Formulation Development and Characterization of *Hibiscus Rosa-Sinesis* Dry Leaves Mucilage as Smart Polymer for Pharmaceutical Use

Shunmuga Vellan Jayaprakasam¹², Lakshmanan Prabakaran¹* Basker Reddy Donthireddy³

¹Department of Pharmaceutical Technology, Faculty of Pharmacy, Asia Metropolitan University, Selangor Darul Ehsan, 43200, Malaysia.
²Faculty of Science Technology and Engineering, La Trobe University, Bendigo, Australia.
³Department of Pharmaceutics, R. R. College of Pharmacy, Bangalore, Karnataka, India.

**Summary.** The present investigation was to extract the *Hibiscus Rosa Sinensis* dry leaves mucilage and prove to be a smart polymer in pharmaceutical formulations. Firstly to formulate and optimize controlled-release floating tablets of Nizatidine (NF1-NF5) using HPMC K 100M and *Hibiscus* dry leaves mucilage (5-10%) along with gas generating agent sodium bicarbonate by direct compression technique. The results revealed that increase the mucilage concentration decrease the release of drug from floating tablets. The NF1 formulation, NF2, NF3 and NF4, and NF5 showed fickian type (n - 0.36), anomalous/non-fickian type (n - 0.5-1.0) and super case II transport mechanism (“n” - 1.449) respectively and secondly to formulate Mesalamine core tablets using *Hibiscus Rosa Sinensis* dry leaves mucilage (5-20%) and to be coated with Eudragit L 100 mixture by dip coating technique (MF1-MFIV) to target the drug release in colon. Release study showed that the MFI and MFII showed first order release (“n” - 0.45), MFIII showed matrix model with the “n” value of 0.5 (fickian diffusion), and MFIV showed peppas model (n -0.6) respectively. It was concluded that the mucilage plays well in both the acidic and alkaline environment of the GI tract, controlled drug release with floating and colon targeting to solve the issues of those particular targets.

**Industrial relevance.** In certain drug like Nizatidine, the therapeutic efficacy is improved if the gastric residence time of the dosage form is increased at the absorption site and if the drug is highly soluble in aqueous environment, it is necessary to reduce/controls the drug release from the formulations. *Hibiscus Rosa Sinensis* leaf mucilage exhibit excellent retarding effect on drug release from the floating tablets. Colon targeted tablets manufactured with conventional excipients, upon reaching the colon, the tablet bursts as it comes in contact with water causing dose dumping that can pose a significant risk to patients, either due to safety issues or diminished efficacy, or both. *Hibiscus Rosa Sinensis* leaf mucilage swells well when contact with water in the colon and release the drug in sustained and controlled manner for long time and alleviating the patient from the said issues. Moreover, eco-friendly, cost effective, and also produces less toxic effects to human body compared to synthetic mucilages. On the other hand, drug solubility is an issue in the formulations nowadays and as this is water soluble mucilages that could make a poorly water soluble drug to be more water soluble.

**Keywords.** Dry leaves mucilage; floating tablets; colon-targeted dosage form; control release of drug; swelling index.

**INTRODUCTION**

A drug delivery system generally focuses on providing and delivering the desired therapeutic action for a particular disease condition. The most preferred route of a drug delivery system by majority of patients is the oral route (Chien YW, 1992). Even though oral route is the most convenient and simple route for drug administration in most health conditions, this route too can be a major drawback when localized action of drugs targeted to the colon is required (Chien YW, 1992). Although, a lot of advancements that have been seen in oral controlled drug delivery system in the last few decades, the major constraint in this route the drug candidates are not absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular segment of GIT only or absorbed to a different extent in various segments of GIT. Such drug candidates are said to have an ‘absorption window’. But, in case of ‘narrow absorption window’ drugs, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption (Sarasija S, 2000). Nizatidine is a histamine H₂-receptor antagonist and it is widely prescribed in gastric and duodenal ulcers, Zollinger- Ellison syndrome and gastroesophageal reflex disease (GERD) but susceptible to metabolism by colonic bacteria, which in turn has ramifications for drug delivery and absorption. Thus, it is logically way to improve the therapeutic efficacy of the drug if the gastric residence time of the dosage form is increased at the absorption site (Amit Kumar N, 2010). Moreover, the drug is highly soluble in aqueous environment, therefore, necessary to reduce/controls the drug release from the formulations. Certain type of drugs could get benefit from using gastroretentive devise. These include drugs that act locally in the stomach, and are primarily absorbed in the stomach, are poorly soluble at an alkaline pH, have a narrow window of absorption and degrade in the colon (Abdul W, 2002).

Colon target drug delivery system is one that can be used when treatment of diseases such as Crohn’s disease, ulcerative colitis, amebiosis, local treatment of colonic pathologies are intended. Besides that, other used of colonic delivery system includes chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction (Deshpande AA, 1996 and...
Oluwatoyin AO, 2005). For the success in treating colonic disease and in formulating drug compounds that exerts its action only upon reaching the colon, it is very essential to understand the physiological principles relating to the colon. For such a drug delivery system, the most essential part would be to preserve the formulation and also preserve the drug from degradation, release and/or absorption in the upper portion of the GIT (Van den Mooter GV, 1995). The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises (Singh BN, 2002). Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor (Ashord, M, 1993).

In the present scenario, need a smart polymer to perform multiple functions. Natural polymers are now extensively used for the development of solid dosage forms for sustained/controlled release drug delivery systems. A large number of polysaccharides have already been studied for their potential for sustained/controlled release as well as colon-specific drug carrier systems due to their less toxicity that is encountered by synthetic polymers. *Hibiscus Rosa-Sinesis* leaf (Fig. 1) mucilage is a highly desirable choice of mucilage that is being studied extensively to become a natural polymer *Hibiscus rosa-sinesis* plant itself has many medicinal uses to mankind. The organic soluble plant parts exhibits several characteristics such as anti-inflammatory, analgesic, antiestrogenic, antipyretic, antispasmodic, antibacterial, fungicidal, hypoglycemic, spasmolytic, CNS depressant and many more (Fukui E, 2000 and Adhirajan N, 2003). However, the water soluble polymer is left unused and essentially goes to waste. This leaves have abundant amount of water soluble mucilages that are of no use and this mucilage swells and produces an aqueous colloidal suspension when it comes in contact with water that would enhance the drug water solubility, controlled drug release. Moreover, acidic nature of this polymer would perform well in alkaline pH with low aqueous GI tract (colon) (Prabakaran L, 2011). This was motivated us to investigate the efficiency of this dry leaves mucilage as an excipient for pharmaceutical use. Therefore, the present investigation aimed to extract and prove that the *Hibiscus Rosa Sinensis* dry leaves mucilage gives good swelling properties and controls the release of drug throughout the GI tract pH conditions as smart polymer. Primarily, the objective was to formulate and optimize controlled-release floating tablets of Nizatidine in an effort to prolong its residence time in the stomach by direct compression technique and its stability studies. Secondly, to use this mucilage as excipient to formulate Mesalamine core tablets which is then further coated with pH sensitive polymer (Eudragit L 100) for colon targeted release to improve the water solubility in low water condition as well as to control the drug release (Anil Kumar, 2012). Pre compression and post compression parameters were evaluated on the tablet formulations including their release kinetics and stability study for the suitability of this mucilage and feasibility in large scale production. The *Hibiscus Rosa Sinensis* dry leaves water soluble mucilage can be considered to be economical, non toxic, biocompatible polymer suitable controlled release of drug in upper GI tract and high efficient in low water content lower GI tract (colon) targeted formulations as excipient to improve the solubility as well as to control the release of poorly soluble drugs.

**Figure 1. Leaves of *Hibiscus Rosa Sinensis***

### MATERIALS AND METHODS

The drugs Nizatidine and Mesalamine were procured from Shasun pharmaceuticals Ltd, Pondicherry, India and Dr. Reddy’s Laboratory, Hyderabad, India respectively as gift sample. The leaves of hibiscus species (red flower) were authenticated from Institute of Bioscience, University Putra Malaysia, Malaysia and the water soluble mucilage was extracted from our Pharmaceutical Technology laboratory. Microcrystalline cellulose was purchased from R & M Chemicals; Essex, U.K. HPMC K 100 was give as gift sample from colorcon Asia Pvt Ltd, Maharashtra, India. The other chemicals and solvents were of AR grade.

**Standard Calibration curve of Nizatidine and Mesalamine.**

A solution of Nizatidine containing 10µg/ml was prepared in 0.1N HCl and scanned in the range of 200 – 400 nm using UV-Visible spectrophotometer. Mesalamine was diluted with distilled water, 0.1N HCl and phosphate buffer pH 7.4. The absorbance was obtained using UV-spectrophotometer. All the readings were duplicated for the consistency.

**Extraction of dry water soluble mucilage.** The method was followed from the literature (Ahmed A, 2013). The matured leaves from hibiscus species were collected, washed, dried at 37°C for 24 hr. Then, crushed and soaked in warm water for 2-3 hr and heated up to 80-90°C for 30-45 min. The leaves mixture was left for 24 hr for complete release of the water soluble mucilage/polysaccharide into the solvent. The mucilage/polysaccharide was then be extracted by using a cheese cloth bag to remove the marc and get concentrate viscous solution. Acetone was added to the concentrate viscous solution with constant stirring. The gel like precipitate was formed and then separated by filtration. The precipitate was washed 2-3 times with...
Acetone. After complete washing of the precipitate, it was dried in oven (40°C±1°C) followed by air dry (overnight). The compact mass was collected, grounded, passed through a sieve (ASTM 50) and stored in a desiccator until further use. The dry powder was considered as water soluble mucilage/polysaccharide for pharmaceutical use.

**Prototype formulae for Nizatidine.** Prototype formulations were made with HPMC K 15M, HPMC K 100M, Zanthan gum, Bees wax polymers alone and in combination with Hybiscus mucilage at various concentrations for their suitability in developing controlled floating drug delivery system of Nizatidine. The tablets were prepared by direct compression technique and qualified to achieve the target release.

**Formulation of floating tablets of Nizatidine.** Floating tablets containing Nizatidine (NF1 – NF5) were prepared by direct compression technique using varying concentrations of HPMC K 100M and Hibiscus mucilage (5-10%). All the ingredients except magnesium stearate were blended in 5min and then the powder blend was lubricated with magnesium stearate and talc. The tablets were compressed by using Rimek Mini Press I rotary tablet punching machine (10 stations). The compositions of tablets are shown in Table 1.

**Formulation of core Mesalamine tablets.** Mesalamine was used as a model drug for colon delivery tablets (MFI – MFIV) by direct compression method (Ravi Kumar, 2012). Four formulations were prepared using different concentrations of *Hibiscus Rosa Sinensis* leaves mucilage (5-20%) as shown in Table 2. All the core tablets were contained 400 mg of mesalamine, mixed properly with *Hibiscus Rosa Sinensis* leaves mucilage, diluents (microcrystalline cellulose) and then lubricated with talc and magnesium stearate. The tablets were prepared by direct compression technique using Rimek Mini Press I rotary tablet punching machine (10 stations).

### Table 1. Composition of Nizatidine floating tablets.

<table>
<thead>
<tr>
<th>Ingredients*</th>
<th>NF1</th>
<th>NF2</th>
<th>NF3</th>
<th>NF4</th>
<th>NF5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nizatidine</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Hibiscus mucilage</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>MCC</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Citric acid</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total weight</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

*All quantities are in mg.

### Table 2. Composition of core Mesalamine tablets.

<table>
<thead>
<tr>
<th>Ingredients*</th>
<th>MF1</th>
<th>MF2</th>
<th>MF3</th>
<th>MF4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine*</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td><em>Hibiscus Rosa Sinensis</em> leaves mucilage*</td>
<td>35</td>
<td>70</td>
<td>105</td>
<td>140</td>
</tr>
<tr>
<td>Diluent (Microcrystalline cellulose)*</td>
<td>256</td>
<td>221</td>
<td>186</td>
<td>151</td>
</tr>
<tr>
<td>Magnesium stearate†</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Talc</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total weight of tablet*</td>
<td>700</td>
<td>700</td>
<td>700</td>
<td>700</td>
</tr>
</tbody>
</table>

*Quantities are in mg. †Quantities are in percentage.

### Fourier Transform Infrared (FTIR) study.

Drugs alone and additive mixture with KBr were taken in 1:100 ratio in a mortar and triturated. A small amount of triturate was taken into a pellet maker and was compressed at 10 kg/cm² to form a transparent pellet using a hydraulic press. The pellet was kept in the sample holder and scanned between 4000 – 400 cm⁻¹ using IR spectrometer (Sipra lab Ltd).

### Evaluation on floating tablets. Angle of repose.

The frictional force in a loose powder was measured by conventional funnel method. The powder was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed using the formula 1.

\[
\tan \theta = \frac{h}{r} \quad \text{………………1}
\]

Where \(\theta\) = angle of repose, \(h\) = height, \(r\) = radius

**Carr’s index.** The flowability of powder was evaluated by comparing the bulk density (\(D_b\)) and tapped density (\(D_t\)) of the powder and the rate at which it packed down using the formula 2.

\[
carr’s\text{\index} \left( \% \right) = \frac{D_t - D_b}{D_b} \times 100 \quad \text{………………2}
\]

Where \(D_b\) = bulk density, \(D_t\) = tapped density
**Drug content (%).** Tablet crush equivalent to 400mg of drug was dissolved in 100ml of 0.1N HCl in volumetric flask and allowed to dissolve the drug in the solvent. The solution was filtered, 1ml of filtrate was taken in 100ml volumetric flask and diluted to mark with 0.1N HCl and analyzed by double beam UV spectrophotometer at 242nm. The concentration of Nizatidine in mg/ml was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch.

**Buoyancy lag time (min) and Total floating time (hr).** The time taken by the tablet to emerge onto the surface of the medium after adding to the dissolution medium is called Buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on surface of medium called Total floating time (TFT). Both BLT and TFT were determined by placing the tablet in 900ml of simulated gastric fluid without pepsin at pH 1.2, temperature 37±0.5ºC using stopwatch.

**In vitro dissolution studies.** *In vitro* release studies were carried out using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900ml of simulated gastric fluid (pH 1.2) at 37±0.5°C and 75rpm. Sample of 5ml were withdrawn at predetermined time intervals, replaced with 5ml of fresh dissolution medium and filtered. The collected samples were suitably diluted with dissolution fluid and analyzed at 242 nm by using double beam UV spectrophotometer. Each dissolution study was performed for three times and the mean values were taken.

**Evaluation on colon release core tablets.** *Swelling index.* The extent of swelling was measured in terms of % weight gain by the tablets from all the batches. The swelling behaviour of all formulation was studied. Six tablets from each formulation was randomly selected, weighed individually (W1) and placed separately in a wire basket which were placed in a 100 ml beaker containing 0.1 N HCL for first 2h and in pH 6.8 phosphate buffer for remaining 6h. At the end of 6h, the tablets were withdrawn from wire basket and excess water was removed using tissue paper. The swollen tablets were reweighed (W2) and swelling index of each tablet were calculated by using the formula 4 and the average was considered; 

\[
\text{Swelling index} = \frac{w_2-w_1}{w_1} \times 100\% \quad 4
\]

**Dissolution study.** The ability of Mesalamine tablets incorporated with *Hibiscus rosa-sinensis* leaves mucilage to remain intact in the physiological environment of stomach and small intestine was tested in different pH condition by mimicking mouth to colon transit. The dissolution studies were carried out in 0.1N HCl for first 2 hr (as the average gastric transit time is ~ 2 hr), then in 7.4 pH Phosphate buffer for next 6 hr (as average intestinal transit time) using USP dissolution apparatus II (Paddle). The apparatus were maintained at 37±0.5°C and at 100 rpm. The height of paddle was adjusted at about 2.5cm above the bottom of the beaker surface. About 5 ml of aliquot was withdrawn at regular intervals of time and diluted to 10 ml in volumetric flask and the drug concentrations were measured at 298 nm using double beam UV-spectrophotometer. The other tests such as friability, thickness and diameter, hardness, weight variation, content uniformity and thickness test were also performed on floating and core colon target formulations to ensure the quality of the formulated tablets.

**Kinetics and mechanism of drug release.** To analyze the mechanism of release and release rate kinetics on both of the dosage forms, the data obtained from *in vitro* dissolution studies were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson-Crowell model using PCP-DISSO-v3 software and the ‘r’ value and best-fit model was also obtained.

**Zero order equation.** Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the formula 5; 

\[
Q_t = K_0 t + Q_0 \quad 5
\]

Where \(Q_t\) = amount of drug dissolved in time t.

\(Q_0\) = initial amount of the drug in the solution and 

\(K_0\) = zero order release constant.

Formula 6 describes the systems where the drug release rate is independent of its concentration and a graph is plotted between cumulative % drug releases vs. time.

\[
C = k_0 t \quad 6
\]

Where, \(K_0\) is zero-order rate constant expressed in units of concentration / time and ‘t’ is the time.

**First order equation.** The drug release from the system where release rate is concentration dependent and a graph is plotted between log cumulative of % drug remaining vs. time (Formula 7) which would yield a straight line with a slope of \(-K/2.303\);

\[
\log C = \log C_0 - Kt / 2.303 \quad 7
\]

Where, \(C_0\) is the initial concentration of drug and \(K\) is first order constant.

**Higuchi equation.** Higuchi (1961) described the release of drugs from insoluble matrix as a square root of time dependent process based on fickian diffusion and a graph is plotted between cumulative percentage drug releases versus square root of time (Formula 8);

\[
Q = K^2 t^{1/2} \quad 8
\]

Where, \(K^2\) is release rate constant.
**RESULTS AND DISCUSSION**

A strong absorption peak observed at 242 nm and 298 nm for Nizatidine in 0.1N HCl and Mesalamine in phosphate buffer pH 7.4 respectively. The 4 weeks physicochemical study such as odour, colour, texture, liquefaction, Rf value, FTIR and λ<sub>max</sub> on drugs and excipients mixture confirmed that there was no interaction and found to be almost similar results with their initial observations.

FTIR spectroscopy was carried out to check the compatibility between the drugs and excipients mixture, where spectral measurements of drug alone and with polymers were taken at ambient temperature and analyzed for major interaction. The peaks identified for the pure drug (Nizatidine) such as CH<sub>3</sub> – N Stretching (2782.24), N-H Deformation (1583.37), CH<sub>1</sub> Deformation (1436.22), CH<sub>3</sub> Stretching (2942.96), C=C (1617.56), C=S (691.53) Stretching, C-NO<sub>2</sub> (aliphatic) Stretching (1391.02) C-N (aromatic) Stretching (1354.65) and C-N (aliphatic) Stretching (1225.65) were identical with the peaks of pure drug and HPMC K100M mixture, pure drug and Hibiscus mucilage mixture and pure drug with all other excipients mixture which ensured that there was no any chemical interaction between them.

The tablets formed on both of the drugs fit the formulation requirements and stable until for further evaluations while using direct compression technique. Nizatidine, the tablets were used as such for their further studies, whereas, Mesalamine tablets were further coated with pH dependent polymer to achieve the target release by dip coating technique.

In Nizatidine, the five formulations contain different concentrations of Hibiscus Rosa Sinensis dry leaves mucilage were formulated with 12mm diameter and 400 mg (±5) of total tablet weight. The formulations with HPMC K 100M and Hibiscus mucilage (5 – 10%) combinations gave longer floated time and also showed good controlled release.

In Mesalamine, the four formulations contain different concentrations of Hibiscus Rosa Sinensis dry leaves mucilage (5 - 20%) were formulated as core tablet with 12mm diameter and 700 mg (±5) of total tablet weight and further coated with Eudragit L 100 (4%).

Pre-compression parameters on Nizatidine powder blend such as angle of repose range from 23.45° to 28.15° indicating good flow property of the blend, the values of bulk density found to be in the range from 0.372gm/cm<sup>3</sup> to 0.394gm/cm<sup>3</sup> and tapped density from 0.444gm/cm<sup>3</sup> to 0.456gm/cm<sup>3</sup> which gave the compressibility index value ranges between 11.65% to 17.54% that ensured the mixture would give good compaction and Hausner’s ratio range from 1.131 to 1.215 indicated that the powder blend have the required flow property for direct compression. The pre-compression parameters of Nizatidine powder mixture (NF1 to NF5) are shown in Table 3.

**Table 3.** Pre-compression parameters of Nizatidine powder mixture.

<table>
<thead>
<tr>
<th>Code</th>
<th>Angle of repose* (°)</th>
<th>Bulk density* g/cm&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Tapped density* g/cm&lt;sup&gt;3&lt;/sup&gt;</th>
<th>% Compressibility index*</th>
<th>Hausner’s ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>23.45±0.010*</td>
<td>0.380±0.020</td>
<td>0.444±0.026</td>
<td>14.41±0.021</td>
<td>1.168</td>
</tr>
<tr>
<td>NF2</td>
<td>26.76±0.021*</td>
<td>0.372±0.019</td>
<td>0.452±0.030</td>
<td>17.69±0.030</td>
<td>1.215</td>
</tr>
<tr>
<td>NF3</td>
<td>24.58±0.015*</td>
<td>0.381±0.021</td>
<td>0.451±0.028</td>
<td>15.32±0.027</td>
<td>1.183</td>
</tr>
<tr>
<td>NF4</td>
<td>22.19±0.030*</td>
<td>0.394±0.025</td>
<td>0.446±0.032</td>
<td>11.65±0.036</td>
<td>1.131</td>
</tr>
<tr>
<td>NF5</td>
<td>28.15±0.028*</td>
<td>0.376±0.026</td>
<td>0.456±0.036</td>
<td>17.54±0.029</td>
<td>1.212</td>
</tr>
</tbody>
</table>

*All the evaluations were triplicates (± S.D)

Post-compression parameters on Nizatidine floating tablets such as the mean thickness was almost uniform in all the five formulations and found to be in the range from 3.38mm to 3.41mm, the measured hardness of tablets of each batch ranged between 4.7kg/cm<sup>2</sup> to 4.8kg/cm<sup>2</sup> that ensured the good handling characteristics of all batches, the % friability was less than 1 in all five formulations ensuring that the tablets were mechanically stable, the content uniformity was also in the limit (±5%) and all formulations passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% with low standard deviation. The post-compression parameters of Nizatidine floating tablets (NF1 to NF5) are shown in Table 4.
Table 4. Post-compression parameters of Nizatidine floating tablets.

<table>
<thead>
<tr>
<th>Code</th>
<th>Weight variation*</th>
<th>Hardness* (kg/cm²)</th>
<th>Thickness* (mm)</th>
<th>Friability* (%)</th>
<th>Drug content* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>0.403±0.005</td>
<td>4.75±0.05</td>
<td>3.38±0.02</td>
<td>0.74±0.04</td>
<td>98.72</td>
</tr>
<tr>
<td>NF2</td>
<td>0.402±0.006</td>
<td>4.78±0.04</td>
<td>3.39±0.04</td>
<td>0.72±0.06</td>
<td>97.78</td>
</tr>
<tr>
<td>NF3</td>
<td>0.402±0.005</td>
<td>4.82±0.03</td>
<td>3.40±0.05</td>
<td>0.45±0.02</td>
<td>97.07</td>
</tr>
<tr>
<td>NF4</td>
<td>0.401±0.010</td>
<td>4.83±0.06</td>
<td>3.39±0.03</td>
<td>0.56±0.04</td>
<td>96.13</td>
</tr>
<tr>
<td>NF5</td>
<td>0.403±0.008</td>
<td>4.78±0.05</td>
<td>3.41±0.04</td>
<td>0.61±0.07</td>
<td>99.67</td>
</tr>
</tbody>
</table>

*All the evaluations were triplicates (± S.D)

The tablets floated with less than 5 min for F1 to F3 and around 6 min for F4 to F5 as lag time, and remained buoyant without disintegration till 10 hr for formulation NF1 and the remaining formulations NF2 to NF5 were more than 12 hr. The buoyancy study is shown in Fig. 2.

In *in vitro* release study, the Nizatidine formulation NF1 released 92.4% of drug within 6 hr of the study indicated that the polymer combination is insufficient to control the drug release. Tablet of batch NF2, NF3, NF4 and NF5 showed 90%, 78.6%, 69.7% and 61% at the end of 8 hr respectively. Formulation NF3 containing equal amounts of HPMC K 100M and Hibiscus mucilage showed better control of drug release and able to release entire amount of drug in 12 hr than the other formulations and therefore it may be considered as the optimized formulation. It was an evident from the *in vitro* dissolution data that increase in Hibiscus mucilage concentration decrease the release rate of the drug. *In vitro* dissolution study of the formulations (NF1 to NF5) is shown in Fig. 3.

The results of dissolution data of Nizatidine floating tablets were fitted to various kinetic equations to analyze the release mechanism. The formulations NF2, NF3, and NF4 showed ‘n’ value between 0.49 to 0.89 that indicate the drug release occurred via non-Fickian diffusion mechanism that depicts the release was initially dry, hydrophilic glassy polymers and swell when added to water, become rubbery show anomalous diffusion where the drug release was controlled by both diffusion and erosion mechanism as a result of the rearrangement of macromolecular chains. The ‘n’ value of formulation NF1 was 0.36 indicate that the drug release was followed fickian diffusion which depends on diffusion of the drug and the ‘n’ value of formulation NF5 was 1.44 that indicated the drug release follow super case II transport mechanism due to more concentration and erosion of the polymer. NF1 to NF4 formulations followed Peppas’ model as best fit and having higher correlation coefficient (‘r’ value) and the formulation NF5 followed Zero order kinetics as best fit due to the higher concentration of the mucilage. The release kinetics of Zero order, Higuchi and Peppas models for the formulations NF1 to NF5 are shown in Fig. 4, 5 and 6 respectively.

*In vitro* evaluations on Mesalamine core tablets such as friability that was found to be less than 1% indicates passes the test for all the formulations (MFI to MFIIV), in swelling study, the MFI and MFIII formulation completely dissolved in phosphate buffer pH 6.8 whereas the MFI and MFIIV gave a significant swelling index of 192.71% and 51.12 respectively during the 8 hr study but FIH gave two fold swelling in the alkaline medium which ensures the formulation would perform best in *in vivo* condition that to in low water alkaline colonic condition.

![Figure 2. *In vitro* buoyancy study of Nizatidine floating tablets.](image-url)
In vitro dissolution study on Mesalamine formulations, MFI formulation showed insignificant drug release in first 2 hr in 0.1N HCl (as the average gastric transit time is ~ 2 hr) followed by the study in phosphate buffer pH 7.4 until 6.0 hr with every half an hour sampling with the drug release of ≈ 45%. Same study was conducted on MFI, MFIII and MFIIV formulations and showed the drug release (6 hr) of ≈ 30%, ≈ 25% and ≈ 20% respectively. These results indicate the release may be around 75%-80% in 16 hr study by adjusting the mucilage concentration whereby the formulation can be considered for once in a day. Other than that, the formulation was also differentiated by the concentration of *hibiscus rosa sinensis* dry leaves mucilage.
In swelling test, it showed that the higher percentage of *Hibiscus rosa-sinensis* dry leaves mucilage, the more swelling index which will dissolves and retains the drug for a longer period in alkaline environment (colon). MFI and MFII formulations were swelling well but disintegrated fast. Whereas, the formulation MFIII and MFIV showed very good swelling but compare to FII, the formulation FIV swelling index was low which may be due to the higher concentration of the mucilage.

![Figure 6. Drug release kinetics of Nizatidine floating tablets (Peppas’ model).](image)

The results of dissolution data of Mesalamine were fitted to various kinetic equations to analyze the release mechanism. The MFI and MFII formulations were followed the first order release with the ‘n’ value of 0.59 (non-fickian diffusion) and 0.45 (fickian diffusion) which indicates that the hydrophilic polymer swell when added to water which shows the anomalous diffusion and diffusion respectively as a result of the rearrangement of macromolecular chains but the release was not controlled by the polymer due to low concentration of the mucilage. The MFIII formulation was followed the matrix release with the ‘n’ value of 0.5 (fickian diffusion) which shows the release pattern by diffusion and also ensured that the drug was hold by the polymer and releases the drug in slow and steady manner. Whereas, the MFIV formulation showed the peppas’ release pattern with the ‘n’ value of 0.63 that indicates the diffusion followed by erosion release mechanism and also ensured that the drug was hold by the polymer and release the drug in very slow manner due to higher concentration of the mucilage.

Stability studies were carried out on optimized formulation NF3 and MFIII at 25°C/60% RH for 3 months. The results revealed that there is no change in physical appearance, hardness and drug content (< 5%) indicating the formulation was stable.

**CONCLUSION**

Gastroretentive floating tablets of Nizatidine was successfully formulated using HPMC K 100M and *Hibiscus rosa-sinensis* dry leaves mucilage as a floating and release retardant materials in different concentrations by direct compression technique. Among the formulations, formulation NF3 with equal concentration of HPMC K100M and Hibiscus mucilage showed good controlled release and able to release the drug completely in 12 hr than the other formulations and therefore it was considered as the optimized formulation. Formulated tablets gave satisfactory results for various physicochemical evaluations and also evident from the *in vitro* dissolution data shows increase in Hibiscus mucilage concentration that decrease the drug release rate. Mesalamine colon targeted formulations with *Hibiscus Rosa Sinensis* dry leaves mucilage was proven to give good swelling properties and controlled release of drug in alkaline medium respect with the polymer concentration. *In vitro* drug release was fast in MFI and slow in MFIV that indicated the increase in concentration of *Hibiscus Rosa Sinensis* dry leaves mucilage decreases the drug release. As a whole, the formulation MFIII contain 20% of *Hibiscus Rosa Sinensis* dry leaves mucilage gave good swelling property in alkaline medium and releases the drug slowly for desired time that could achieve good therapeutic effect in colon. The results of stability studies for optimized formulations NF3 and MFIII revealed no change in physical appearance, hardness and drug indicating the formulation was stable. In conclusion, the *Hibiscus Rosa Sinensis* dry leaves mucilage able to be extracted with more yield and proved that it could be used as an excipient for entire GI tract pharmaceutical formulations (mouth to colon) as a fast as well as slow release excipient with economical, toxic less, biocompatible (natural polymer) smart polymer.

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