Atenolol Gastro Retentive Floating Matrix Tablets: Formulation and In-Vitro Evaluation

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Abstract
Gastroretentive floating drug delivery systems (GFDDS) of atenolol, an antihypertensive drug, with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed and optimized using 3² full factorial design. Hydroxypropyl methyl cellulose of different viscosity grades (K4M and 50 cps) were used as the polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. The tablets were prepared by direct compression method. Estimation of atenolol in the prepared tablet formulations was carried out by extracting the drug with methanol and measuring the absorbance at 225.3 nm. The prepared formulations were further evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, in vitro drug release pattern, short-term stability and drug excipient interactions. Majority of the designed formulations displayed nearly first order release kinetics, releasing more than 80% drug in 10 hours and remained buoyant than 24 hours. The optimized formulation containing atenolol 50 mg, HPMC (50 cps) 100 mg and sodium bicarbonate 30 mg has displayed almost zero order release kinetics with a floating lag time of only 2.9 minutes. This formulation released more than 90% drug in 9 hours. This study proves that GFDDS of atenolol can be designed using HPMC 50 cps as matrix polymer, which provides nearly zero order release kinetics and thus possible enhancement of oral bioavailability of the drug.

Introduction
Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes. Oral controlled release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages and applications. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. Controlled Drug Delivery System provides drug release at a predetermined, predictable and controlled rate to achieve high therapeutic efficiency with minimal toxicity. Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents and oral drug delivery is by far the most preferable route of drug delivery because of low cost of therapy. Ease of administration leads to high levels of patient compliance and the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Consequently much effort has been put into development of strategies that could improve patient compliance through oral route.

Floating drug delivery system (FDDS):
Floating drug delivery systems (FDDS) were first described by Davis in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different
technologies, i.e. non-effervescent and effervescent systems, have been used in the development of FDDS. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. These considerations have led to the development of oral floating dosage forms possessing gastric retention capabilities. Thus when a drug possesses a narrow ‘absorption window’, design of sustained release preparation require both prolongation of gastrointestinal transit time of dosage forms and controlled drug release.

**Classification of floating drug delivery system:**
Based on the mechanism of buoyancy, FDDS can be classified into:

**Single unit floating dosage system**

**Effervescent system:**
These buoyant systems utilize matrices prepared with swellable polymer like HPMC, polysaccharide like chitosan, effervescent component like sodium bicarbonate, citric acid and tartaric acid or chamber containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate, for gas generation is reported to be 0.76:1. In effervescent systems a gas generating agent usually sodium bicarbonate or sodium carbonate is mixed with matrices prepared with swellable polymers, when the systems comes in contact with gastric fluids, the carbon dioxide is liberated by the acidity of gastric contents and the gas is entrapped in the viscous hydrocolloid. Thus produces an upward motion of the system maintaining buoyancy. Excipients used most commonly in these systems include HPMC, polyacrylate polymer, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. Penners et al. prepared an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus stays in stomach over an extended period of time. In addition to this, gas forming agents were also incorporated so as soon as the gas formed, the density of system was reduced and thus the system tended to float in the gastric environment.

**Non-effervescent system:**
In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosages forms. The commonly used excipients in this type of drug delivery system are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonates, polycrylates etc. In one approach, gel forming hydrocolloid swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and the bulk density of less than one within gastric environment. Shah S.H. et al. system may be referred to as the ‘plug-type systems’ since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier, micro porous compartment system, alginate beads, and hollow microsphere.

**Multiple-Unit Dosage Forms:**
The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit dosage form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanocrylate. Spherical polymeric microsponges, also referred to as “microballoons” have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In carbon dioxide generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of 12 to 18 mm in their expanded state is exceeded.

**Non-effervescent system:**
A little or no much report was found in the literature on non effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

**Effervescent system:**
A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and
concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with non floating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5 hours was observed for floating beads. The non floating beads had a shorter residence time with a mean onset emptying time of 1 hour.

Materials and Method

Materials
Citric acid and Hydrochloric acid received as a gift sample from Merck india ltd. Mumbai, Hydroxypropyl methyl cellulose (K4M) and (K15M) and microcrystalline cellulose-101 receive from Yarrow chem. Products Mumbai, methanol, magnesium stearate, potassium chloride, sodium bicarbonate, sodium hydroxide, and talc received from new Bengal drug house Calcutta.

Method

Angle of Repose
The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

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

Where,
\( h \) = Height of power cone, and,
\( r \) = Radius of the power cone

Poured Density & Tapped Density
Both poured density and tapped density were determined. A quantity of 2 g of powder from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. Poured & tapped densities were calculated using the following formulas:

Poured Density = Weight of powder/bulk volume of the packing
Tapped Density = Weight of the powder/tapped volume of the packing

Carr’s Index and Hausner’s Ratio
Compressibility index and Hausner’s ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index and the Hausner’s ratio were determined by measured both the bulk density and the tapped density of a powder.

The compressibility index and Hausner’s ratio was calculated as follows:

\[ C = 100 \times \left(1 - \frac{\rho_B}{\rho_T}\right) \]
\[ H = \frac{\rho_T}{\rho_B} \]

Where,
\( C \) = Compressibility index,
\( H \) = Hausner’s ratio,
\( \rho_B \) = Bulk density,
\( \rho_T \) = Tapped density.

Preparation of Floating Tablets of Atenolol
The floating tablets of Atenolol were prepared by direct compression technique. All the ingredients used in the formulation were initially passed through sieve #40 separately before mixing. The required quantity of Atenolol and other ingredients except talc and magnesium stearate were weighed out accurately and transferred to a mortar and triturated for thorough mixing. To the above mixture, talc and magnesium stearate was added and further mixed for 2 minutes. Finally the mixture was compressed into tablets of 250 mg each using approx 9 mm concave punches in ten station tablet punching machine.
Table: Composition of floating tablets of Atenolol

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Atenolol (mg)</th>
<th>HPMC K4M (mg)</th>
<th>HPMC K15M (mg)</th>
<th>NaHCO₃ (mg)</th>
<th>Tartaric Acid (mg)</th>
<th>MCC (mg)</th>
<th>Magnesium Stearate (mg)</th>
<th>Talc (mg)</th>
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<tbody>
<tr>
<td>F1</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>20</td>
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<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>25</td>
<td>25</td>
<td>45</td>
<td>20</td>
<td>10</td>
<td>17.5</td>
<td>2.5</td>
<td>5</td>
</tr>
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<td>F4</td>
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<td>20</td>
<td>10</td>
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<tr>
<td>F5</td>
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<td>5</td>
</tr>
<tr>
<td>F6</td>
<td>25</td>
<td>35</td>
<td>45</td>
<td>20</td>
<td>10</td>
<td>07.5</td>
<td>2.5</td>
<td>5</td>
</tr>
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<td>F7</td>
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<td>F8</td>
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<td>20</td>
<td>10</td>
<td>07.5</td>
<td>2.5</td>
<td>5</td>
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<td>F9</td>
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<td>45</td>
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<td>20</td>
<td>10</td>
<td>97.5</td>
<td>2.5</td>
<td>5</td>
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</tbody>
</table>

Evaluation of Formulations
Compatibility study
FTIR, DSC, XRD studies were carried out in order to determine any possible interaction between drug and excipients.

Fourier Transform Infra-red Spectroscopy Study: 5,8,16
The tablet was crushed to form fine powder and compressed with KBr on Minipress (Jasco, Japan) to form a disk. The compressed disks were scanned over 400 to 4,000 cm⁻¹, and characteristic peaks were recorded. The FTIR spectra of pure drug, polymers (HPMC K4M and K15M), excipients, physical mixture and formulation F-3 were recorded on Fourier transform infrared (FT-IR) instrument (Shimadzu, Japan) and characteristic peaks were recorded and matched with the standard peaks of pure atenolol with the physical mixture of drug-excipients and formulation F-3.

Differential Scanning Calorimetry Study
The thermograph of formulation F-3 was done by Pyris Diamond TG/DTA. For DSC the heating rate was kept at 200 min⁻¹ up to 2000 min⁻¹ to better integrate the information and the flow of argon was kept at 80 ml/min. Finally comparison was made between the thermograph of pure atenolol, the physical mixture of drug-excipients and formulation F-3.

X-ray Diffraction Study
The crushed powder of the formulation (F-3) was packed into the rotating sample holder of X-ray diffractometer (Rigaku, Japan) equipped with Cu rotating anode (radiation; λ=1.54 nm) generated at 18 kW. The diffractograph of formulation F-3 was recorded and compared with the diffractograph of pure atenolol, physical mixture of drug-excipients and formulation F-3. Powder diffractometer operating on Bragg–Brentano geometry was fitted with a curved crystal graphite monochromator in the diffraction beam from the range of 20–40° (2θ).

Weight variation test
The USP weight variation test is run by weighing 20 tablets individually, calculating the average weight & comparing the individuals tablet weight to the average. The tablets meets the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Thickness and Diameter
The thickness and diameter of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

Hardness
Three tablets of the each formulation were measured in the hardness examination. The hardness was examined using a Monsanto hardness tester. The hardness was measured in kg/cm².

Friability
For tablets with a unit mass equal to or less than 650 mg a sample of whole tablets corresponding to 6.5 g, was taken. For tablets with a unit mass of more than 650 mg, a sample of 10 whole tablets was taken. The sample of tablets was carefully deducted prior to testing. The tablet sample was accurately weighed, and placed in the drum. The drum was rotated 100 times (25±1 rpm), and the tablets were removed. Any loose dust from the tablets was removed as before, and the tablets were accurately weighed. Then percentage friability was then calculated.

\[ \% F = 100 \left( \frac{W_1 - W_2}{W_1} \right) \]

% Friability of tablets less than 1% are considered acceptable.

Where,
\[ \% F = \text{Percentage friability} \]
\[ W_1 = \text{Initial weight of tablets} \]
Drug content uniformity

The weight variation test is clearly not sufficient to assure uniform potency of tablets of moderate or low dose drugs, in which excipients make up the bulk of the tablet weight. To assure uniform potency for tablets of low-dose drugs, a content uniformity test was done. Content uniformity test was carried out as per USP 2009. In this test 30 tablets were randomly selected for the sample and at least 10 of them were assayed individually. Nine of the tablets must contain not less than 85% or more than 115% of the labelled drug content. The tenth tablet may contain less than 75% or more than 125% of the labelled content. If this condition is not met, the tablets remaining from the 30 must be assayed individually and none may fall outside of the 85% to 115%.

Scanning Electron Microscopy study

The SEM image of the tablet was used to examine surface topography, texture, and morphology of fractured surface. SEM analysis was conducted using JOEL, JSM6360 scanning microscope for optimized formulation. Tablet sample (Batch F3) was removed from the dissolution apparatus at predetermined time interval, the specimen was then position on the sample holder so as to present a cross-section of the tablet under the microscope. Sample were coated with platinum and visualized under scanning electron microscope (SEM). The samples were then examined with 100X and 150X magnifications using scanning electron microscope (Jeol JSM-6360A). SEM photomicrographs were taken by scanning electron microscope for studying surface morphology of matrix tablet before and after dissolution. Each sample was mounted on to aluminium stub using double-sided adhesive tape and then coated with gold palladium alloy using Jeol/EO fine coat sputter.

Result and Discussion

Fourier Transform Infra-red Spectroscopy Studies

![FT IR Spectra of pure Atenolol (Sample)](image)

IR study was performed with the supplied sample of Atenolol. This IR spectrum was found concordant with the IR of Atenolol reported in official monograph and the peaks were matched with the standard peaks of pure Atenolol. The characteristic peaks were depicted in the above table.

Differential Scanning Calorimetry (DSC) Analysis:

![Differential Scanning Calorimetry of pure drug (Atenolol)](image)
The result of DSC thermograms of Atenolol, was shown in (Fig-5.5). The pure Atenolol showed a sharp endothermic peak at 154.35°C corresponding to the melting point of the drug.

X-ray Diffraction Study:

X-ray diffraction study of pure drug was carried out and characteristic high intensity diffraction peaks at 2θ = 6, 10, 16, 20, 22, 24 and 26. The absence of these peaks of pure drug in the diffractogram of physical mixture of drug excipients and formulation indicated the drug was completely dispersed in the polymer bed. The Atenolol showed sharp peaks showing crystalline phase while the drug containing formulation showed less intense peaks showed the conversion of crystalline phase of drug to the amorphous phase. Furthermore, the absence of peaks can be explained by the crystalline thermal transformation of sodium bicarbonate. Sodium bicarbonate has an interesting thermal property in that it decomposes to carbon dioxide gas, sodium carbonate and water at temperatures above 50°C. The crystalline state of sodium bicarbonate gradually transformed to the anhydrous sodium carbonate form with time. When stored at 100 °C for 180 min, a peak at 18.3° (2θ), which corresponds to sodium bicarbonate, was not observed suggesting complete thermal transformation to anhydrous sodium carbonate. These finding are in
agreement with Shefter et al. who reported that approximately 90% of sodium bicarbonate crystals transformed to anhydrous sodium carbonate after 75 min at 93 °C.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Diameter (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight Variation (mg)</th>
<th>Content Uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.45±0.2</td>
<td>8.80±0.2</td>
<td>4.80</td>
<td>0.704</td>
<td>252±0.09</td>
<td>99.33</td>
</tr>
<tr>
<td>F2</td>
<td>3.50±0.2</td>
<td>8.80±0.2</td>
<td>4.30</td>
<td>0.672</td>
<td>250±0.10</td>
<td>99.83</td>
</tr>
<tr>
<td>F3</td>
<td>3.66±0.2</td>
<td>8.80±0.2</td>
<td>5.10</td>
<td>0.558</td>
<td>251±0.10</td>
<td>96.7</td>
</tr>
<tr>
<td>F4</td>
<td>3.54±0.3</td>
<td>8.80±0.2</td>
<td>5.20</td>
<td>0.661</td>
<td>250±0.05</td>
<td>99.75</td>
</tr>
<tr>
<td>F5</td>
<td>3.49±0.2</td>
<td>8.80±0.2</td>
<td>4.70</td>
<td>0.672</td>
<td>250±0.14</td>
<td>0.16</td>
</tr>
<tr>
<td>F6</td>
<td>3.75±0.2</td>
<td>8.80±0.2</td>
<td>4.60</td>
<td>0.672</td>
<td>252±0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>F7</td>
<td>3.54±0.2</td>
<td>8.80±0.2</td>
<td>4.60</td>
<td>0.672</td>
<td>251±0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>F8</td>
<td>3.75±0.2</td>
<td>8.80±0.2</td>
<td>4.50</td>
<td>0.672</td>
<td>253±0.24</td>
<td>98.91</td>
</tr>
<tr>
<td>F9</td>
<td>3.68±0.0</td>
<td>8.80±0.2</td>
<td>4.50</td>
<td>0.672</td>
<td>253±0.24</td>
<td>98.00</td>
</tr>
</tbody>
</table>

The results of physicochemical characterizations are given in above table. The thickness of formulations from F1 to F9 was measured by digital thickness tester and was found to be between 3.45±0.2 to 3.75 mm. The hardness of formulations from F1 to F9 was measured by Monsanto tester and was found to be between 4.30 and 5.20 Kg/cm². The friability of all the formulations was measured by roche friabilator and was found to be in the range of 0.52 to 0.80%. The weight variation for different formulations (F1 to F9) was found to be 250±0.10 to 253.24%, showing satisfactory results as per Indian pharmacopoeia (IP) limit. The content uniformity of all the formulations was within the limit (Atenolol 100±2 %). The evaluated properties were good quality enough for further studies.

Conclusion

Gastro retentive drug delivery system offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The floating tablets of Atenolol provide a better option for increasing the bioavailability and reliability for treatment of hypertension by allowing a better control of fluctuations observed with conventional dosage forms. Formulation F3 appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate clinical safety of these floating tablets in suitable animal and human models. IR spectroscopic studies indicated that there are no drug excipients interactions in the optimized formulation. By comparing fig.5.3.11.(FT-IR of atenolol) with fig. 5.3.11 (FT-IR of physical mixture of drug-excipients) & fig. 5.3.12 (FT-IR of formulation F-3) that there is no physical and chemical interaction between atenolol and other excipients during the formulation process, because all the principle peaks of pure drug were still there in the FT-IR spectra of different formulations. So we can conclude that there is no chemical interaction between drug & excipients. Hydrodynamically balanced systems of atenolol with shorter lag time can be prepared by direct compression method using HPMC K4M and K15M as polymer and sodium bicarbonate and citric acid as gas generating agent. All the prepared tablet formulations were found to be good without capping and chipping. The weight variation, content uniformity, thickness, hardness & friability of the final optimized formulation are within the specified limit of U.S.P.NaHCO₃ was used in the tablet formulation of atenolol as a floating agent which help to retain the tablet dosage form of atenolol in the gastric fluid by maintaining an optimized floating lag time (FLT) & total floating time (TFT), without disturbing the drug release profile.Magnesium stearate was used as a lubricant in optimum concentration which does not affect the desirable release of drug. Also a fixed amount of talc is used in all formulations as glidant. As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of microcrystalline cellulose increases the drug releases increases and at the same time floating lags time decreases. The optimized formulation F3 can be considered as a promising gastro retentive drug delivery system of Atenolol, providing nearly zero order drug release over a period of 12 hours. Short term stability studies of optimized formulation F-3 indicate, that there are no significant changes in drug content and dissolution parameter values after 20 days storage at 45±1°C.

References

11. Atenolol, www.drugs.com