INTRODUCTION

The oral route of drug administration is the most important method of administering the drug for systemic effect. To achieve and maintain the concentration of administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this result in fluctuating levels in plasma. Controlled drug delivery systems have been introduced to overwhelm the drawbacks of fluctuating levels associated with conventional dosage form [1]. The gastro-retentive system can remain in the gastric rejoin for several hours and significantly prolong gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduce drug waste, improve solubility of drug that is less soluble in high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine.

Controlling the residence time of drug delivery system in a particular region of GI tract can be achieved by several approaches, muco adhesive system, super porous hydrogels and expandable system and floating drug delivery system [2].

Atorvastatin is an oral drug that lowers the level of cholesterol in the blood. It belongs to the class of statins, that is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A [hydroxyl methyl glutaryl-CoA reductase], which is the rate-limiting enzyme in cholesterol biosynthesis. It is widely used in treatment of hypercholesterolemia. The present study deals with design and evaluation of Atorvastatin gastric floating tablet by the effervescent floating method. Methyl cellulose and Poly Vinyl Pyrrolidone k30 (PVP) were used as polymers and sodium bicarbonate and Citric acid were used as gas releasing agents [3].

Selection of excipients is an important strategic decision for designing a dosage form with consistence and controlled residence in the stomach. Water soluble cellulose derivatives represent a typical class of polymers best suited for such purposes. It has been suggested that higher molecular weight polymers and slower rates of polymer hydration are usually associated with better floating behavior. Therefore, high molecular weight and less hydrophilic polymers are expected to improve floating properties of delivery systems [4].

MATERIALS AND METHODS

Drugs and chemicals

Atorvastatin was purchased from Microlabs,

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Bangalore. Methocel K 15 M and Methocel K 100 M was purchased from Sd fine chemicals, Mumbai. Sodium bicarbonate and Talc were purchased from Prowess lab chemicals, Ottappalam, Citric acid and Lactose were purchased from Nice chemicals, Kochi. PVP K 30 and Magnesium stearate were purchased from HIMEDIA laboratories, Mumbai.

**Preparation of Atorvastatin Floating tablet**
The tablets of Atorvastatin were prepared by wet granulation method using PVP paste in the mixture of drug, Methocel, PVP, Sodium bicarbonate and Citric acid. Here, Sodium bicarbonate and Citric acid were using as gas generating agent and PVP as a binding agent. Each formulation was composed of drug and excipients in various proportions as shown in table 1. For formulation Atorvastatin, PVP, sodium bicarbonate and citric acid were sifted through the mesh (#10) and mixed well in a mortar. The paste of PVP in isopropyl alcohol was used as the granulating agent. Then the mass again passed through the mesh (#10) and dried in an oven at 60°C for 30 min. magnesium stearate and talc were added as lubricants and compressed into a tablet [5-7].

**Table 1. Design of Atorvastatin floating tablets**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>MethocelK100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MethocelK15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>90</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>Citric acid</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PVP</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Talc</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Lactose</td>
<td>150</td>
<td>160</td>
<td>170</td>
<td>150</td>
<td>160</td>
<td>170</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

**EVALUATION PARAMETERS**

**Pre-compression parameters**

**Angle of repose**
The static angle of repose ($\theta$) was measured according to the fixed funnel and free standing cone method. It is the maximum angle possible between the surface of a pile of powder and horizontal plane. The funnel was clamped with its tip 2 cm above a paper placed on a flat horizontal surface. The tablet granules were poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameter of the base of powder cones was determined and the tangent of the angle of repose calculated using the equation, [8-9]

$$\text{Angle of repose (}\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

Where h=height of the granule pile
r=radius of granule pile

**Bulk and tapped density**
Bulk density is the ratio of the total mass of powder to the bulk volume of powder. Required quantity of powder sample was in a measuring cylinder and the volume $V_b$, occupied by each of the samples without tapping the measuring cylinder was noted. After 100 taps on the table, the volume $V_t$ was noted. The bulk and tap densities were calculated using following equations [10]

- **Bulk density**
  $$\text{Bulk density} = \frac{\text{weight of the sample}}{\text{Bulk volume}} (V_b)$$
- **Tapped density**
  $$\text{Tapped density} = \frac{\text{weight of sample}}{\text{Tapped volume}} (V_t)$$

**Hausner’s ratio**
This was calculated as the ratio of tapped density to the bulk density [2].

$$\text{Hausner’s ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

**Compressibility index**
Compressibility index was calculated by equation

$$\text{Compressibility index} = \frac{(\text{tapped density} - \text{bulk density})}{\text{tapped density}}$$

**Post Compression Parameters**

**Thickness and Diameter**
The thickness and diameter of the tablets were determined by screw gauge. Thickness and diameter of each tablet from each batch were determined and tabulated [10].

**Hardness**

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined by Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

**Weight variation test**

20 tablets from each formulation weighed individually Shimadzu digital balance and the test was performed according to the official method. Randomly selected pre-dusted tablets weighed again and the change in variation of weight is noted and tabulated.

\[
\text{% Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100
\]

**Friability test**

The friability of the tablets was determined using Roche friabilator. It is expressed friability and operated at 25 rpm for 4 min or run up to 100 revolutions. Then the tablets were weighed again.

\[
\text{% friability (F)} = \frac{\text{Initial weight (w_1)} - \text{Final weight (W_f)}}{\text{Initial weight}} \times 100
\]

Percentage friability of tablet less than 1% are considered acceptable.

**Buoyancy study**

In-vitro floating studies include floating lag time and total floating time. Floating lag time indicates the time required for the tablet to rise to the surface and float and total floating time indicates the time by which the dosage form remain

Buoyancy study of the tablet was described by Dave et al (200A) in a 250ml beaker containing 0.1N HCl, pH 1.2 maintained at 37°C±0.5°C in a water bath. Time for raise the tablet to the surface if 0.1N HCl and total time which the tablet float is measured. During this period, the physical state of each tablet is measured.

**In-vitro dissolution study of prepared Atorvastatin tablets**

The in-vitro dissolution studies were done as one of the most important quality control test performed during the project period on pharmaceutical dosage forms and serve as a tool for predicting bioavailability in some cases.

RESULTS AND DISCUSSION

Precompression Parameters of Atorvastatin Granules

**Fig 1. Angle of repose of Atorvastatin granules**

![Angle of repose](image)

**Inference:** The angle of repose of formulation F1 was found to be better compared to other formulations as indicated in the fig 1.
Fig 2. Compressibility index of atorvastatin granules

![Compressibility Index Chart]

**Inference:** The compressibility index of formulation F1 was found to be better compared to other formulations as shown in the fig 2.

Fig 3. Hausner’s ratio of Atorvasatin granules

![Hausner’s Ratio Chart]

**Inference:** The hausner’s ratio of formulation F1 was found to be better compared to other formulations and is shown in the figure 3.

**Post Compression Parameters**

**Thickness and Diameter**
The thickness and diameter of the tablets were determined by screw gauge. Thickness and diameter of each tablet from each batch were determined and tabulated in the table 2.

**Table 2. Thickness and Diameter**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness (mm)</th>
<th>Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.34</td>
<td>12.23</td>
</tr>
<tr>
<td>F2</td>
<td>0.36</td>
<td>12.31</td>
</tr>
<tr>
<td>F3</td>
<td>0.38</td>
<td>12.13</td>
</tr>
<tr>
<td>F4</td>
<td>0.37</td>
<td>12.23</td>
</tr>
<tr>
<td>F5</td>
<td>0.37</td>
<td>12.12</td>
</tr>
<tr>
<td>F6</td>
<td>0.36</td>
<td>12.34</td>
</tr>
</tbody>
</table>
**Inference:** The Thickness of formulation F3 was found to be 0.38 mm and Diameter of formulation F6 was found to be 12.34 mm.

**Hardness test**
Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined by Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined and indicated in the table 3 and figure 4.

**Table 3. Hardness test of Atorvastatin floating tablet**

<table>
<thead>
<tr>
<th>Hardness (kg/cm²)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.33</td>
<td>3.33</td>
<td>3.5</td>
<td>3.16</td>
<td>3.33</td>
<td>3.16</td>
</tr>
</tbody>
</table>

**Fig 4 Hardness of atorvastatin floating tablet**

**Inference:** The hardness of formulation F3 was found to be better compared to other formulations.

**Weight variation test**
20 tablets from each formulation weighed individually, the test was performed according to the official method. Randomly selected pre-dusted tablets weighed again and the change in variation of weight is noted and tabulated.

**Friability test**
The friability of the tablets was determined using Roche friabilator and are tabulated in table 4 and figure 5. It is expressed friabilator and operated at 25 rpm for 4 min or run up to 100 revolutions. Then the tablets were weighed again (Wf). The percentage friability was then calculated by,

\[
\%\text{friability} (F) = \frac{(\text{initial weight (w1)} - \text{final weight (Wf)})}{\text{initial weight}} \times 100
\]

Percentage friability of tablet less than 1% are considered acceptable.

**Table 4. Friability test of Atorvastatin floating tablet**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.46</td>
</tr>
<tr>
<td>F2</td>
<td>0.29</td>
</tr>
<tr>
<td>F3</td>
<td>0.51</td>
</tr>
<tr>
<td>F4</td>
<td>0.33</td>
</tr>
<tr>
<td>F5</td>
<td>0.36</td>
</tr>
<tr>
<td>F6</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Fig 5. Friability test of Atorvastatin floating tablet

![Friability test graph]

Inference: The friability of formulation F3 was found to be high when compared to other formulations.

Buoyancy study
In-vitro studies include floating lag time and total floating time. Floating lag time indicates the time required for the tablet to rise to the surface and float and total floating time indicates the time by which the dosage form remain on the solution.

Buoyancy study of the tablet was described by Dave et al (200A) in a 250ml beaker containing 0.1N HCl, pH 1.2 maintained at 37°C ±0.5°C in a water bath. Time for raise the tablet to the surface if 0.1N HCl and total time which the tablet float is measured and indicated in the table 5 and figure 6.

Table 5. Buoyancy time and Total Floating time of Atorvastatin floating tablet

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Buoyancy time (sec)</th>
<th>Total Floating time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>105</td>
<td>05:30</td>
</tr>
<tr>
<td>F2</td>
<td>90</td>
<td>08:30</td>
</tr>
<tr>
<td>F3</td>
<td>50</td>
<td>10:00</td>
</tr>
<tr>
<td>F4</td>
<td>58</td>
<td>06:30</td>
</tr>
<tr>
<td>F5</td>
<td>65</td>
<td>07:00</td>
</tr>
<tr>
<td>F6</td>
<td>70</td>
<td>07:30</td>
</tr>
</tbody>
</table>

Fig 6. Buoyancy time of Atorvastatin floating tablet

![Buoyancy time graph]
Inference: The buoyancy time of formulation F1 was found to be highest and the buoyancy time of formulation F3 was found to be least compared to other formulations.

Fig 7. Total floating time of Atorvastatin floating tablet

Inference: The total floating time of formulation of F3 was found to be highest and formulation F1 was found to be least when compared to other formulations as indicated in the figure 7.

In-vitro dissolution study
The in-vitro dissolution studies were done as one of the most important quality control test performed during the project period on pharmaceutical dosage forms and serve as a tool for predicting bioavailability in some case.

Table 6. Percentage drug release of Atorvastatin floating tablet

<table>
<thead>
<tr>
<th>Time(hr)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>5.56</td>
<td>3.75</td>
<td>1.52</td>
<td>6.13</td>
<td>4.13</td>
<td>2.13</td>
</tr>
<tr>
<td>2</td>
<td>18.75</td>
<td>15.28</td>
<td>8.35</td>
<td>19.98</td>
<td>18.38</td>
<td>12.28</td>
</tr>
<tr>
<td>3</td>
<td>23.58</td>
<td>22.81</td>
<td>15.28</td>
<td>25.39</td>
<td>26.41</td>
<td>19.15</td>
</tr>
<tr>
<td>4</td>
<td>33.51</td>
<td>29.59</td>
<td>22.61</td>
<td>38.28</td>
<td>34.58</td>
<td>25.98</td>
</tr>
<tr>
<td>5</td>
<td>46.81</td>
<td>35.18</td>
<td>28.38</td>
<td>49.31</td>
<td>40.18</td>
<td>30.11</td>
</tr>
<tr>
<td>6</td>
<td>53.25</td>
<td>48.23</td>
<td>34.56</td>
<td>58.39</td>
<td>50.13</td>
<td>38.47</td>
</tr>
<tr>
<td>7</td>
<td>61.23</td>
<td>57.25</td>
<td>41.18</td>
<td>66.24</td>
<td>59.88</td>
<td>46.18</td>
</tr>
<tr>
<td>8</td>
<td>70.81</td>
<td>65.83</td>
<td>48.35</td>
<td>74.08</td>
<td>69.13</td>
<td>54.83</td>
</tr>
</tbody>
</table>

Inference: The in vitro dissolution study shows that the formulation F3 had the least percentage cumulative release and can be considered as a better-controlled release when compared to other formulations as shown in the table 6 and fig 8.
DISCUSSION

Atorvastatin, a crystalline compound is BCS-II drug which is a potent and specific inhibitor of 3-hydroxyl-3-methyl-glutaryl CoA reductase. Thus it arrests the key step for cholesterol biosynthesis in liver and hence widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. The drug is highly soluble in higher pH of GI tract and as such the stomach specific controlled delivery of the drug is higher in two steps mainly, to overcome the bypass effect, improving the bioavailability of the drug and reducing the frequency of the administration. The drug is stable at pH 1.2. So the drug is suitable for development of stomach-specific drug delivery system.

Determination of $\lambda_{\text{max}}$

The $\lambda_{\text{max}}$ of the drug was determined in 0.1N HCl solution. The solution was scanned in UV spectrophotometer at 247.5nm.

Evaluation of Atorvastatin granules

The parameters like bulk density, tapped density, compressibility index, Hausner’s ratio and angle of repose were evaluated.

Evaluation of fabricated tablets

All the formulations were prepared according to the formula. The prepared floating tablets were evaluated. All the batches were produced under similar conditions to avoid processing variables. All the formulations were evaluated for various physical parameters such as weight variation, thickness, diameter, hardness, friability, buoyancy time and total floating time. The hardness of the 3.16-3.5 Kg/cm².

Buoyancy study

The results of buoyancy study indicates that the increased concentration of Methyl cellulose decreases the floating time of the tablet. The effect of Methylcellulose and PVP K30 promote the increased buoyancy time.

Total floating time

The floating properties due to gas generating agents, which is a mixture of Citric acid and Sodium bicarbonate. These compounds generate CO₂ on reaction with water. The bubbles of the gas help the tablet to become buoyant and remain entrapped in the polymer layer.

In vitro release study

Dissolution is the process by which a solid drug substance becomes dissolved.

The main aim of the study was the preparation of floating tablets to target the upper GIT. The Atorvastatin floating tablets were prepared by Methocel, PVPK30, Sodium bicarbonate, Citric acid, Talc, Lactose and Magnesium stearate. Before the development of formulation, the drug and excipients compatibility study was performed by using FT-IR technique. It reveals there is no interactive peaks appeared between drug and excipients. The granules prepared and characterized for Bulk density, Tapped density, Carr’s index, Hausner’s ratio and Angle of repose. The granules were compressed by using Rimek minipress and
evaluated for Thickness, Diameter, Weight variation, Hardness, Friability, Buoyancy, Total floating time and in vitro release. The results of study indicate the Methocel K100M controls the drug release pattern. The result indicates the F3 formulation was considered optimized formulation because of longer floating time, reduced buoyancy and maximum in-vitro release pattern. All the formulation shows controlled release pattern.

CONCLUSION
In the current work, formulation and evaluation of floating tablet incorporating Atorvastatin are described. The most successful formulation F3 contain Atorvastatin (40mg), Methocel K100M (70mg), sodium bicarbonate (130mg), citric acid (10mg), PVPK30 (50mg), talc (30mg) and lactose (170mg). This formulation needs 50 sec to become buoyant, appropriate hardness (3.5kg/cm²) and percentage cumulative release of 4.35%

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CONFLICT OF INTEREST
No conflict of interest

REFERENCES