FORMULATION, IN-VITRO EVALUATION AND OPTIMIZATION OF GI FLOATING TABLET OF RANITIDINE HCl

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ABSTRACT

Objective: The objective of the research was to formulate, evaluate and optimize the GI floating tablet of Ranitidine HCl.

Introduction: Ranitidine HCl, the model drug for this study, is a histamine H2-receptor antagonist used for the treatment of duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease and erosive oesophagitis. Floating drug delivery systems remain buoyant in the gastric fluid ensuring prolonged gastric residence time and continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

Methods: Thirteen batches of floating matrix tablets of Ranitidine HCl (336 mg) were prepared by direct compression technique, using different amount of polymers such as Hydroxy Propyl Methyl Cellulose (HPMC) K4M, HPMC K100M. Sodium bicarbonate and citric acid were incorporated as a gas generating agent. The effect of different polymers on drug release profile and floating properties were investigated. The tablets were evaluated for hardness, percentage friability, weight variation, swelling index, drug content, disintegration time, dissolution study and in-vitro buoyancy study. After evaluation of each batch, Stat Graphica was used to get the contour plot and the surface response curve to get the tentative value of HPMC K4M and HPMC K100M. Using Stat Graphica, the optimized formulation for GI floating tablet of Ranitidine HCl was determined. The optimized formulation was subjected to various physicochemical evaluation parameters.
Results: The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated for quality control were within the acceptable limits. The results of the in vitro drug release studies showed that the optimized formulation could sustain drug release for 8h and remain buoyant for 24h.

Conclusion: In conclusion, effervescent approach is essential for the formulation to have good floating property. The interaction of both HPMC K4M and HPMC K100M had significant impact on the release and floating properties of the delivery system. It was established that floating behavior of the low-density drug delivery systems could successfully prolong the drug release patterns.

Keywords: Ranitidine HCl, Floating drug delivery system, HPMC, Optimization, Buoyancy.

INTRODUCTION
Background
Gastroretentive drug delivery systems are designed to be retained in the gastric region. Prolonged gastric retention improves bioavailability, solubility of drugs that are less soluble in a high pH environment and reduces drug waste (Garg R et al., 2008). Gastro retentive dosage forms greatly improves the pharmacotherapy of the GIT through local drug release, leading to high drug concentrations at the gastric mucosa (eradicating Helicobacter pylori) from the submucosal tissue of the stomach, making it possible to treat duodenal and gastric ulcers, oesophagitis etc reducing the risk of gastric carcinoma (Nayak KA et al., 2010)

Approaches to Gastric Retention
Floating Drug Delivery System
FDDS also called hydro-dynamically balanced system is an effective technology to prolong the gastric residence to improve the optimum bioavailability of the drug. The buoyancy character of the formulation in stomach is obtained by reducing its bulk density as compared to density of gastric fluid. The advantage of this character is that it does not affect gastric emptying rate for a prolonged period of time and the drug is released slowly at a desired rate from the system, controlling the fluctuation of drug concentration in plasma (Shah SH et al., 2009). Floating drug delivery system is classified depending upon the mechanism of buoyancy.

Effervescent Drug Delivery System
These are matrix types of systems which utilize the swellable polymer and include the gas generating agents like sodium bicarbonate and citric acid. After oral administration in the
GIT, CO₂ is liberated from these drug delivery systems and gets entrapped in swollen hydrocolloids which cause the reduction in the bulk density making it float on the gastric fluids. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration (Nayak KA et al., 2010).

**Ranitidine (A Potential Candidate Drug for FDDS)**

Ranitidine HCl is a histamine H₂-receptor antagonist. The recommended adult oral dosage of Ranitidine is 150 mg twice daily or 300 mg once daily. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of Ranitidine HCl is desirable. The short biological half-life of drug (~2.5-3 hours) also favors development of a sustained release formulation. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Moreover, colonic metabolism of Ranitidine is partly responsible for the poor bioavailability of Ranitidine from the colon. These properties of Ranitidine HCl favor the gastro retentive drug delivery system.

**MATERIAL AND METHOD**

**MATERIAL**

<table>
<thead>
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<th>Ingredients</th>
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<th>F2</th>
<th>F3</th>
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Preparation of Ranitidine HCl Floating Tablet by Direct Compression
Initially the active ingredient was sifted through 40 mesh sieve and other ingredients were sifted through sieve number 30. For each 13 batches, all ingredients were weighed and transferred to polythene bag with label. The ingredients were mixed manually in the polythene bag. Then the mixed ingredient was filled into hopper and compressed using 20 station tablet compression machine of 12.5 mm round punches. Initially a single punch was used to adjust the tablet desired weight and hardness. After setting the parameters such as total weight, diameter, thickness, friability and hardness the number of punches were increased. During the process of punching, the tablets were simultaneously measured.

METHODS
Central Composite Design
The experimental formulation of the floating tablets of Ranitidine HCl were prepared according to central composite design using Stat Graphica two level, two factorial, central composite design with four star point(α: 1.414) and central point with one replication resulting in a total of 13 experiments, were used to optimize the chose key variables.

Table 2 : Full factorial central composite design matrix for two variables in five setting in real and coded units

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<th>Formulation</th>
<th>HPMC K4M (mg)</th>
<th>HPMC K100M (mg)</th>
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<td></td>
<td>Uncoded units</td>
<td>Coded units</td>
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<tr>
<td>F13</td>
<td>140</td>
<td>0</td>
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</tbody>
</table>
Evaluation of Tablets (Physical Characterization of Tablets)

Weight variation
From each batches, 20 tablets were weighed in analytical balance. The average value, minimum and maximum weight obtained was calculated.

Hardness
Hardness of 10 tablets from each batch was measured using hardness tester.

Friability
Ten pre-weighed tablets were rotated at 25 rpm for 4 min in Roche Friabilator. The tablets were dedusted, reweighed and the percentage of weight loss was calculated.

\[
\% \text{ Loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

Assay Methods

Standard Preparation
Ranitidine HCl reference standard equivalent to Ranitidine 300 mg was weighed and transferred to 100 ml volumetric flask. 20-30 ml 0.1 M HCL was added to dissolve the Ranitidine. The volume was made up to 100 ml with the same solvent (A). 10 ml from solution (A) was withdrawn and volume was adjusted to 300 ml (B). Again 10 ml from solution (B) was withdrawn and was diluted to 100ml to get 10 mcg/ml in 0.1 M HCl.

Sample Preparation
20 tablets were weighed and crushed to fine powder. Powder equivalent to 300 mg of Ranitidine was weighed and transferred to 100 ml volumetric flask. 20 -30 ml of 0.1 M HCl was added and sonicated for 10 minutes. The volume was made up to 100 ml with the same solvent (A). 10 ml from solution (A) was withdrawn and volume was adjusted to 300 ml (B). Again 10 ml from solution (B) was withdrawn and diluted to 100ml with 0.1M HCl to get 10mcg/ml solution.

Procedure
The absorbance of standard and sample was measured at 314 nm against 0.1M HCl as blank.

In vitro buoyancy study
The in-vitro buoyancy was characterized by floating lag time and total floating time of tablet in 100 ml beaker containing 0.1M HCl.
Swelling Index
The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h in 0.1M HCl at room temperature from the following equation

\[ SI = \frac{\text{Weight of tablet at time (t)} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100 \]

Powder flow properties
Carr’s Index (Ic)
It is expressed in percentage as in equation:

\[ Ic = \frac{D_t - D_b}{D_t} \times 100 \]

Hausner’s Ratio (Hg)
It is expressed in percentage and is expressed by equation:

\[ Hg = \frac{D_t}{D_b} \times 100 \]

Angle of repose
Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h) was obtained. Diameter of heap (D) was measured. The angle of repose (θ) was calculated by equation 1 and 2

\[ \tan \theta = \frac{h}{r} \quad 1 \]
\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \quad 2 \]

In Vitro Dissolution Studies
USP apparatus II was used to test the dissolution profile using 900 ml of 0.1M HCl as dissolution medium at 50 rpm and 37°C ± 0.5°C. Six tablets from each batch were placed into respective basket containing HCl. 10ml of the sample was withdrawn hourly for 8h. The sample was filtered and from the filtrate 3ml was withdrawn. The volume was adjusted to 100ml with 0.1M HCl in the 100ml to prepare 10 mcg/ml solutions. Absorbance of the solution was measured using UV spectrophotometer at 314nm.
Optimized formulation

Table 3. The derived optimized formulation

<table>
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<th>Ingredients</th>
<th>Unit</th>
<th>Optimized formulation</th>
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<tr>
<td>RHCl</td>
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<tr>
<td>NaHCO₃</td>
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</tr>
<tr>
<td>Citric Acid</td>
<td>mg</td>
<td>35</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>mg</td>
<td>15</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>mg</td>
<td>185.459</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>mg</td>
<td>92.5679</td>
</tr>
<tr>
<td>Aerosil</td>
<td>mg</td>
<td>4</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>mg</td>
<td>8</td>
</tr>
<tr>
<td>Talc</td>
<td>mg</td>
<td>10</td>
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<tr>
<td>MCC</td>
<td>mg</td>
<td>93.973</td>
</tr>
<tr>
<td>Total</td>
<td>mg</td>
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</tbody>
</table>

RESULTS

Table 4. Physicochemical characterization of Optimized batch tablets

<table>
<thead>
<tr>
<th>Weight variation (mg)</th>
<th>Hardness (N)</th>
<th>Friability (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>848.65 ± 3.5581</td>
<td>16.2 ± 2.5342</td>
<td>0.57</td>
<td>100.58</td>
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</tbody>
</table>

Table 5. Floating lag time, buoyancy and total floating time of optimized batch.

<table>
<thead>
<tr>
<th>Floating Lag Time</th>
<th>Buoyancy</th>
<th>Total floating time</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 sec</td>
<td>+</td>
<td>&gt;23 hrs</td>
</tr>
</tbody>
</table>

Figure 1. The swelling index of floating tablets of optimized batch.
Table 6. Flow properties of the Ranitidine granules of optimized formulation

<table>
<thead>
<tr>
<th>Angle of repose(°)</th>
<th>Loose bulk density(g/ml)</th>
<th>Tapped bulk density(g/ml)</th>
<th>Hausner’s Ratio (H&lt;sub&gt;R&lt;/sub&gt;)</th>
<th>Carr’s index (I&lt;sub&gt;c&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.3</td>
<td>0.492</td>
<td>0.661</td>
<td>1.343</td>
<td>0.255</td>
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</table>

Figure 2. The cumulative percentage drug release of the optimized formulation.

Statistical Analysis of Dissolution Data

Release profiles of the optimized formulation were compared with release profile of theoretical data and predicted data using similarity factor f<sub>2</sub> and difference factor f<sub>1</sub>. According to this method, release profiles are considered to be similar when its f<sub>2</sub> values ranges from 50 -100 and different when f<sub>1</sub> ranges from 0-15. Similarity factor and difference factor of optimized batch compared with predictable value are 47 and 14 respectively which reveals that the values are near to the range.

DISCUSSION

Floating tablets of Ranitidine HCl helps in sustained release of the drug. The selection of viscosity grade of a polymer is an important consideration in the formulation.

Physical evaluation

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. The result of angle of repose, lose bulk density, and tapped bulk density indicate good flow property of the powder.
Buoyancy lag-time
The formulation F1 having highest polymer concentration show longest total floating time (28 h) while F12 having lowest polymer concentration show shortest total floating time (17h). F9 containing the highest concentration of HPMC K4M i.e. 225 mg showed 7-8 minutes of floating lag time and F3 containing highest amount of HPMC K100M i.e.176.5 mg showed 15-16 minutes of floating lag time.

Swelling characteristics
The swelling index for HPMC K4M was found to be considerably higher than HPMC K100M because lower viscosity grade polymer absorbs more water and swells accordingly. Tablets composed of higher concentration of HPMC K4M polymer showed more swelling index which is shown by formulations F1, F4 and F9 in comparison with formulations F5 and F12.

In-vitro dissolution studies
Two viscosity grades of HPMC, namely K4M and K100M, were used at different concentrations to study their influence on the in-vitro release of Ranitidine HCl from FDDS. The rate of drug release was found to be inversely related to the viscosity grade of HPMC present in the matrix structure. To sustain the drug release, HPMC K4M was used in combination with high viscosity grade HPMC K100M. The release rate decreases significantly and the drug release prolongs as the polymer viscosity was increased. Using the drug release profile of 13 batches of experimental formulations, the amount of both the polymers to be combined in order to get optimized formulation was obtained. The optimized formulation obtained from Stat Graphica suggested optimized concentration of the HPMC K4M to be 185.45 mg (21.81% of total wt. of tablet) and HPMC K100M to be 92.5679 mg (10.89% of total wt. of tablet). This combination of polymers in optimized formulation gave drug release profile similar to required theoretical drug release.

CONCLUSION
This study discusses the preparation of floating tablets of Ranitidine. The effervescent-based floating drug delivery was a promising approach to achieve in-vitro buoyancy. The addition of gel-forming polymer HPMC K4M and HPMC K100M; and gas-generating agent sodium bicarbonate and citric acid was essential to achieve in-vitro buoyancy. The type of polymer affects the drug release rate. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be
achieved by varying the amount of different polymer combinations. The in-vitro drug release profiles obtained for optimized tablets (F14) made with combinations of HPMC K4M and HPMC K100M showed lesser FLT (25 s) and a prolonged floating duration (> 23hrs) which was a sustained release characteristic (95.98%) for 8 h. Since, the formulation showed sufficient release for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided.

ACKNOWLEDGEMENTS
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