iron, and acyclovir, are preferentially absorbed from the upper GIT. In this context, gastroretentive dosage forms (GRDFs), is one of the most feasible approaches for achieving a prolonged and predictable drug
delivery profile in the GIT. Following oral administration, this system would be retained in the stomach and release the drug in a sustained manner, so that the drug could be supplied continuously to its absorption site in the upper GIT (Yeole et al., 2005; Kanekar et al., 2014).

The need for GRDFs has led to extensive efforts in both academic and industry towards the development of such drug delivery systems. The main approach that have been examined for GRDFs are, i) low density of GRDF that cause buoyancy (Floating Systems), ii) high density which retain the dosage form in the body of stomach, iii) concomitant administration of drugs or excipients which slow the motility of the GIT, iv) bioadhesion to gastric mucosa and v) swelling to a large size (Hwang et al., 1998; Rubinstein et al., 1998). Gastroretentive systems provides important therapeutic options as they can remain in the gastric region for several hours and hence significantly prolong the gastric residence time (GRT) of drugs. The prolonged gastric retention improves bioavailability, reduces drug wastage, improves solubility for drugs that are less soluble in a high pH environment and can also be helpful for local drug delivery to the stomach and proximal small intestine (Arora et al., 2005; Vishvadeep et al., 2014). GRDFs are especially of particular interest for drugs which are (a) locally acting in the proximal parts of GIT, (b) drugs that are mostly absorbed from the stomach or upper small intestine, (c) drugs having narrow window of absorption, (d) drugs that are poorly soluble at the intestinal alkaline pH, and (e) are unstable in the intestinal or colonic environment (Suma et al., 2008). It has been reported that, when drugs with a narrow absorption window are formulated as gastroretentive sustained release formulations, they have higher bioavailability due to an extended absorption phase (Qassim, 2010). The ciprofloxacin once daily tablet and ofloxacin once daily are the well-known commercially available GRDFs. After oral administration, GRDFs are retained within the stomach and they release the drug in a controlled manner, so the drug is supplied continuously to its absorption sites in the upper GIT. This would be the best mode of administration for these drugs to achieve the optimum pharmacokinetic and pharmacodynamic efficiency of sustained release dosage forms (Hoffman and Stepenisky, 1999).

GRDFs may be formulated as multiparticulate delivery systems e.g. microspheres. However, the methods employed in the manufacture of microsphere based gastroretentive sustained release formulations suffer significant shortfalls and limitations (e.g: the multistep process, use of organic solvents that must be removed from the final formulation, requirement for high shear conditions, and a lengthy post-processing time period) that potentially hinder their commercial success. The preparation of sustained release tablets is well established at the commercial level due to the use of technology similar to that used to manufacture immediate release tablets. Gastroretentive sustained release formulations dosage forms using various approaches, such as high-density systems (Riner et al., 1982), floating systems (Reddy and Murthy, 2002; Eberle et al., 2014), expandable systems (Kedzierewicz et al., 1999; Klausner et al., 2003b), super porous hydrogels (Chen et al., 2000), mucoadhesive/bioadhesive systems (Akiyama et al., 1998) and magnetic systems (Groning and Berntgen, 1996) have been reported in the literature (Rocca et al., 2004). The real challenge in the development of an oral controlled release drug delivery system is not only to control the drug release but also to prolong the residence of the dosage form within the GIT until complete release of the
drug at a desired period of time. Even though lots of technologies are available for gastric retention, the floating approach is most effective due to its additional advantages like random gastric emptying, better bioavailability, less irritation, fewer side effects etc. In the light of these, the present work was carried out to design GRDFs of atenolol.

Atenolol is a cardio selective β-1 adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities used for the treatment of hypertension. It is poorly absorbed from the lower GIT and the oral bioavailability of atenolol has been reported to be ~ 50% (Mason et al., 1979; Martindale, 2004). The human jejunal permeability and extent of absorption is also low (Melander et al., 1979). Thus, it seems that an increase in GRT may increase the extent of absorption and bioavailability of the drug. The drug is slightly water soluble and has elimination half-life, after an oral dose, of 6-7 h. It is prescribed widely in diverse cardiovascular diseases, e.g. hypertension, arrhythmias, angina pectoris, and myocardial infarction (Dollery, 1991; Amidon et al., 1995). A significant beta blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2-4 h and persists for at least 24 hours. The purpose of the present study was to develop GRDFs for atenolol so as to enhance its bioavailability by prolonging the duration of residence of the dosage form in the stomach.

The inclusion of high viscosity polymer hydroxypropyl methyl cellulose (HPMC) in the tablet matrix was designed to provide, swelling and sustain drug release so as to increase the duration of action of the drug and to prevent repetitive drug administration.

**MATERIALS AND METHODS**

Atenolol and HPMC K100 were obtained as a gratis sample from Ind-Swift Ltd., Parwanoo, Himachal Pradesh, India. Lactose and magnesium stearate were procured from Qualikem fine chemicals Pvt. Ltd. (New Delhi, India). Sodium bicarbonate was obtained from Rankem laboratories Ltd. India. Hydrochloric acid was procured from Qualigens Fine Chemicals, Mumbai, India.

**Preparation of granules and tablets**

Wet granulation method has been employed in the current study to develop a hydrodynamically balanced system of atenolol and HPMC K100 (Singh et al., 2006). The composition of different formulation of atenolol floating tablet is summarized in Table 1. All the ingredients were accurately weighed and passed through sieve no. 60. In order to mix the ingredients thoroughly, drug and polymer were blended geometrically in a pestle and mortar for 15 minutes, and then sodium bicarbonate and lactose were added to it. Granulation was done using sufficient amount of isopropyl alcohol. The granules (40 mesh) were dried in conventional hot air oven at 45°C. The dried granules were sized through sieve no. 40 and citric acid was mixed to the blend and blend was lubricated with magnesium stearate (2%) and then compressed on a 12 station rotary machine (Kim and Shin, 2004).

Table 1: Composition (in mg/tablet) of different formulations of floating atenolol tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>AT1</th>
<th>AT2</th>
<th>AT3</th>
<th>AT4</th>
<th>AT5</th>
<th>AT6</th>
<th>AT7</th>
<th>AT8</th>
<th>AT9</th>
<th>AT10</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>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>HPMC K100</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>275</td>
<td>300</td>
<td>325</td>
<td>340</td>
</tr>
<tr>
<td>Sod. bicarbonate</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Citric acid</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Mag. Stearate</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lactose</td>
<td>310</td>
<td>240</td>
<td>240</td>
<td>210</td>
<td>150</td>
<td>90</td>
<td>85</td>
<td>50</td>
<td>15</td>
<td>00</td>
</tr>
<tr>
<td>Total weight</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>
Uniformity of weight

The uniformity of weight (mg) of the prepared tablets was performed by randomly selecting twenty tablets. Each tablet was placed in an electronic balance (Shimadzu, AX200, Japan). Also the average weight of the tablets was calculated. The observed data from the tablet weights were analyzed for sample mean and percent deviation.

Content Uniformity

The content uniformity was carried out as per British Pharmacopoeia (2005). Thirty tablets were selected and ten out of these tablets were assayed individually. Tablet was powdered and dissolved in distilled water by sonication to ensure complete solubility of the drug. The sample was filtered, suitably diluted and analyzed.

Friability Test

Friability of the prepared tablets was carried out using 10 tablets after dusting, placing them in the Roche friabilator (Electrolab, EF-2, Mumbai, India), and operating the friabilator vertically at 25 rpm, dropping the tablet at a distance of six inches with each revolution. Preweighed tablet sample was placed in the friabilator, which was then operated for 100 revolutions. After dusting the total remaining weight of the tablet was recorded and the percent was calculating according to:

\[
\text{Percent friability} = \frac{\text{Initial weight of tablets - Final weight of tablets}}{\text{Initial weight of tablets}} \times 100
\]

In vitro buoyancy test

The prepared tablets were subjected to in vitro buoyancy test by placing them in 250 ml beaker containing 200 ml 0.1 N Hydrochloric acid (HCl) (pH 1.2, at 37°C ± 0.5). The time between introduction of the dosage form into the medium and its floating was taken as the floating lag time. The duration of time for which the tablets floated onto the medium was taken as the total buoyancy time. The readings of time were rounded up to represent the nearest time unit in hours (Kim and Shin, 2004).

Drug interaction studies

To rule out a possibility of drug-polymer interaction in the present formulation the drug-polymer blend was subjected to FT-IR analysis (Shimadzu 8400-S, Japan). The FT-IR of the drug-polymer mixture was compared with the FT-IR of the pure drug to identify any changes in the peaks due to interaction between drug and the polymer (Gupta and Jain, 2004).

In-vitro dissolution studies

Drug release was evaluated in vitro using USP II apparatus (Electro Lab, TDT-08L, Mumbai). The dissolution studies for different formulations were carried out in 900 ml of 0.1 N HCl (pH 1.2) for a period of 12 h. The temperature of the dissolution medium was kept at 37°C ± 0.5 and the paddle was set at 50 rpm (Singh et al., 2006). Dissolution medium (10 ml) was withdrawn at specified interval of time and filtered through Whatman filter paper (pore size 0.22 μm). The sample solutions were further diluted and the absorbance was measured at a \( \lambda_{\text{max}} \) of 273 nm using UV visible spectrophotometer (Shimadzu, 1700, Japan) and the concentration of atenolol was calculated.

Statistical analysis

All the data obtained for dissolution and drug content were evaluated statistically. The data were tested by one-way analysis of variance (ANOVA) and t-test using Graphpad prism 5, graphpad software, Inc., CA, USA, to test the effects of various treatments. P value less than 0.05 was considered statistically significant. The data points provided in the graph is an average of six trials. The error bars represents the standard deviation.

RESULTS AND DISCUSSION

The compatibility studies to assess any possible interaction between the drug and excipients were carried out and analyzed using IR for a period of 4 weeks. The
observed FTIR spectra showed all the principal peaks of the drug and excipients without any alteration in the respective IR peaks, suggesting no possible interaction between excipients and atenolol (Data not shown). The physical properties of prepared GRDFs, such as weight variation, friability, thickness, floating lag time and total buoyancy were determined by using standard protocols. The results obtained were recorded in Table 2. It can be seen from Table 2 that the weight variation obtained for all the formulations were well in the range of official limit (500 ± 20 mg or 100 ± 4 %). The friability of the tablet formulation was found to vary between 0.34 ± 0.13 to 0.65 ± 0.22%, which indicate that there was no significant difference among the formulations and possess good physical integrity (Table 2). Similarly, no significant differences in thickness values were observed between different formulations. The drug content study proved that the amount of atenolol between formulations did not vary by more than 5% and were in the range of 100 ± 5%, and the assay values were statistically insignificant (P>0.001). The data observed here signify that the physical properties of the prepared formulations did not show any significant variations and possess adequate physical integrity (Table 2).

Table 2: Physical characterization and in vitro buoyancy test for atenolol tablets (n=3)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Weight variation (%)</th>
<th>Friability (%)</th>
<th>Thickness (mm)</th>
<th>Mean floating lag time (sec)</th>
<th>Total buoyancy time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT-1</td>
<td>498 ± 5.25</td>
<td>0.57 ± 0.12</td>
<td>4.0 ± 0.38</td>
<td>95</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>AT-2</td>
<td>486 ± 4.20</td>
<td>0.34 ± 0.13</td>
<td>4.1 ± 0.65</td>
<td>85</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>AT-3</td>
<td>491 ± 3.29</td>
<td>0.38 ± 0.12</td>
<td>4.1 ± 0.86</td>
<td>76</td>
<td>&gt; 4</td>
</tr>
<tr>
<td>AT-4</td>
<td>492 ± 5.45</td>
<td>0.55 ± 0.24</td>
<td>4.1 ± 0.77</td>
<td>67</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>AT-5</td>
<td>505 ± 2.55</td>
<td>0.59 ± 0.22</td>
<td>4.2 ± 0.68</td>
<td>61</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>AT-6</td>
<td>495 ± 5.48</td>
<td>0.51 ± 0.27</td>
<td>4.0 ± 0.95</td>
<td>54</td>
<td>&gt;12</td>
</tr>
<tr>
<td>AT-7</td>
<td>507 ± 4.56</td>
<td>0.49 ± 0.22</td>
<td>4.1 ± 0.79</td>
<td>49</td>
<td>&gt;12</td>
</tr>
<tr>
<td>AT-8</td>
<td>506 ± 5.43</td>
<td>0.47 ± 0.25</td>
<td>4.0 ± 0.63</td>
<td>42</td>
<td>&gt;14</td>
</tr>
<tr>
<td>AT-9</td>
<td>492 ± 3.32</td>
<td>0.65 ± 0.22</td>
<td>4.1 ± 0.58</td>
<td>153</td>
<td>&gt;16</td>
</tr>
<tr>
<td>AT-10</td>
<td>501 ± 3.39</td>
<td>0.59 ± 0.23</td>
<td>4.2 ± 0.62</td>
<td>172</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

Floating capacity of the prepared tablets was determined in 0.1 M HCl and the results of floating lag time (sec) and total buoyancy (h) are listed in Table 2. Formulation AT8 showed the minimum lag time of 42 seconds while maximum lag time was found in case of AT10 amounting to 172 sec, indicating statistically significant difference (P<0.0001) in the floating lag time, among the formulations. However, the increase in citric acid amount decreases the floating lag time (Table 2). Further, it is also observed the increase in HPMC content increases the buoyancy time, in the current experimental condition. The floating time was found to be little more than 2 h for formulation AT1 and AT2, while for AT3 it was more than 4 h. Formulations AT6 to AT10 showed a floating time of more than 12 h, which increased to more than 16 h in AT9 and AT10 tablets (Table 2).

**In vitro release study**

Figure 1 shows the in vitro drug release profiles of different atenolol formulations. AT1 and AT2 were excluded due to their short floating time (less than 3 h). It is apparent from the Figure 1 that there was significant difference in drug release pattern between the prepared formulations in the study period (12 h) suggesting that the release of atenolol was influenced by the formulation composition. Decrease in drug release from the prepared tablets was observed with increase in the concentration of HPMC. The drug release was rapid in case of batch AT3 as the entire atenolol was released in the initial hour itself (Figure 1). On the other hand, as amount of HPMC in
tablets was increased, the drug release was found to be retarded and was significantly low in batches AT9 and AT10. Formulation AT10 showed less than 50% release at the end of 12 h which can be attributed to the highest content of HPMC K100 and the lowest lactose content. From the above observation, it can be said that the amount of HPMC K100 and lactose had a significant role on release of atenolol from the prepared tablets, in the current experimental condition.

Figure 1. In vitro release profiles showing the cumulative percentage drug release versus time profile of formulations AT3 to AT10. Each data represents the mean ± SE of six experiments.

Upon development of a novel delivery system, drug release/dissolution from solid pharmaceutical dosage form is necessary to ensure that the drug dissolution occurs in an appropriate manner. Several theory’s/kinetic models describe drug dissolution from immediate and modified release dosage. These represents the drug dissolution profiles where f is a function of “t” (time) related to the amount of drug dissolved from the pharmaceutical dosage forms. The quantitative interpretation of the value obtained from the dissolution assay is facilitated by mathematical equation which translates the dissolution curve in a function of some parameters related with the pharmaceutical dosage forms (Kim and Shin, 2004). In the present study, data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of atenolol from the floating tablets. The kinetic model is used were a Zero order equation, First order equation, Higuchi release and Korsmeyer-Peppas models.
Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disintegrate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

\[ Q_t = Q_o + K_o t \]

Where \( Q_t \) is the amount of drug released in time “t”, \( Q_o \) is the initial amount of drug in the solution, \( K_o \) is the zero order release constant.

The pharmaceutical dosage forms following this profile, release the same amount of drug per unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action. This relation can be used to achieve higher pharmacological response (Varelas et al., 1995).

First Order Kinetics

Gibaldi and Feldman (1967) first described the application of this model as given in the equation shown below:

\[ \log Q_t = \log Q_o + K_t t/2.303 \]

Where, \( Q_t \) is the mount of drug released in time “t”, \( Q_o \) is the initial amount of drug in the solution, \( K_t \) is the first order release constant. The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices (Mulye and Turco, 1995), release the drug in a way that is proportional to amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

Higuchi Model

Higuchi (1963) developed several theoretical models to study the release of water soluble drugs incorporated in semi-solid and/or solid matrixes. The simplified equation is given below:

\[ f_t = k_H t^{1/2} \]

Where, \( k_H \) is the Higuchi diffusion constant, \( f_t \) is the fraction of drug dissolved in time “t”. Higuchi describes drug release as a diffusion process based on the Fick’s law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix water soluble drugs.

Korsmeyer-Peppas Model

Korsmeyer et al., (1983) developed an equation to describe drug release as a function of time elapsed (t):

\[ F_t = a t^n \]

Where, \( a \) is the constant incorporating structural and geometric characteristics of the drug dosage form, \( n \) is the release exponent, \( f_t = M_t / M_\infty \) = fraction of drug released.

Hixon-Crowell cube root law

Hixon-Crowell cube root law describes drug release from the systems that undergo change in surface area and diameter in tablets. In case of drug particles which consist of uniform size particles an equation may be derived based on the cube root of the particles:

\[ Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \]

Where \( Q_t \) is the amount of drug released in the time t, \( Q_0 \) is the initial amount of drug in the tablet and \( K_{HC} \) is the rate constant for Hixon-Crowell equation.

The drug release obtained from the developed formulations (AT4 to AT10) was fitted into all the above said models and the observed regression coefficient (\( r^2 \)) are summarized in Table 3. AT3 was not exposed to this study due to the rapid drug release as the entire atenolol was released in the initial hour itself.

From the kinetic release data of the various developed formulation, the \( r^2 \) value was found to be maximum for Korsmeyer Peppas model in formulations AT4, AT5, AT7, AT10, Hixon Crowell cube root model for formulation AT6, Zero order for formulation AT8 and first order for AT9. Among the developed formulations, batch
AT6, AT7 and AT8 provided a typical release profile to provide steady release of atenolol for a period of 12 h. In nutshell it can be said that the prepared tablets (AT8) could be utilized for the oral delivery of atenolol to enhance its bioavailability.

Table 3: Kinetic release data of different model for selected formulations (AT4 to AT10)

<table>
<thead>
<tr>
<th>Mathematical model</th>
<th>Regression Coefficient (r²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AT4</td>
</tr>
<tr>
<td>Zero order</td>
<td>0.951</td>
</tr>
<tr>
<td>First order</td>
<td>0.931</td>
</tr>
<tr>
<td>Higuchi model</td>
<td>0.955</td>
</tr>
<tr>
<td>Korsemeyer Peppas model</td>
<td>0.963</td>
</tr>
<tr>
<td>Hixon Crowell cube root model</td>
<td>0.961</td>
</tr>
</tbody>
</table>

**Conclusion**

The present study investigates the feasibility of developing a gastroretentive delivery system for atenolol. Different formulations of floating tablets of atenolol (AT1-AT10) were prepared and evaluated in vitro. The prepared tablets were found to comply with the usual tablet tests. The formulation AT8 showed the stable, reliable and persistent buoyancy and followed zero order drug release. The data observed in the current study substantiate the objective of developing a gastroretentive delivery system for atenolol, although in vivo studies are required to support this finding.

**REFERENCES**


