Formulation and Evaluation of Sustained Release Mucoadhesive Atenolol Tablets for Gastric Retention
Sunena Jha\(^*\), Arun Nanda\(^2\)
1 Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar,(125001), India
2 Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak (124001), India.

ABSTRACT
An oral sustained release gastroretentive dosage form comes out as better alternative for drugs having narrow absorption window. Atenolol conventional tablets have been reported by many scientists to exhibit poor oral bioavailability and fluctuations in plasma drug concentration. This results, either in precipitation of side effects or reduction in drug concentration at the target site. Thus objective of present study was to develop, optimize and evaluate a gastroretentive, mucoadhesive tablet for sustained release. A \(^2\) factorial design was employed to systematically study the drug release profile and bioadhesive strength. Sodium carboxymethyl cellulose (CMC) and carbopol 934P were selected as independent variables. Tablets were prepared by direct compression and were evaluated for tablets characteristics, swelling study, adhesion strength and percent drug released. Optimized formulation was compared with marketed formulation (ATEN-50). In vitro wash off test was applied to study the gastroretentive behavior. Tablets prepared show good tablet characteristics, optimum swelling behavior and high adhesion strength. The optimized batch follows zero order drug release profile with non fickian transport mechanism. The mucoadhesion time for optimised batch (M4) was found to be more than four hours and compared with plain tablet which was found to be very less (less than half hour). Thus, the gastretension by mucoadhesion proven to be a potential tool for drug atenolol which improves its bioavailability with reduction in dosing frequency and dose related side effects.

Keywords: Mucoadhesion, Gastroretentive drug delivery, Atenolol HCl, Carbopol 934P, Sodium Carboxymethyl Cellulose (CMC), Factorial design.

1. INTRODUCTION
Amongst the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the Gastro intestinal tract (GIT) is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, \(\text{e.g., gastro retentive dosage forms (GRDFs)}\), will provide us advanced and better therapeutic opportunities. Gastroretentive systems, mainly mucoadhesive drug delivery systems have emerged as an efficient means for enhancing the bioavailability of drugs having narrow absorption window \((1,2,3)\). Atenolol is a \(\beta\)-blocker, is used widely in various cardiovascular diseases, \(\text{e.g., hypertension, angina pectoris, arrhythmias, myocardial infarction and in prophylactic treatment of migraine}\). Oral absorption of atenolol is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Thus atenolol gastroretentive drug delivery system would give better therapeutic results \((4)\). Carbopol 943P and sodium carboxy methylcellulose, both have good mucoadhesive potential \((5)\). Many hydrophilic polymers adhere to mucosal surfaces as they attract water from the mucus gel layer adherent to the epithelial surface. This is the simplest mechanism of adhesion and has been defined as “adhesion by hydration”. Several types of adhesive force, \(\text{e.g. hydrogen bonding between the adherent polymer and the substrate, i.e. mucus, are involved in mucoadhesion at the molecular level. Carbopol polymers have been}\)
demonstrated to create a tenacious bond with the mucus membrane resulting in strong bioadhesion (6). In brief gastroretentive dosage forms with the development of novel, advanced and mucosa-compatible polymers, are providing new commercial and clinical opportunities for delivery of drugs with narrow absorption window at the target site. These tailored polymers offer better opportunities for and broader applicability to highly variable and challenging drugs and therapy of various gastrointestinal disorders (7).

2. MATERIALS AND METHODS

2.1. Materials

Atenolol HCl was obtained as a gift sample from Yarrow Chem. Products, Mumbai. Carbopol, sodium CMC, magnesium stearate and talc were supplied by Loba Chemie Pvt. Ltd., Mumbai. All other chemicals were of analytical grade and were used as such.

2.2. METHODS

2.2.1. IDENTIFICATION OF DRUG:

Ultraviolet spectroscopy: Solutions of atenolol concentration ranging from 5-35 mcg/ml is prepared with double distilled water. The absorbance of these solution were measured at 223 nm in 1 cm cell against a reagent blank (distilled water) using Systronics UV/Visible Double Beam Spectrophotometer. A mean of five readings were obtained and the method of linear regression was applied on the data. A standard curve was constructed by the plotting absorbance versus concentration in microgram/ml. The results are compiled in Table 1 and plotted in Figure 1.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Concentration (micrograms/ml)</th>
<th>Mean absorbance (experimental)</th>
<th>Absorbance (by regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>0.118</td>
<td>0.154</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.314</td>
<td>0.314</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>0.513</td>
<td>0.474</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>0.661</td>
<td>0.634</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>0.831</td>
<td>0.794</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>0.916</td>
<td>0.954</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>1.114</td>
<td>1.114</td>
</tr>
</tbody>
</table>

Table 1: Absorbance profile of atenolol hcl in water at 223 nm (N=5)

2.2.2. Preparation of mucoadhesive tablets:

The matrix tablets were prepared by direct compression method by rotary tableting machine (PHARMAC-076, Manufactured by- Pharmaceutical machinery manufacturing works, Indore-452006) using 12mm round, concave punches. Lactose is used as diluent. Mixture of talc and magnesium stearate (2:1) was used as lubricant. All the component were sieved (250 micro meter) separately and mixed by spatulation method in mortar and pastel.

In-vitro dissolution studies:

Dissolution studies were carried out using USP dissolution (paddle type six basket) apparatus at 50 rpm and temperature 37±0.5°C. Each beaker contains 900ml of distilled water and a single tablet. Samples of 1 ml were taken from the medium at the definite time intervals and the volume replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 223nm (9).

Drug release kinetics study:

Zero- order release model, first- order release model, Higuchi drug release model and Ritger- Peppas model were applied on the dissolution profile data of batch M4 mucoadhesive tablets (10,11).

Comparative studies:

Mucoadhesive tablet M4 versus marketed immediate release tablet (ATEN-50; Cadila):

Dissolution studies were performed for marketed immediate release tablet {ATEN-50 (50 mg) Cadila} by using same procedure as described above.
Swelling index (SI) was calculated using the following formula (12):

\[ SI = \frac{W_t - W_o}{W_o} \]

Where \( W_o \) and \( W_t \) is weight of tablets at 0 and t time.

This procedure was performed for 6 tablets of the batch. The Swelling index of mucoadhesive tablets at different time intervals are given in Table 9.

Table 9: Swelling index of mucoadhesive tablets

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time (hrs)</th>
<th>Square root of cumulative time (hrs)</th>
<th>% drug release</th>
<th>Log % drug release</th>
<th>Log time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.5</td>
<td>5.6</td>
<td>0.748</td>
<td>1.176</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0.707</td>
<td>8.9</td>
<td>0.939</td>
<td>1.477</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>0.866</td>
<td>10.9</td>
<td>1.037</td>
<td>1.653</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.911</td>
<td>13.2</td>
<td>1.120</td>
<td>1.788</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1.214</td>
<td>23.62</td>
<td>1.373</td>
<td>2.079</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>0.214</td>
<td>46.98</td>
<td>1.671</td>
<td>2.38</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>2.449</td>
<td>71.26</td>
<td>1.852</td>
<td>2.556</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>2.828</td>
<td>95.63</td>
<td>1.980</td>
<td>2.681</td>
</tr>
</tbody>
</table>

Table 10: Swelling index of mucoadhesive tablets

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Swelling index</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.43</td>
</tr>
<tr>
<td>3</td>
<td>0.551</td>
</tr>
<tr>
<td>4</td>
<td>0.734</td>
</tr>
<tr>
<td>5</td>
<td>0.952</td>
</tr>
<tr>
<td>6</td>
<td>1.35</td>
</tr>
</tbody>
</table>

In - vitro mucoadhesion study (In-vitro wash-off test): The mucoadhesive property of the tablet was evaluated by an in-vitro adhesion testing method known as the wash-off method. Freshly excised piece of intestinal mucosa (2x2 cm) from sheep was mounted on to the glass...
slide (3×1 inch) with cyanoacrylate glue. The tablet was stucked to the tissue by applying slight pressure with thumb and the support was tied to the paddle with cotton thread of a USP dissolution apparatus containing 900ml of distilled water and rotated at the speed of 25 rpm. When the dissolution apparatus was operated, the tissue was given a slow, regular rotation in the test fluid (distilled water) at 37°C contained in the vessel. The test was conducted till the tablet remain stucked to the tissue. The time of adherence is noted known as mucoadhesion time (13). In-vitro wash off test for measurement of mucoadhesion time using sheep intestine is shown in Figure 9.

Figure 2: Cumulative percentage drug release of different batches of mucoadhesive formulations

Figure 3: Zero order release model for optimized formulation M4

Figure 4: First order release model for optimized formulation M4

Figure 5: Higuchi release model for optimized formulation M4

Figure 6: Ritger- Peppas model for optimized formulation M4

Figure 7: Comparative drug release profile of atenolol hydrochloride immediate release tablet (ATEN-50; Cadila) and mucoadhesive formulation M4

Figure 8: In-vitro wash off test – measurement of mucoadhesion time using sheep intestine
3. RESULTS AND DISCUSSION

The present study is an attempt to develop, optimize and evaluate a suitable gastro retentive drug delivery system using atenolol as model drug.

Optimization of drug formulation using factorial design ($2^2$):

In the start of study three batches were made, ratio of carbopol-934 (factor-A) and sodium CMC (factor-B) in various batches are given in Table 1 and complete formula of various formulations is given in Table 2. Effects of factor-A and factor-B and their interaction were calculated using ($2^2$) factorial design (14). Furthermore evaluation was done by in vitro dissolution study and results are given in Table 3. Mucoadhesion time for Carbopol-934 is much higher than Sodium CMC. As effect of carbopol-934 is much more than sodium CMC and their magnitude of interaction (5.5%) is very less so final formulation prepared for further study was chosen that only contain Carbopol-934(10-40%). Finally four batches of mucoadhesive formulations were made with carbopol (10-40%) as given in Table 4 and 5.

Effect of factor A (i.e., carbopol) on mucoadhesion time:

\[
= \frac{1}{2}[(ab+a)-(b+1)]
= \frac{1}{2}[(220+180)-(30+1)]
= \frac{1}{2}(400-31)
= \frac{1}{2}(369)
= 184.5
\]

Effect of factor B (i.e., Sodium CMC) on mucoadhesion time:

\[
= \frac{1}{2}[(ab+a)-(b+1)]
= \frac{1}{2}[(220+30)-(180+1)]
= \frac{1}{2}(250-181)
= \frac{1}{2}(69)
= 34.5
\]

Carbopol-934 has got more significant effect on mucoadhesion time.

Magnitude of interaction

\[
= \frac{1}{2}[(1+ab)-(a+b)]
= \frac{1}{2}[(1+220)-(180+30)]
= \frac{1}{2}(221-210)
= 5.5
\]

Drug release Study:

Drug release pattern show that percentage drug release at different time intervals goes on decreasing as the carbopol concentration increases. From the study of mucoadhesion time and drug release pattern for different batches of mucoadhesive tablets we find batch that M4 was the best formulation having 180 minutes of mucoadhesion time and 95% of drug release in eight hours. Cumulative percentage release of drug for different batches are given in Table 6 and shown in Figure 2.

Drug release kinetics of mucoadhesive formulation:

The mucoadhesive formulation follows zero order drug release profile, which will describe the sustained drug release profile of mucoadhesive formulation. From Ritger-Peppas model value of $n$ found to be 0.839 which is in between 0.5 and 1, so follow non-Fickian transport for drug release. Kinetic analysis data and values of correlation coefficients are given in Table 7;8 respectively and figures 3; 4; 5;6.

Comparative study:

Marketed immediate release tablet (ATEN-50; Cadila) release 94.15 % of drug in the first half hour whereas mucoadhesive tablet (M4) release 95.63 % of drug in eight hours. Comparative drug release profile of atenolol hydrochloride immediate release tablet (ATEN-50; Cadila) and mucoadhesive formulation M4 are given Table 9 and shown in Figure 7.

Ex-vivo mucoadhesion study:

The mucoadhesion time for mucoadhesive tablet (M4) was found to be more than four hours. Mucoadhesion time for plain tablets was found to be very less (less than half hour) as compared to formulated tablet. In-vitro wash off test for measurement of mucoadhesion time using sheep intestine is shown in Figure 8.

Swelling index:

Swelling index of tablets was found to be increasing 0.2 to 1.35 with time (up to 6 hrs). It shows that tablets have good swelling power. The Swelling index of mucoadhesive tablets at different time intervals are given in Table 10 and shown in Figure 9.

Weight variation:

It was observed that no single tablet was out of limit (±5%).

Hardness:

The hardness of tablets was found in range 6.6 to 8.1 with Pfizer tablet hardness tester.

Friability:

The friability of tablets was found to be 0.0107, which is acceptable, as per prevalent practice (less than 1%).

4. DISCUSSION

The mucoadhesive matrix tablets of atenolol with carbopol 934P, using $2^2$ factorial design were formulated
and evaluated. Mucoadhesive strength was increases with increase in the polymer concentration. The optimized formulation containing 40% carbopol 943P exhibits good mucoadhesive potential. The in vitro release kinetics studies reveal that all formulations fits well with zero order kinetics and the mechanism of drug release is non-Fickian diffusion. It may prove to be more productive than conventional tablets by virtue of prolongation of drug residence time in GI tract. Such formulation would serve as a platform for design of gastroretentive drug delivery systems.

5. REFERENCES


Conflict of Interest: None Declared

Cite this article as: