FORMULATION AND EVALUATION OF FLOATING AND SUSTAINED RELEASE TABLET CONTAINING RANITIDINE

Lakhlani Tixa R* and Kanabar Vishvesh B

Department of Pharmaceutics, School of Pharmacy, R.K. University, Kasturbadham, Rajkot-Bhavnagar Highway, Rajkot-360020, Gujarat, India.

ABSTRACT

GRDDs are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important drugs. Floating preparations are part of the GRDDs which remains on the surface of the gastric fluid and increase the bioavailability of dosage form. Ranitidine (H₂ receptor blocker) effervescent floating tablets were developed in ten different formulations (VT1 to VT10) by employing effervescent agents such as sodium bicarbonate and citric acid at different concentration to find their optimum level. The formulations were evaluated for various physical parameters such as lag time, floating time, weight variation, hardness, thickness, diameter, friability and in vitro dissolution. VT5 formulation showed maximum floating time of greater than 24 hours and gave slow and maximum drug release of ranitidine spread over 9 hours.

Keywords: Ranitidine, Floating drug delivery system, GRDDS, Effervescent floating tablets.

INTRODUCTION

Floating drug delivery systems are low-density systems that have sufficient 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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Thus it is a one type of a gastro retentive drug delivery system. (Patel M, 2014).

The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability and increasing the gastro retentive time. (Prajapati T, 2012).

Advantages of Floating drug delivery system:
1. Advantageous for drugs absorbed through the stomach. E.g. Ferrous salt, antacids.
2. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine. (Nasa P, 2010).
3. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.

When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in
Floating condition in stomach to get a relatively better response. (Chaudhary R, 2012).

Disadvantages of floating drug delivery system:
1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate. (Narayan C, 2011).
3. Some drugs present in the floating system causes irritation to gastric mucosa.

Application of Floating Drug Delivery Systems:
1. Sustained Drug Delivery
2. Site-Specific Drug Delivery
3. Absorption Enhancement

Floating drug delivery systems are classified depending on the use of two formulation variables:
1. Effervescent and

Effervescent Floating Dosage Forms:
1. A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air, or inert gas.
2. The gas in the floating chamber can be introduced either by the volatilization of an organic solvent or by effervescent reaction between organic acid and bicarbonate salts. (Dhiman S, 2011).
3. Thus, there are two methods for effervescent system:
   4. Volatile liquid containing system
   5. Gas generating system
   6. Here, we are preparing the floating tablets by gas generating method.
   7. Gas generating system: These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

MECHANISM OF FLOATING SYSTEMS
While the system is floating on the gastric content the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. (Nayal AS, 2013).

\[ F = F_{buoyancy} - F_{gravity} = (D_f - D_s) g v \]
Where, \( F \) = total vertical force, \( D_f \) = fluid density, \( D_s \) = object density, \( v \) = volume and \( g \) = acceleration.

MATERIALS AND METHOD

Material used for study
The most important and vital components which are used for preparation of this formulation were Ranitidine, Sodium bicarbonate, citric acid, tartaric acid and polymer such as HPMC K4M and HPMC K100M. Ranitidine as drug, sodium bicarbonate as effervescent agent. All other excipients used to prepare tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Method used for study
- Drug, polymer and other ingredients were weighed accurately.
- All ingredients except polymer were mixed thoroughly.
- Polymer was dissolved in sufficient quantity of isopropyl alcohol and added to a powder mixture to prepare a dough wet mass.
- The prepared wet mass was passed through a 20# sieve.
- The granules were allowed to dry in a hot air oven and then resifted through a 40# sieve.
- The granules were collected and other ingredients were added and lubricated.
- Tablets were compressed by a 12-mm diameter at punch with the help of a rotary tablet compression machine.

EVALUATION

In Vitro Buoyancy (Lag Time)
A tablet is placed in a beaker containing 100 – 200 ml dissolution medium & the time for a tablet to emerge on to the surface of the dissolution medium is known as lag time which is measured in minutes or seconds. (Sharma A, 2014).

Floating Time
- It is usually carried out in a USP dissolution apparatus containing 900 ml of 0.1 N HCl as dissolution medium maintained at 37°C.
- After achieving lag time, the time taken for a tablet to remain float on the surface of the dissolution medium is called floating time.
- It is measured in hrs.
Tablet Dimensions
- Thickness and diameter of five tablets randomly selected were measured using vernier calipers.
- The Pharmacopoeia states that the extent of deviation in a batch of tablet should not exceed the limit of ±5% of their determined standard values.

Hardness Test
- The crushing strength kg/cm² of prepared tablets was determined for tablets of each batch by Monsanto tablet hardness tester. (Sandina S, 2012).
- Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.

Friability Test
- The friability of tablets was determined using Roche friabilator.
  - It is expressed in percentage (%) 13 tablets randomly selected were initially weighed (W₀) and transferred into friabilator.
  - As per IP 2007, for this test, take that numbers of tablets which are sufficient enough to make 6.5 gm of weight.
  - Since our tablet weight was 500 mg so 13 tablets were taken to evaluate same test.
  - The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions.
  - The tablets were weighed again (W final). The percentage friability (%F) was then calculated by following equation:
  
  \[ \% F = \left(1 - \frac{W}{W_0}\right) \times 100 \]

  Where, \( W_0 \) = weight of tablet before test, \( W \) = weight of tablet after test.

Weight Variation Test
- Twenty tablets were selected randomly from each batch and weighed individually using electronic balance to check for weight variation.
- Pharmacopoeial parameters are displayed in Table 2.

Drug Content Estimation
- Ten tablets were randomly selected and powdered.
  - A quantity of powder equivalent to 10 mg of ranitidine was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1 N HCl and the volume was made with 0.1 N HCl (pH 1.2).
  - The solution was filtered through Whatman filter paper.
  - 1 ml of the above solution was transferred to a 100 ml volumetric flask and diluted to 100 ml with 0.1 N HCl and the absorbance was measured at 225 nm using UV / visible spectrophotometer.
  - The percentage of ranitidine hydrochloride was determined using calibration curve.

In Vitro Drug Release Study
- In vitro drug release study of Ranitidine tablets was performed using USP (United States Pharmacopoeia) apparatus II fitted with a paddle (50 RPM) at 37 ± 0.5°C using a simulated gastric fluid (pH 1.2; 900 ml) as a dissolution medium. (Narang N, 2011).
- The tablet was added to the dissolution medium.
  - At pre-determined time intervals, 5 ml samples were withdrawn, filtered through a 0.45-μm membrane filter and analyzed at 225 nm using a double-beam spectrophotometer.
  - Cumulative percentage drug release was calculated using an equation obtained from a calibration curve, which was developed in the range 2-20 μg/ml for 0.1 N HCl.

RESULTS
Specific parameters
- By seeing specific parameter, it was concluded that VT5 batch was showing comparatively better lag time (lowest) and floating tome (highest).

General parameters
- Tablets prepared by wet granulation are evaluated for hardness, friability, weight variation, drug content, and acid neutralization capacity. Results obtained are described in table no 4.
  - According to post compression parameter all criteria has been pass according to their specific standards.

In vitro drug release profile
- Data for in vitro drug release are shown in the table below.
  - It was conclude that optimum amount of sodium carbonate, citric acid and tartaric acid is able to release the drug in sustained manner (90%) up to 9 hour.
  - From above all formulations, VT5 formulation was showing comparative sustained release among all formulations.
  - So F5 formulation was selected as an ideal formulation.

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>VT1</th>
<th>VT2</th>
<th>VT3</th>
<th>VT4</th>
<th>VT5</th>
<th>VT6</th>
<th>VT7</th>
<th>VT8</th>
<th>VT9</th>
<th>VT10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>185</td>
<td>185</td>
<td>185</td>
<td>185</td>
<td>200</td>
<td>185</td>
<td>185</td>
<td>185</td>
<td>185</td>
<td>185</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>140</td>
<td>150</td>
<td>160</td>
<td>170</td>
<td>180</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>180</td>
<td>170</td>
<td>160</td>
<td>150</td>
<td>140</td>
</tr>
<tr>
<td>NaHCO3</td>
<td>65</td>
<td>70</td>
<td>75</td>
<td>80</td>
<td>85</td>
<td>85</td>
<td>80</td>
<td>75</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>17</td>
<td>19</td>
<td>21</td>
<td>23</td>
<td>25</td>
<td>25</td>
<td>23</td>
<td>21</td>
<td>19</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 1. Different formulation for optimization of floating dosage form
Since the average weight of the tablets is 500 mg; the percentage deviation is taken as ± 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VT1</th>
<th>VT2</th>
<th>VT3</th>
<th>VT4</th>
<th>VT5</th>
<th>VT6</th>
<th>VT7</th>
<th>VT8</th>
<th>VT9</th>
<th>VT10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>12±0.02</td>
<td>12±0.03</td>
<td>12±0.04</td>
<td>12±0.02</td>
<td>12±0.01</td>
<td>12±0.02</td>
<td>12±0.03</td>
<td>12±0.02</td>
<td>12±0.02</td>
<td>12±0.02</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>4±0.02</td>
<td>4±0.03</td>
<td>4±0.02</td>
<td>4±0.02</td>
<td>4±0.01</td>
<td>4±0.02</td>
<td>4±0.04</td>
<td>4±0.06</td>
<td>4±0.03</td>
<td>4±0.02</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>2.5±0.1</td>
<td>3±0.3</td>
<td>2.5±0.4</td>
<td>3±0.1</td>
<td>3.5±0.2</td>
<td>2±0.6</td>
<td>2.5±0.6</td>
<td>2±0.1</td>
<td>3±0.2</td>
<td>3±0.1</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.9912</td>
<td>0.9924</td>
<td>0.9906</td>
<td>0.9954</td>
<td>0.9986</td>
<td>0.9994</td>
<td>0.9954</td>
<td>0.9946</td>
<td>0.9954</td>
<td>0.9970</td>
</tr>
<tr>
<td>Drug Content (%)</td>
<td>98.45±0.2</td>
<td>96.45±0.05</td>
<td>98.87±0.03</td>
<td>99.23±0.02</td>
<td>99.49±0.1</td>
<td>99.23±0.02</td>
<td>98.87±0.03</td>
<td>99.23±0.02</td>
<td>98.45±0.03</td>
<td>99.23±0.03</td>
</tr>
</tbody>
</table>

Table 2. IP standards of percentage of weight variation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average weight of tablet</th>
<th>Percentage deviation allowed under weight variation test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 mg or less 10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>More than 60 mg but less than 250 mg 7.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>250 mg or more 5</td>
<td>5</td>
</tr>
</tbody>
</table>

Since, the average weight of the tablets is 500 mg; the percentage deviation is taken as ± 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
<th>VT1</th>
<th>VT2</th>
<th>VT3</th>
<th>VT4</th>
<th>VT5</th>
<th>VT6</th>
<th>VT7</th>
<th>VT8</th>
<th>VT9</th>
<th>VT10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time (Second)</td>
<td>1</td>
<td>12±2</td>
<td>14±1</td>
<td>15±2</td>
<td>13±2</td>
<td>9±1</td>
<td>12±1</td>
<td>13±2</td>
<td>14±3</td>
<td>11±1</td>
<td>12±1</td>
</tr>
<tr>
<td>Floating time (Hour)</td>
<td>2</td>
<td>18±0.05</td>
<td>19±0.05</td>
<td>15±0.05</td>
<td>17±0.05</td>
<td>24±0.05</td>
<td>21±0.05</td>
<td>19±0.05</td>
<td>20±0.05</td>
<td>19±0.05</td>
<td>18±0.05</td>
</tr>
</tbody>
</table>

Table 3. Lag time and floating time of parameter of all formulation

Table 4. Post compression parameter of all formulation

Table 5. In vitro drug release of all formulation
DISCUSSION AND CONCLUSION
The principle of this treatment is formation of gas which is generated by sodium carbonate, citric acid and tartaric acid as effervescent forming agent in appropriate amount i.e. 2:1. Sodium bicarbonate act as gas generating agent and citric acid and tartaric acid play vital role to maintain optimum acidic condition and prevent excess acidity in stomach. From all the formulation, VT5 formulation was considered to be an ideal one because it was having lowest lag time, highest floating time as well as % cumulative drug release up to 9 hour (90%) compare to all the formulation. The drug was also compatible with other ingredients used in formulation.

REFERENCES
