DEVELOPMENT AND OPTIMIZATION OF HYDRODynamically BALANCED GASTRORETENTIVE FLOATING TABLETS OF ATENOLOL

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ABSTRACT
The present work was aimed to develop a floating drug delivery system of Atenolol based on novel approaches and to investigate there in vitro drug release and buoyancy performance. The interaction between the excipients and Atenolol was also studied through FTIR spectroscopy. Tablets were then prepared by direct compression technique using different combinations of polymers. All the formulations were analyzed for pre-compression and post-compression parameters. The pre-compression and post-compression parameters of all the formulations were within the required and acceptable limit. From the in-vitro buoyancy studies the floating lag time and duration of buoyancy were found to be satisfied. In vitro drug release studies revealed that F3 shows much higher dissolution rate. In vitro release data were fitted to various kinetic models. The mechanism of drug release from tablets was found to be non-Fikian, anomalous transport. Results from various evaluations suggested that matrix type Atenolol floating tablets could be used as hydrodynamically balanced gastroretentive floating drug delivery devices.

Keywords: Floating drug delivery, Atenolol, Hydrodynamically balanced, Gastro retentive.

INTRODUCTION
Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design, ease of production and low cost. The concept of floating drug delivery systems (FDDS) was described in the literature as early as 1962. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability [1].

Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastrointestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than one. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [2, 3].

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and a better control on the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal. The object floats better if floating force is on the higher. This floating force helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations [3].

MATERIALS AND METHODS

Materials
The following materials were used: Atenolol (Yarrow Chem Pvt Ltd., Mumbai), HPMC (Chemdyes Corporation, Rajkot), Chitosan & Sodium carboxy methyl cellulose (Yarrow Chem Pvt Ltd., Mumbai), Sodium bicarbonate (Nice Chemicals Pvt Ltd, Cochi), Magnesium stearate (CDH Laboratories, Mumbai), Talc (Nice Chemicals Pvt Ltd, Cochi).

METHODS
Determination of solubility
Solubility of Atenolol was performed in solvents like water and methanol.

Determination of melting point
Melting point of pure Atenolol was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Atenolol by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100°C min rise of temperature per minute. The rise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded. This was performed thrice and the average value was calculated.

Preparation of Floating matrix Tablet [4, 5]
Floating matrix tablet containing Atenolol was prepared by direct compression technique using different combinations of polymers. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except lubricant all other ingredients were blended uniformly in a glass mortar. After sufficient mixing of drug as well as other components, magnesium stearate and talc were added as lubricant and mixed together. Then the powder blend was compressed into tablets by using a multi station rotary tablet press.

Evaluation of Floating matrix Tablets [6]
Drug–polymer compatibility studies [7]
In the preparation of tablets formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the
instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Atenolol and the selected polymers. Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Atenolol was compared with FT-IR spectra of polymers. Pre-compression parameters [8]

Angle of Repose

The frictional force in a loose powder or granules can be measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane.

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

Where, \( \theta \) is the angle of repose

\( h \) is height of pile

\( r \) is radius of the base of pile

Bulk Density

Loose bulk density (LBD) and tapped bulk density (TBD) of Atenolol and the tablet blends were determined using bulk density apparatus. The pure drug was passed through #18 sieves to break the clumps, if any. Accurately weighed 5 g of the drug or 25 g of polymers was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 200 times from a distance of 14 ± 2 mm. The tapped volume was measured to the nearest graduated unit. The tapping was repeated additional 200 times. Again the tapped volume was measured to the nearest graduated unit. The same thing was done for powder blends of the tablets. The LBD and TBD were calculated in g per ml using following formula.

\[ \text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}} \]

\[ \text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}} \]

Compressibility Index (Carr’s Index)

The compressibility index of the granules was determined by carr’s compressibility index.

The formula for Carr’s Index is as below:

\[ \text{Carr’s Index} \times 100 = \frac{\text{(TBD-LBD)}}{\text{TBD}} \]

Hausner ratio

The hausner ratio of the powder was determined by the following equation.

\[ \text{Hausner ratio} = \frac{\text{TBD}}{\text{LBD}} \]

Post-compression parameters [9, 10]

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content, and in vitro drug release studies.

Hardness Test

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. “Hardness factor”, the average of the six determinations, was determined and reported. The force was measured in kilograms per centimeter square

Friability Test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test was performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

Friability was calculated by using following formula.

\[ \%F = \frac{100( - W_f/W)}{W_0} \]

Whereas,

\( W_0 \) = final weight of tablets

\( W_f \) = Original weight of tablets.

Weight Uniformity Test

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits.

Drug content determination

100mg of powdered formulation is dissolved in 5ml of methanol, made up to 100ml with 0.1N HCl and filtered. 1ml of the filtrate was made up to 100ml with 0.1N HCl 10μg/ml solution was prepared from the above solution and analyzed for the drug content by UV spectrophotometer at a λmax244 nm.

In-vitro buoyancy studies [11]

The in-vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N Hydrochloric acid. The time of duration of floatation was observed visually. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) or Buoyancy lag time (BLT). The duration of time the dosage form constantly remained on the surface of a medium was determined as the total floating lag time (TFT).

Water uptake study (determination of swelling index) [11]

Swelling of the tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particles may be due to saturation of capillary space within the particles or hydration of the macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in the terms of % weight gain by tablet. One tablet was weighted and placed in a beaker containing 100 ml of 0.1N HCl. After each hour, the tablet was removed from a beaker and weighed again up to 8 hrs. The % weight gain by the tablet was calculated by the formula

\[ \text{Swelling index} = \frac{(W_t – W_o)}{W_o} \times 100 \]

Where,

\( W_t \) = weight of tablet at time t, and

\( W_o \) = weight of tablet before immersion

In vitro drug release studies

Dissolution of tablets of each formulation was carried out using USP type II dissolution apparatus (Paddle type). 900 ml of 0.1 N HCl (pH 1.2) was filled in a dissolution vessel and the temperature of medium were set at 37±0.5°C. Tablets were placed in dissolution vessel and the rotational speed of paddle was set at rpm 50. The 1 ml of sample was withdrawn at predetermined time interval and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1 N HCl as a blank at wavelength of 244nm using double beam UV-Visible spectrophotometer. The content of drug was calculated using the equation generated from standard curve. The %cumulative drug release was calculated.

Kinetics of in-vitro drug release

To study the release kinetics of in-vitro drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time,
Higuchi as % drug released Vs time, Korsmeyer- Peppas as log %drug released Vs log time and Hixon-Crowell as (% drug retained) Vs time. By comparing the r-values obtained, the best-fit model was selected.

### Stability studies

To study the effect of temperature and humidity on the tablets, they were stored at 40ºC and 75% RH in Stability chamber (LabTop Instruments Pvt.Ltd.). After three months disintegrating time, drug content and FTIR spectrum were recorded to observe any effect on the tablets by the exposure to humidity and temperature.

### RESULTS AND DISCUSSION

Atenolol was found to be soluble in water and freely soluble in methanol. The melting point of Atenolol was found to be 155ºC, which complied with BP standards thus indicating purity of obtained drug sample.

#### Preparation of Atenolol Floating tablets

#### Table 1: Formulation design of Atenolol Floating tablets.

<table>
<thead>
<tr>
<th>Ingredients (mg)</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>
</tbody>
</table>

#### Table 2: Pre-compression parameters of Atenolol Floating tablets.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Bulk density (g/cc)</th>
<th>Tapped density (g/cc)</th>
<th>Angle of repose (°)</th>
<th>Carr’s index</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.567</td>
<td>0.719</td>
<td>29.62</td>
<td>21.14</td>
<td>1.27</td>
</tr>
<tr>
<td>F2</td>
<td>0.586</td>
<td>0.720</td>
<td>30.56</td>
<td>18.61</td>
<td>1.23</td>
</tr>
<tr>
<td>F3</td>
<td>0.618</td>
<td>0.738</td>
<td>31.12</td>
<td>16.26</td>
<td>1.19</td>
</tr>
<tr>
<td>F4</td>
<td>0.574</td>
<td>0.724</td>
<td>29.89</td>
<td>20.72</td>
<td>1.26</td>
</tr>
<tr>
<td>F5</td>
<td>0.606</td>
<td>0.723</td>
<td>31.25</td>
<td>16.18</td>
<td>1.19</td>
</tr>
<tr>
<td>F6</td>
<td>0.624</td>
<td>0.766</td>
<td>30.49</td>
<td>18.54</td>
<td>1.23</td>
</tr>
</tbody>
</table>

The pre-compression parameters were within the required and acceptable limit. The hardness values ranged from 4.6 to 5.7 kg/cm² for all formulations (Table 3). The entire tablets passes weight variation test as the average % weight variation was the pharmacopoeial limit of 5% (Table 3). The friability values were found to be within the limit (Table 3). The drug content of prednisolone determined at 244nm ranges from 95.84mg to 99.22mg and complies with IP standard. The floating lag time and duration of buoyancy was found to be satisfied.

#### Table 3: Hardness, friability, Drug content and weight variation of Atenolol Floating tablets.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Weight variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.8</td>
<td>0.508</td>
<td>99.22</td>
<td>±1.24</td>
</tr>
<tr>
<td>F2</td>
<td>5.7</td>
<td>0.473</td>
<td>97.32</td>
<td>±0.90</td>
</tr>
<tr>
<td>F3</td>
<td>5.1</td>
<td>0.656</td>
<td>96.63</td>
<td>±1.3</td>
</tr>
<tr>
<td>F4</td>
<td>5.2</td>
<td>0.578</td>
<td>97.65</td>
<td>±1.07</td>
</tr>
<tr>
<td>F5</td>
<td>4.7</td>
<td>0.397</td>
<td>95.84</td>
<td>±1.24</td>
</tr>
<tr>
<td>F6</td>
<td>4.6</td>
<td>0.642</td>
<td>96.78</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

#### Table 4: Floating lag time, Total floating time and Swelling index of Atenolol Floating tablets.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Floating lag time (sec)</th>
<th>Total floating time (Hrs)</th>
<th>Swelling index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>50</td>
<td>198.16</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>2 min</td>
<td>208.48</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>5 min</td>
<td>262.64</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>5 min 25 sec</td>
<td>213.59</td>
<td></td>
</tr>
<tr>
<td>F5</td>
<td>4 min 55 sec</td>
<td>192.32</td>
<td></td>
</tr>
<tr>
<td>F6</td>
<td>4 min 20 sec</td>
<td>188.76</td>
<td></td>
</tr>
</tbody>
</table>

#### Dissolution Kinetics of Drug Release

The release data obtained was subjected to zero order, first order, Higuchi’s, Korsmeyer’s in order to establish the drug release mechanisms and kinetics of drug release from the tablet formulations. Criteria for selecting the most appropriate model were based on the best goodness of fit indicated by the value of regression coefficient(r). The in vitro release profiles of drug from all the formulations could be best expressed by zero order equation.

#### Stability studies

The results of accelerated stability studies indicated that there was no significant change in the tablets. The drug content was found to be within 100±5% for all the formulations at the end of 90 days. FTIR analysis suggested that there was no significant degradation or changes taking place in the tablets during the study period.

### CONCLUSION

The objective of the present study was to design and develop the formulation of Hydrodynamically balanced Atenolol floating tablets by direct compression technique. The formulation F3 was selected as an optimized formulation because it gave the best results in terms of the...
required in vitro buoyancy study, good matrix integrity and drug release in sustained release manner. All the formulations were presented a dissolution behavior controlled by non-Fikian, anomalous transport mechanism, it also followed best-fit model for all batches were zero order equation. The floating dosage form of Atenolol has been formulated to improve the absorption, by retaining the drug in stomach for prolonged period of time.

ACKNOWLEDGEMENT
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REFERENCE