FORMULATION AN DEVALUATION OF DILTIAZEM FLOATING TABLETS

Maheen Tabassum1, P. Sravani2*, J. Hindu2, K. Rajeshwar Dutt3, Farha Nazneen1, K. Ramya1

1Student, Nalanda College of Pharmacy, Cherlapally, Nalgonda, Telangana-508001, India.
2Asst. Prof, Nalanda College of Pharmacy, Cherlapally, Nalgonda, Telangana-508001, India.
3Professor, Nalanda College of Pharmacy, Cherlapally, Nalgonda, Telangana-508001, India.

ABSTRACT
Floating 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. In the present investigation, for the formulation of floating tablets of diltiazem were prepared by wet granulation technique. HPMC K4 M and ethyl cellulose is used as a matrix forming agent. Other excipients like sodium bicarbonate and citric acid as gas generating agents, PVP K 30 as binder, microcrystalline cellulose (Diluent) and Magnesium stearate as a lubricant. The drug and polymers granules are subjected to various preformulation studies such as Angle of repose, Bulk density, Tapped density, Compressibility Index, Hausner ratio. The tablets were compressed using the tablet punching machine. Prepared tablets were subject to various evaluation parameters such as Thickness, Hardness, Weight variation, Friability, Disintegration, Buoyancy study and In-vitro drug release study, Kinetic Parameters as per ICH guidelines. Results of floating properties study reveals that all tablets had good floating properties. This might be due to the presence of gas generating agent i.e., NaHCO3, content. F5 showed a minimum lag time of 1.49 min and maximum floating time of more than 12 hrs with maximum % drug release 98.87±0.23.

KEYWORDS: Diltiazem, Buoyancy.
INTRODUCTION
Floating system or dynamically controlled systems are low density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentrations. In which the Gas generating systems these are matrix type of systems prepared with the help of swellable polymers such as methyl cellulose and chitosan and various effervescent compounds e.g. Sodium bicarbonate, tartaric acid and citric acid. Floating Effervescent Tablet are prepared by direct compression, wet granulation, Hot melt extrusion method. Diltiazem is a potent vasodilator, increasing blood flow and variably decreasing the heart rate via strong depression of A-V node conduction. Its pharmacological activity is somewhat similar to verapamil, another nondihydropyridine (non-DHP) calcium channel blocker. It is a vasodilator of coronary and peripheral vessels, which reduces peripheral resistance and after load, though not as potent as the dihydropyridine (DHP) calcium channel blockers. This results in minimal reflexive sympathetic changes. In the present study diltiazem floating tablets are prepared by wet granulation technique due to its low half life frequency administration drug is reduced by the sustained release system called floating drug delivery system.

MECHANISM OF FLOATING

MATERIALS AND METHODS
Diltiazem is obtained from hetero Pharma Ltd, ethyl cellulose, HPMC, micro crystalline cellulose iso propyl alcohol, magnesium stearate, PVP, aerosil obtained from SD fine chemicals ltd.
Preparation of diltiazem floating tablets

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>INGREDIENT</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diltiazem</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
</tr>
<tr>
<td>2.</td>
<td>HPMC K4M</td>
<td>35mg</td>
<td>40mg</td>
<td>45mg</td>
<td>50mg</td>
<td>55mg</td>
</tr>
<tr>
<td>3.</td>
<td>MCC</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>4.</td>
<td>Ethyl cellulose</td>
<td>15 mg</td>
<td>17mg</td>
<td>19 mg</td>
<td>21 mg</td>
<td>23mg</td>
</tr>
<tr>
<td>5.</td>
<td>PVP</td>
<td>15mg</td>
<td>15mg</td>
<td>15mg</td>
<td>15mg</td>
<td>15mg</td>
</tr>
<tr>
<td>6.</td>
<td>IPA</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
</tr>
<tr>
<td>7.</td>
<td>Aerosil</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10mg</td>
</tr>
<tr>
<td>9.</td>
<td>Magnesium stearate</td>
<td>3 mg</td>
<td>3 mg</td>
<td>3 mg</td>
<td>3 mg</td>
<td>3 mg</td>
</tr>
</tbody>
</table>

The powder mixture containing drug, polymers and other excipients were weighed as per required quantity and thoroughly blended in a mortar and pestle and then passed through sieve No. 100. An Appropriate amount of the mixture was weighed and fed into the die of Minipress II using 8 mm punch to get tablets of average weight of 250mg.

Evaluation of floating tablet

Precompression parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested are as given below,

A) Angle of repose

The frictional force between the particles can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the granules to the horizontal plane. If more granules are added to the pile, it slides down the sides of the pile until the friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius(r) of the base of the conical pile was measured the angle of repose (θ) was calculated using the following formula

$$\tan \theta = \frac{h}{r}$$

Where; 

h = height of the cone

r = radius of the cone base

θ = Angle of repose
Angle of repose | Category
---|---
25-30 | Excellent
30-35 | Good
35-40 | Fair
40-45 | Poor
45-50 | Very poor

B) Bulk density
Density is defined as weight per unit volume. Bulk density, $\rho_b$, is defined as the mass of the sample taken divided by the bulk volume and is expressed as gm/cm$^3$. The bulk density primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for the handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10g of sample was introduced into a dry 100 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, $V_o$, was read. The bulk density was calculated using the formula

$$\rho_b = \frac{M}{V_o}$$

Where:
$\rho_b$ = Apparent bulk density
M = Weight of sample
$V_o$ = Apparent volume of powder

C) Tapped density
After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped 500 times initially by an additional taps of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, $V_t$ was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the following formula

$$\rho_{tap} = \frac{M}{V_t}$$

Where, $\rho_{tap}$ = tapped density
M = weight of sample
$V_t$ = tapped volume of powder

D) Carr’s Index
The compressibility index (Carr’s index) is a measure of the porosity of a granules/powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less
compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions.

In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences reflected in the Carr’s index which is calculated using the following formulas:

\[
\text{Compressibility index} = \frac{\rho_{\text{tap}} - \rho_b}{\rho_{\text{tap}}} \times 100
\]

Where,
\(\rho_{\text{tap}}\) = tapped density
\(\rho_b\) = bulk density

<table>
<thead>
<tr>
<th>Compressibility index(%)</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>Excellent</td>
</tr>
<tr>
<td>11-15</td>
<td>Good</td>
</tr>
<tr>
<td>16-20</td>
<td>Fair</td>
</tr>
<tr>
<td>21-25</td>
<td>Passable</td>
</tr>
<tr>
<td>26-31</td>
<td>Poor</td>
</tr>
<tr>
<td>32-37</td>
<td>Very poor</td>
</tr>
<tr>
<td>≥38</td>
<td>Very very poor</td>
</tr>
</tbody>
</table>

E) Hausner’s ratio
Hausner’s ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

\[
\text{Hausner’s ratio} = \frac{Tapped \ density (\rho_{\text{tap}})}{Bulk \ density (\rho_b)}
\]

<table>
<thead>
<tr>
<th>Limit</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.25</td>
<td>Better flow</td>
</tr>
<tr>
<td>1.25-1.5</td>
<td>Moderate flow</td>
</tr>
<tr>
<td>≥1.5</td>
<td>Poor flow</td>
</tr>
</tbody>
</table>

4.6.2. POST COMPRESSION EVALUATION PARAMETERS:
A) Appearance
The tablet should be free from cracks, depressions, pinholes etc. The colour and the polish of the tablet should be uniform on whole surfaces. The surface of the tablets should be smooth.
B) Weight Variation test
To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight and standard deviation of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

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

<table>
<thead>
<tr>
<th>Average weight of Tablets (mg) (I.P)</th>
<th>Average weight of Tablets (mg) (U.S.P)</th>
<th>Maximum percentage deviation allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 80</td>
<td>Less than 130</td>
<td>10</td>
</tr>
<tr>
<td>80-250</td>
<td>130-324</td>
<td>7.5</td>
</tr>
<tr>
<td>More than 250</td>
<td>More than 324</td>
<td>5</td>
</tr>
</tbody>
</table>

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance, individual weight of each tablet was also calculated using the same and compared with average weight.

C) Thickness test
The crown thickness of individual tablet may be measured with vernier callipers, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding callipers scale. The tablet thickness was measured using vernier callipers.

D) Hardness test
Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

E) Friability test
It is a measure of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets (10 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test,
the tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets and is expressed in percentage as

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

Where,

\[W_1 = \text{Initial weight of 10 tablets}\]
\[W_2 = \text{Weight of the 10 tablets after testing}\]

USP limits: 0.5 to 1%

F) Determination of Drug Content

Ten tablets with pre-determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and the filtrate was sufficiently diluted and the absorbance was recorded against the blank at 237 nm. The drug content of the Standard containing the drug powder was also determined. The Drug content was determined by the formula.

\[
\text{Drug content} = \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100
\]

The tablet passes the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount. The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets intended for oral administration where the range of size of the dosage form available includes 50 mg or smaller sizes. For content uniformity test, representative samples of 30 tablets are selected and 10 are assayed individually. At least 9 must assay within ± 15% of the declared potency and none may exceed ± 25%.

i. Standard Preparation

About 120 mg of Diltiazem hydrochloride was weighed accurately and transferred into a 50 ml volumetric flask. It was dissolved, and then it was suitably diluted and made up to volume with 0.1 N HCL buffer and mixed.
ii. Sample Preparation
5 tablets were weighed and finely powdered. An accurately weighed portion of the powder equivalent to about 120 mg of Diltiazem hydrochloride was transferred into a 50 ml volumetric flask and was dissolved in 0.1 N HCl. It was sonicated for 30 min and was filtered through 0.45 μm membrane filter by discarding the first few ml. It was then diluted suitably up to the mark.

Procedure
The absorbance of both the standard preparation and the sample preparation, after suitable dilutions were measured in a UV-visible Spectrophotometer at 237 nm using 0.1 N HCl. The same procedure was repeated for 3 times.

iii. CALCULATION
The amount of drug present in tablet can be calculated using the formula

$$A_t/A_s \times S_w/20 \times 100/S_t \times A_v$$

Where,

- $A_t$ = Absorbance due to sample preparation.
- $A_s$ = Absorbance due to standard preparation.
- $S_w$ = Amount of drug in standard sample (mg).
- $S_t$ = Weight of the tablet (mg).
- $A_v$ = Average weight of tablet (mg).

G) In-vitro disintegration time
The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

Method
For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration.

One tablet in each of the 6 tubes of the basket is to be placed and the apparatus subjected to run. The assembly should be raised and lowered between 50 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in
the apparatus was measured and recorded. Disintegration or more specifically dispersion times were measured in 900 ml 0.1 N HCl buffers pH 1.2 without using disc at room temperature (37°C ± 0.5°C).

**H) In-vitro dissolution studies**

*In vitro* release studies were carried out using tablet USP XXIII dissolution test apparatus. Two objectives in the development of *in-vitro* dissolution tests was to show that,

- Release of the drug from the tablet is as close as possible up to 100% and
- Rate of drug release is uniform from batch to batch and is the same as the release rate from those proven to be bioavailability and clinically effective. Summary of general *in-vitro* dissolution conditions employed throughout the study to determine the *in-vitro* dissolution rate for all the formulation is given in table.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Parameter</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dissolution medium</td>
<td>900 ml 0.1 N HCl buffer pH 1.2</td>
</tr>
<tr>
<td>2.</td>
<td>Temperature</td>
<td>37°C ± 0.5°C</td>
</tr>
<tr>
<td>3.</td>
<td>Rotation speed</td>
<td>100 rpm</td>
</tr>
<tr>
<td>4.</td>
<td>Volume withdrawn</td>
<td>5ml for every 5 min up to for 45 min</td>
</tr>
<tr>
<td>5.</td>
<td>λmax</td>
<td>237nm</td>
</tr>
<tr>
<td>6.</td>
<td>Beer’s law limits</td>
<td>5-25</td>
</tr>
<tr>
<td>7.</td>
<td>Tablet taken</td>
<td>1 tab (known drug content)</td>
</tr>
</tbody>
</table>

The dissolution study of multilayer floating tablets was performed over a 12 hr period using USP type II (paddle) Dissolution Testing Apparatus (Electrolab) 900ml of 0.1N Hcl was used as dissolution medium agitated at 50 RPM, at temperature of 37O± 0.5OC. 5 ml samples were withdrawn at 5, 10, 15, 30, 45 and 60 min for 1 hr to estimate the release of Diltiazem, and at 1, 2, 4, 6, 8, 10 and 12 hrs for estimating dilitiazem release. The samples were analyzed for dilitiazem by UV Spectrophotometry at their respective λ max values 237nm. The samples collected for first hour were analyzed for diltiazem content at 237 nm in UV spectrophotometer by keeping the solution containing 0.1N HCL formulation as blank to minimize the interference. The samples collected for 1 – 12 hrs were analyzed for the release of diltiazem at 237 nm in UV spectrophotometer by keeping the solution containing 0.1 N HCL formulation as blank to minimize the interference.
I) In-vitro buoyancy study
Floating behavior studies were performed on the floating tablet. The study was carried out in a USP Dissolution Test Apparatus (Type II) at paddle speed 75 rpm in 900 ml of 0.1 N HCl at 37 ± 0.5°C to mimic in-vivo conditions. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time.

Also the duration of system floatation and the relative matrix integrity was observed visually. In vitro buoyancy was characterized from floating lag time and total floating time. The test was performed using a USP dissolution test type II apparatus (Electro lab) using 900 mL of 0.1 N HCl at rotation of 50 rpm at 37 ± 0.5°C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium was recorded as floating lag time and total floating time, respectively.

J) Swelling index
The swelling properties of floating tablets were determined by placing the tablet in the dissolution test apparatus, in 900 mL of 0.1 N HCl at 37 ± 0.5°C. After a specified time intervals, the tablet was withdrawn, blotted to remove excess water and weighed. Swelling characteristics were expressed as percentage water uptake (%WU).

\[ SI = \frac{W_t - W_0}{W_0} \times 100 \]

\(SI\) = Weight of swollen tablet
\(W_0\) = Initial weight of tablet

K) Moisture content
Moisture was determined by loss on drying. Micromatrices were dried at ambient temperature by keeping 1000mg of microspheres in desiccators until a constant weight was achieved. The % moisture content was calculated using the following formula.

L) Wetting time
A piece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of buffer solution simulating saliva, pH 6.8 in which eosin (water soluble dye) was dissolved. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the paper at room temperature and the time taken for the complete wetting was noted. Three tablets from each formulation
were randomly selected and the average wetting time was calculated. The different steps involved in determination of wetting time.

RESULTS AND DISCUSSION

Construction of Calibration curve

Standard graph of Dilitiazem

FTIR STUDIES

From the FTIR Spectral analysis, it was concluded that there was no interference in the functional group as the principal peaks of the drug were found to be unaltered in the drug polymer physical mix. All the occupants had peaks nearly to the drug peaks it means the drug and excipients does not show any pharmaceutical interactions so all the occupants were compatible with each other.

A) Pre compression evaluation parameters of Dilitiazem floating tablets

<table>
<thead>
<tr>
<th>FORMULATION CODE</th>
<th>ANGLE OF REPOSE (°)</th>
<th>BULK DENSITY (g/cc)</th>
<th>TAPPED DENSITY (g/cc)</th>
<th>CARR’S INDEX (%)</th>
<th>HAUSNER’S RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25.23±0.16</td>
<td>0.524±0.25</td>
<td>0.563±0.34</td>
<td>26.1±0.98</td>
<td>1.10±0.98</td>
</tr>
<tr>
<td>F2</td>
<td>26.56±0.78</td>
<td>0.63±0.47</td>
<td>0.62±1.11</td>
<td>27.1±0.17</td>
<td>1.24±0.87</td>
</tr>
<tr>
<td>F3</td>
<td>27.02±0.56</td>
<td>0.625±0.87</td>
<td>0.882±0.34</td>
<td>29.54±0.35</td>
<td>1.24±0.55</td>
</tr>
<tr>
<td>F4</td>
<td>30.12±0.23</td>
<td>0.635±0.46</td>
<td>0.867±1.56</td>
<td>24.12±0.87</td>
<td>1.24±0.55</td>
</tr>
<tr>
<td>F5</td>
<td>27.19±0.17</td>
<td>0.67±0.19</td>
<td>0.91±0.34</td>
<td>26.98±0.65</td>
<td>1.37±0.34</td>
</tr>
</tbody>
</table>

Post compression parameters

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight variation</th>
<th>thickness</th>
<th>Swelling index %</th>
<th>hardness</th>
<th>friability</th>
<th>Drug content</th>
<th>disintegration time</th>
<th>floating lag time</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>196±0.18</td>
<td>4.71±0.81</td>
<td>29.1</td>
<td>6.4±0.04</td>
<td>0.32</td>
<td>76.28</td>
<td>2.05</td>
<td>12.25</td>
</tr>
<tr>
<td>F2</td>
<td>202±2.26</td>
<td>4.26±0.31</td>
<td>28.8</td>
<td>7.8±0.02</td>
<td>0.44</td>
<td>67.54</td>
<td>2.23</td>
<td>9.42</td>
</tr>
<tr>
<td>F3</td>
<td>198±2.65</td>
<td>4.56±0.09</td>
<td>46.93</td>
<td>7.5±0.08</td>
<td>0.42</td>
<td>72.20</td>
<td>3.00</td>
<td>6.31</td>
</tr>
<tr>
<td>F4</td>
<td>201±1.24</td>
<td>3.98±0.61</td>
<td>27.11</td>
<td>7.9±0.06</td>
<td>0.36</td>
<td>83.59</td>
<td>3.28</td>
<td>3.18</td>
</tr>
<tr>
<td>F5</td>
<td>306±1.69</td>
<td>4.23±0.31</td>
<td>43</td>
<td>7.7±0.05</td>
<td>0.65</td>
<td>97.62</td>
<td>3.47</td>
<td>1.49</td>
</tr>
</tbody>
</table>
CONCLUSION

From the above experimental results it was concluded that buoyancy was effected by the concentration of sodium bicarbonate F5 showed a minimum lag time of 1.49 min and maximum floating time of more than 12 hrs with maximum % drug release 98.87±0.23 and considered as a optimized formulation. From the studies it was shown the that F5 was considerably showing sustained drug delivery more than 12 hrs.

REFERENCES


