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Isolation and Preliminary Evaluation of *Borassus Flabellifer* Fruit Mucilage As A Novel Excipient for Matrix of Ranitidine HCl Floating Tablet

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ABSTRACT

The present investigation was aimed at estimating the effectiveness of the edible mucilage of *Borassus flabellifer* fruit as a polymer in the development of a gastric floating dosage form of ranitidine HCl. *Borassus flabellifer* fruit mucilage, was shown to aid in the formulation of floating tablets. In the present study, it was used as a pharmaceutical excipient and its efficiency was compared with HPMC in the formulation of ranitidine HCl floating tablets. Sodium bicarbonate was used as a gas-generating agent, ranitidine HCl tablets were prepared by direct compression method. The prepared tablets were evaluated for physicochemical parameters and found to be within range viz. hardness, swelling index, floating capacity, thickness, and weight variation. Further, tablets were evaluated for in vitro release characteristics for 12 hrs. All in all, the formulation F3 manifested a prolonged release of the active ingredient. The optimized formulation F3 followed higuchi's mechanism. Based on the diffusion exponent (n) value, the drug release was found to be diffusion controlled. From the study, it was evident that the mucilage manifested all the characteristics of a good pharmaceutical excipient that can be used for the formulation of floating tablets.

Keywords: floating tablets, *Borassus flabellifer* fruit mucilage, ranitidine HCl, sustained release, *in vitro* buoyancy.

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INTRODUCTION

For effective therapy or to improve therapeutic efficiency of the drug through improved bioavailability, may overcome the absorption drawbacks associated with certain class of drugs. Drug delivery systems may overcome these drawbacks in some cases. Among the drug delivery systems, gastric oral floating drug delivery systems may be desirable especially when the bioavailability of the drugs reduces due to the pathophysiology of the patient. Prolonged gastric retention of the therapeutic moiety may offer numerous advantages, including improved bio-availability therapeutic efficiency and possible reduction of dose[1-3]. It has been reported that prolonged local availability of anti bacterial agents may augment their effectiveness in treating *H. pylori* infection in peptic ulcer disease[4]. Further the bactericidal effects of clarithromycin, garcinol and reveratrol are time and concentration dependent. Menon *et al*[5] have compared the bioavailability of furosemide in the form of floating dosage with that of commercial product of non floating dosage form and found that the better bioavailability from floating dosage form. Floating drug delivery systems (FDDS) or hydrodynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. After the release of drug residual system is emptied from the stomach. This results in increase in the gastric residence time and a better control of fluctuation in plasma drug concentration. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non effervescent FDDS approach was attempted to release the drug from FDDS. These systems when reached to stomach, CO_2 is liberated by the acidity of gastric contents and is entrapped in the jellified hydrocolloid. This produces an upward motion of the dosage form to float on the chime. The CO_2 generating components Viz: sodium carbonate or calcium carbonate or citric acid and tartaric acid mixtures may be used[6-9].

Ranitidine hydrochloride (RHCl) is a histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. 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 RHCl is desirable. The short

biological half-life of drug (~2.5-3 hours) also favors development of a sustained release formulation[10-11]. 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. 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. In context of the above principles, a strong need was recognized for the development of a dosage form to deliver RHCl in the stomach and to increase the efficiency of the drug, providing sustained action.

The *Borassus flabellifer* is a tall and erect palm, with large, fan-shaped leaves which are quite unlike the pinnate leaves of other palms. The endosperm contains a high proportion of mucilage. The two major polysaccharides present in this endosperm are galactomannan and mannan. Literature survey reveals that, the endosperm of fruit contains a huge amount of mucilage. During earlier study in our laboratory, the disintegrating, binding, gelling, suspending, matrix forming properties of *Borassus flabellifer* mucilage (BFM) were evaluated. But the possibility of this mucilage as a polymer for floating drug delivery has not been exploited. The endosperm of *Borassus flabellifer* swells and form gelatinous mass when it comes in contact with water due to its hydrophilic nature. So in the present study, an attempt has been made to investigate the possibility of *Borassus flabellifer* fruit mucilage as a polymer for the development of floating drug delivery of ranitidine HCl.

MATERIALS AND METHODS

Materials

Borassus flabellifer endosperms were procured from the local market. Diclofenac sodium was obtained as gift sample from Cadila Pharmaceuticals Ltd, Ahmedabad, India. All other materials, excipients, solvents and reagents were either analytical or Pharmacopoeial grade and they were procured from S.D.fine Chemicals Mumbai.

Isolation and purification of mucilage from Borassus flabellifer endosperm[12]

The endosperm of Borassus flabellifer fruit contains mucilage. To increase the yield of the mucilage the endosperm of Borassus flabellifer fruit were extracted by different solvents. The endosperm of Borassus flabellifer were collected, cut into small pieces and dried using tray dryer at 37°C for 24 h at room temperature, made fine powder by crushing in a mixer. The fine powder

was soaked in different solvents such as water, hot-water, phosphate buffer solution (PBS) of pH 4.0, 6.8, 9.2, separately for 2-3h and heated up to 80-90°C for 30-45 min for complete release of the water soluble mucilage into the solvents. The mucilage was then extracted by using a multi layer muslin/cheese cloth bag to remove the marc and concentrated viscous solution under reduced pressure at 60-70°C. Acidified ethanol (5% HCl in 75% ethanol) was added to the concentrated viscous solution with constant stirring. The gel like precipitate was formed and separated by filtration. The precipitate was washed 2-3 times with 75% and 95% ethanol. After complete washing of the precipitate with ethanol 95%, brownish white powder was obtained. The powder was dried in an oven at 37°C, collected, grounded, passed through a # 80 sieve and stored in a desiccator till use. The brownish white powder was considered as mucilage for pharmaceutical use. Physicochemical characterization, phytochemical screening and toxicity studies of the isolated mucilage were carried out as per the reported procedure[13-16].

Drug- polymer interaction studies

Fourier Transform Infra-Red (FT-IR) spectral analysis

Fourier–Transform Infrared (FT–IR) spectrums of pure diclofenac and combination of drug and excipients were obtained by a Fourier-Transform Infrared spectrophotometer, (FTIR-8300, Shimadzu, Japan) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was $1cm^{-1}$. This spectral analysis was employed to check the compatibility of drugs with the excipients used.

Preparation of RHCL floating tablets

Effervescent Floating tablets containing RHCL were prepared by direct compression technique using varying concentrations of BFM with sodium bicarbonate and citric acid.

Table 1: Composition of different batches of RHCL floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
RHCL	336	336	336	336	336	336	336	336
BFM	40	80	120	160	--	--	--	--
HPMC K4M	--	--	--	--	40	80	120	160
Sodium bicarbonate	50	50	50	50	50	50	50	50
Citric acid (Anhydrous)	10	10	10	10	10	10	10	10
Magnesium stearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Avicel	152	112	72	32	152	112	72	32
Total weight of tablet	600	600	600	600	600	600	600	600

*HPMC K4M: indicates hydroxy propyl methylcellulose. All batches contained 336 mg RHCL equivalent to 300mg daily dose, 1% w/w talc and 1% w/w magnesium stearate.

All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, then lubricated with magnesium stearate and talc, and further mixed for additional 2-3 minutes. The tablets were compressed using Cemach (Ahmedabad, India) Multi station tablet press fitted with 12 mm flat-faced punches. The weights of the tablets were kept constant for all formulation. The composition of each formulation of RHCL floating tablets is given in table 1.

Pre-compression evaluation of RHCL powder blend[17-19]

The flow properties of powders (before compression) were characterized in terms of bulk density, tapped density, Hausner's ratio, angle of repose and Carr's index as per the reported procedure.

Post-compression evaluation of RHCL floating tablets[20-21]

Organoleptic evaluation

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated.

Thickness and diameter

The thickness and diameter of the tablets were measured by Vernier Calipers. Five tablets from each formulation were used and average values were calculated. It is expressed in mm.

Weight Variation

20 tablets were selected randomly from each formulation and weighed individually using an electronic balance and average weights were determined. Then the individual tablet weight was compared to the average tablet weight to check the weight variations as per Indian Pharmacopoeia.

Hardness

The hardness of the tablet was determined using Monsanto hardness tester for each formulation. It is expressed in kg/cm^2.

Friability (F)

The friability of the tablet was determined using Roche Friabilator (Electro Lab, Mumbai, India). It is expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 mins (100 revolutions). The tablets were weighed again (W_{final}). The % friability was then calculated by

$$F = W_{initial} - W_{final} / W_{initial} * 100$$

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1NHCl, the drug content was determined measuring the absorbance at 314 nm after suitable dilution using a Shimadzu UV- Vis double beam spectrophotometer 1601.

***In vitro* buoyancy studies**

The *In vitro* buoyancy studies were performed for all the formulations by placing the tablet in a 250 ml glass beaker, containing 200 ml of 0.1N HCl, pH 1.2, maintained at 37 ±0.5°C in a water bath. Their physical state was observed for 12 h. The time between introduction of the dosage form and its buoyancy on the 0.1N HCl (buoyancy lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually. Five replicates of each formula were performed.

Swelling index of RHCL floating tablets

Floating tablet of RHCL was weighed individually (designated as W_1) and placed separately in glass beaker containing 200 ml of 0.1N HCl and incubated at 37ºC ±1ºC. At predefined time intervals until 12h, the tablet was removed from beaker, and the excess surface liquid was removed carefully using the filter paper. The swollen tablet was then re-weighed (W_2) and swelling index (SI) was calculated using the following formula.

$$SI = (W_2 - W_1)/W_1 \text{ X}100$$

***In vitro* drug release studies of RHCL floating tablets**

The release rate of RHCL from floating tablets was determined using the United States Pharmacopoeia (USP) XXIII dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37±0.5°C and 75rpm. A sample (10ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 314nm using a Shimadzu UV-Vis double beam spectrophotometer 1601. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) of intact tablet containing formulation (F3) was done before and after dissolution of 12 hours. The morphological characters of these 2 scans were compared to hypothesize the mechanism of drug release and floating. The surface of the tablets was studied by SEM.

Drug release kinetics

To analyze the mechanism of drug release from the optimized formulations (F3), the data obtained from *in vitro* release studies were subjected to Higuchi's model, zero order model and Korsmeyer's model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. The selected tablets of RHCL (F3) packed in high density polyethylene bottle, and various replicates were kept in the humidity chamber maintained at 40°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters.

Evaluation of gastric retention using X-Ray imaging[22-25]

The animals used in the toxicity studies were sanctioned by the Institute Animal Ethical Committee (Approval No:KCP/IAEC/Ph.Ceutics/05/2011-2012). The selected tablet formula (F3) for *in vivo* investigation was reformulated with 15% $BaS0_4$ as opaque agent. *In vivo* study was performed in rabbits by using X ray imaging technique. This X-ray study was performed in 6 healthy rabbits of either sex, weight 2kg- 2.5kg.The animal was housed individually under environmental condition (25^0C, 12 h light and dark cycle). The rabbit was administrated with selected formulation (F3). A radiograph was made just before the administration of the $BaS0_4$ loaded tablet to ensure the absence of radio-opaque material in the stomach. Then the tablet was administered orally by placing them in hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulb. Rabbit was placed upright posture for checking the position of tablet in gastric region by using X-ray machine. X-rays were taken at different time intervals like 1hr, 2 hr, 4hr, 8hr and 12hr.

RESULTS AND DISCUSSION

Drug-Excipients Compatibility Studies

Fourier transform infrared (FTIR) analysis

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between RHCL and the excipients used. Drug has given peaks due to furan ring, secondary diamine, alkene and two peaks due to nitro functional groups. From

the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The results of drug-excipients compatibility studies by FTIR were represented in figure 1 and 2 respectively.

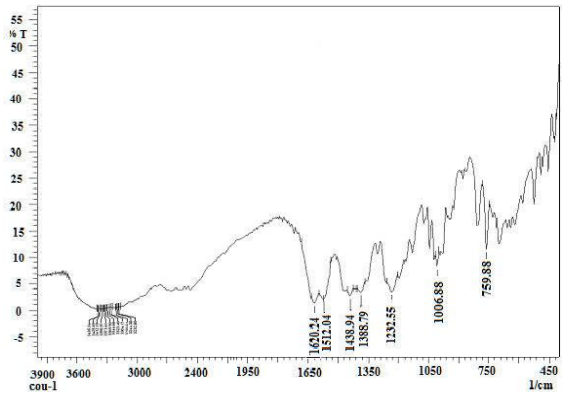


Figure 1: FTIR spectrum of RHCL

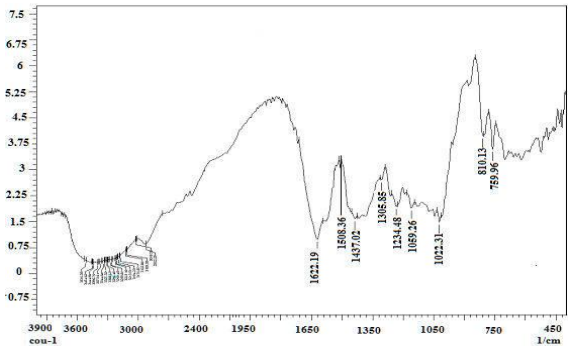


Figure 2: FTIR spectrum of physical mixture of RHCL and BFM

Evaluation of the precompression parameters of RHCL powder blend

Formulation of proper powder/granule blend is the key factor in the production of tablet dosage form involving floating extended release of drug from matrix type particle. Physical parameters such as specific surface area, shape, hardness, surface characteristics and size can be significantly affect the rate of dissolution of drugs contained in a complex system. The formulated powder blends of different formulations (F1 to F8) were evaluated for angle of repose, tapped density, bulk density, Carr's index and Hausner ratio. Angle of repose and compressibility index (%) ranged from 26.3±0.02 to 32.6±0.04 and 17.9±0.02 to 24.3±0.01, respectively. The results of LBD and TBD ranged from 0.53±0.04 to 0.57±0.02 and 0.67±0.03 to 0.74±0.02 respectively. The results of angle of repose (<30) indicated good flow properties of the entire formulated powder blend except for formulation (F7). The compressibility index value (<25) further support good to excellent flow properties of powder blend. Formulated powder blends density; porosity and hardness are often interrelated properties and are likely to influence

compressibility, porosity, dissolution profile and properties of tablets made from it. All these results indicate that the formulated powder blend possessed satisfactory flow properties and compressibility. The results of precompression parameters of RHCL powder blend were presented in table 2.

Table 2: Results of precompression properties of the RHCL powder blend

Formulation code	Angle of repose(θ)*	Bulk density (gm/cm^3)*	Tapped density (gm/cm^3)*	Carr's index (%)*	Hausner ratio (H_R)*	Bulkiness (cc/g)*
F1	28.1±0.01	0.57±0.01	0.71±0.04	19.7±0.01	1.24±0.01	1.75±0.02
F2	26.3±0.02	0.55±0.02	0.67±0.03	17.9±0.02	1.22±0.02	1.81±0.04
F3	27.6±0.03	0.55±0.01	0.70±0.01	19.9±0.02	1.27±0.03	1.81±0.05
F4	26.9±0.04	0.54±0.03	0.73±0.03	21.5±0.01	1.35±0.01	1.85±0.01
F5	26.9±0.05	0.53±0.04	0.67±0.03	20.8±0.02	1.26±0.02	1.89±0.03
F6	28.0±0.01	0.57±0.01	0.74±0.01	23.1±0.01	1.29±0.01	1.75±0.02
F7	32.6±0.04	0.56±0.01	0.74±0.02	24.3±0.01	1.32±0.04	1.79±0.02
F8	27.3±0.05	0.57±0.02	0.73±0.02	21.9±0.01	1.28±0.02	1.75±0.03

*All values are expressed as mean ± SD, n=3.

Evaluation of RHCL floating matrix tablets

Tablets of all the formulations were subjected to many in-process parameters evaluation such as physical appearance, thickness, diameter, content uniformity, weight variation, hardness, and friability tests. The shape of the tablets of all formulations remained circular with no visible cracks. The thickness and diameter of the tablets ranged from 2.7±0.01 to 3.2±0.02 mm and 10.8±0.02 to 11.2±0.01 mm respectively. It indicated that thickness and diameter of all the formulations showed more or less uniform. Good uniformity in drug content was found among different formulations of the tablets, and the percentage drug content was more than 95%. The drug content of all the formulations was found to be more or less uniform. In a weight variation test, the Pharmacopoeial limit for the percentage deviation for the tablets of more than 250mg is ±5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of all the formulation was between 4.5 to 6.0 kg/cm^2. The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. This indicates that the tablets can withstand the mechanical shocks reasonably well during handling. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability. The results of post compression parameters of RHCL floating matrix tablets were presented in table 3.

Table 3: Results of post compression properties of RHCL floating Tablets

code	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm^2)*	Friability (%)***	Drug content (%)*	Wt variation (mg)**	Buoyancy lag time(min)*	Total buoyancy Time(h)*	Buoyancy on disturbing	Matrix integrity
F1	3.0±0.01	11.0±0.02	4.5±0.2	0.25±0.01	96.5±0.02	600±0.04	1.0±0.11	8±0.12	Settle	-
F2	2.9±0.02	10.9±0.02	5.0±0.1	0.30±0.06	98.0±0.01	599±0.02	1.3±0.17	10±0.15	Float	-
F3	2.8±0.03	11.1±0.02	5.5±0.12	0.45±0.04	99.0±0.01	602±0.02	1.5±0.22	>12±0.13	Float	+
F4	3.0±0.01	11.2±0.01	6.0±0.16	0.55±0.02	99.5±0.05	600±0.02	1.8±0.13	>12±0.16	Float	+
F5	2.9±0.05	11.0±0.03	5.5±0.09	0.21±0.03	98.0±0.01	598±0.03	0.9±0.32	4±0.15	Settle	-
F6	2.7±0.01	11.0±0.04	5.0±0.08	0.35±0.03	99.0±0.01	601±0.01	1.1±0.13	6±0.16	Float	-
F7	3.0±0.01	11.2±0.04	5.5±0.07	0.40±0.02	98.5±0.02	602±0.05	1.7±0.16	8±0.12	Float	-
F8	3.1±0.02	10.8±0.02	5.0±0.12	0.25±0.03	99.5±0.02	600±0.01	2.0±0.10	10±0.15	Float	-

*All values are expressed as mean ± SE, n=5; **All values are expressed as mean ± SE, n=20; ***All values are expressed as mean ± SE, n=10, **+ =** Matrix integrity retained; **-** = matrix integrity lost.

***In vitro* buoyancy studies**

From the results of floating behaviour studies, it was found that as the concentration of effervescent mixture increase, the floating lag time, floating duration and matrix integrity decreased and vice versa. A reverse trend was observed on increasing the polymer concentration. The initial batches were prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces CO_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/mL, and the tablet becomes buoyant. It was found that as the amount of sodium bicarbonate increases, the floating lag time decreases. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. Thus, sodium bicarbonate 50 mg was essential to achieve optimum *in vitro* buoyancy (i.e., floating lag time of 1 to 2 minutes and floating duration of 12 hours). Therefore the concentration of the effervescent mixture was chosen so as not to compromise the matrix integrity with the possible shortest lag time and floating duration upto 12 h. It was observed that all tablets ascended to the upper one third of the dissolution vessels within a short time and remained floated until the completion of release studies. All the formulations had desired floating lag time (<4min) and total floating time between 4-12 hrs was found to be the function of concentration of BFM incorporated. This may be because of the fact that at lower concentrations, the BFM has lesser ability to form as gel. This was mainly due to

the evolution of CO_2 entrapped into the matrix of swollen polymer of the matrix and well protected by gel formation by the hydrated polymer resulting from interaction between the gas generating agent (sodium bicarbonate) and dissolution medium (0.1N HCl with pH 1.2) that leads to lowering the density and enabling the tablet to float.

These results indicate that the overall duration of buoyancy increases with an increase in the concentration and viscosity of HPMC and BFM. This is in agreement with literature reports showing that, with the increase in the polymer concentration, the viscosity of the gel layer around the tablet increases, thereby limiting the release of active ingredient. The higher concentration of polymer also helps to retain the generated carbon dioxide for a longer period thereby conferring good floating properties on the formulations. The gastro retentive tablets (F5-F8) with HPMC K4, exhibited buoyancy lag time of 0.9±0.32, 1.1±0.13, 1.7± 0.16, 2.0±0.10 minutes respectively and all floated for less duration of time (<12 h) as compared to tablets F1-F4 which containing BFM, with less buoyancy lag time of 1.0±0.11, 1.3±0.17, 1.5±0.22, 1.8±0.13 minutes respectively, with total buoyancy time of more than 12 h. The formulations F1 (BFM), and F5 (HPMC K4) settled on disturbing during dissolution studies which might be due to their higher moisture gain which was resulted in dramatic increase in swelling of tablets which in turn, showed decrease in floating capability upon disturbing. This indicated that molecular weight distribution or viscosity of gel forming polymers influenced the *in vitro* buoyancy.

Swelling index studies of RHCL floating tablets

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the formulation. floating tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the formulation. Swelling study was performed on all the batches (F1 to F8) for 12h. The results of swelling index are shown in figure 3. From the results it was observed that the swelling indexes were increased with increasing concentration of BFM. It was also observed that swelling increases as the time passes because the mucilage gradually absorbs water due to hydrophilicity of mucilage. Tablets containing BFM, showed less swelling index at the beginning but higher swelling index was observed at the end of 6 h. While HPMC K4, swelled rapidly at the beginning in 0.1N HCl and could not remain their matrix integrity up to 12 h. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. Swelling was strong enough to avoid premature disintegration as well as burst effect and retards the release of drug for a layer

period of time. For floating of tablet, there should be appropriate balance between swelling and water uptake.

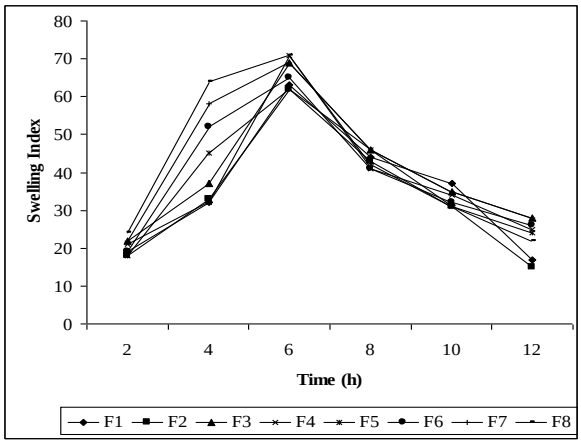


Figure 3: Swelling index profiles of the RHCL floating tablets

***In vitro* dissolution studies of RHCL floating tablets**

In vitro dissolution studies of all the formulations of floating tablets of RHCL were carried out in 0.1N HCl. The study was performed for 12 h and cumulative drug release was calculated at every one hour time interval. The results of *in vitro* release profile of different batches of RHCL are shown in figure 4. To study the effect of BFM on release rate of RHCL from the tablets, different concentrations of BFM (40 to 160 mg) were employed. After 1 h the drug dissolved from gastro retentive tablets of RHCL containing BFM was 20.92±0.81, 12.16±0.42, 9.315±0.10, 8.592±0.12 respectively was less than tablets containing HPMC K4 was 32.68±1.20, 26.53±0.64, 23.53±0.57, 20.04±1.08 respectively. This showed that HPMC hydrated more rapidly than BFM in the presence of 0.1 N HCl. But the tablets containing BFM (F3 and F4) showed the drug release up to 12 h in controlled manner without changing their physical integrity in dissolution medium. Moreover the HPMC containing tablets F5, F6, F7 and F8 could not retain their matrix shape until 12 h and they released the drug before 12 h. Tablets F1 could not retain its matrix integrity more than 8 h with release of 93.27 % of drug. Tablets F4 showed release of 90.63 % at the end of 12 h; and F5 lost their integrity just after 4 h with release of 95.65 % of drug. Tablets containing BFM (F3) showed constant drug release up to 12 hr (97.63). This controlled release of drug from F3 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix.

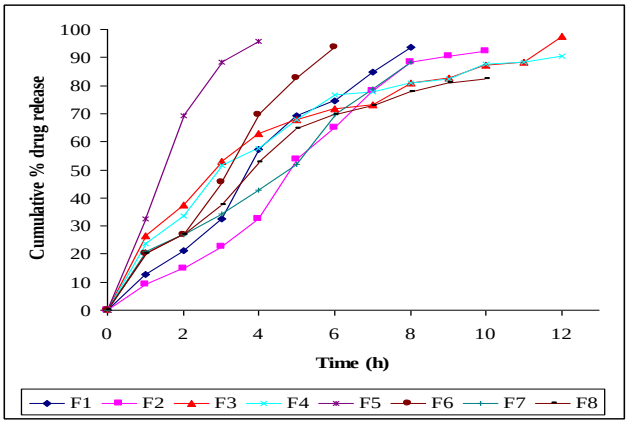


Figure 4: *In vitro* drug release profile of RHCL floating tablets of batches F1 toF8

The optimized batch of RHCL floating Tablet (F3) was selected on the basis of *in vitro* controlled drug release, *in vitro* buoyancy studies, buoyancy lag time (min), total buoyancy time (h) and their physical properties for further studies.

Drug Release Kinetic Study of RHCL Floating Tablets

The data obtained from *in vitro* dissolution study of optimized batch (F3) was fitted to zero-order, first-order, Higuchi and Korsemeyer-Peppas equations. The zero-order plots (r^2 =0.9844) and Higuchi models (r^2=0.9733) were found to be fairly linear as indicated by their high regression values. Zero order release describes the release rate independent of drug concentration. Higuchi square root kinetic model describes, release drug from the insoluble matrix as square root of time dependent process. It describes release of drug by simple diffusion mechanism. To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation. The slope value (n) for the optimized formulation was found to be 0.5171 (n is more than 0.5) suggest that the release of RHCL from floating tablets followed non-Fickian diffusion mechanism. However as indicated by the values of r^2 both of the models (Higuchi and Peppas) were found to be efficient in describe the release of RHCL from the floating Tablets.

Scanning Electron Microscopy

The SEM images of the tablet were taken before and after dissolution. The SEM images of RHCL floating tablet (F3) is shown in figure 5. SEM images showed intact surface without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Thus, it was concluded that the drug was released from matrix by diffusion mechanism.

Before dissolution study (0 hrs) **After dissolution study (12 hrs)**

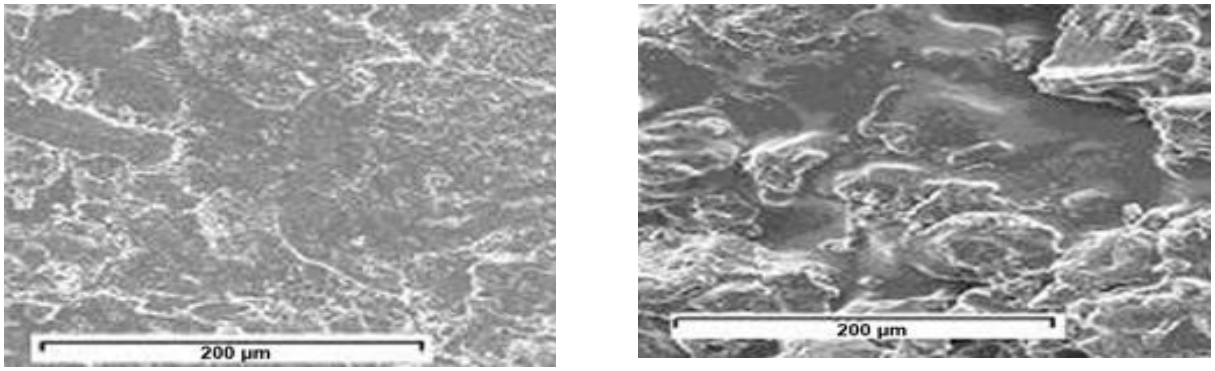
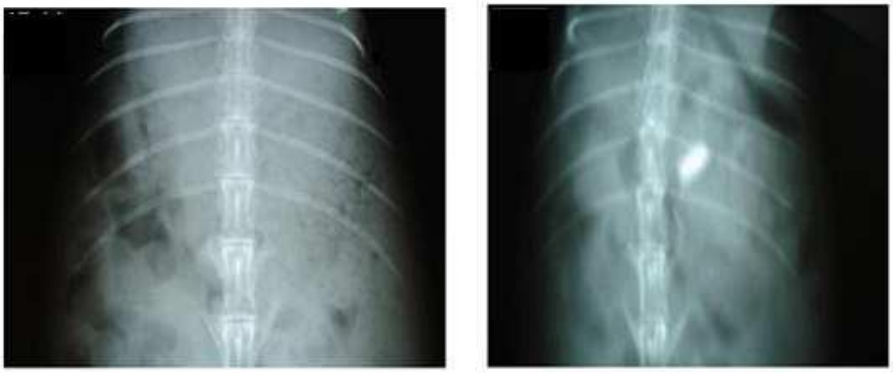


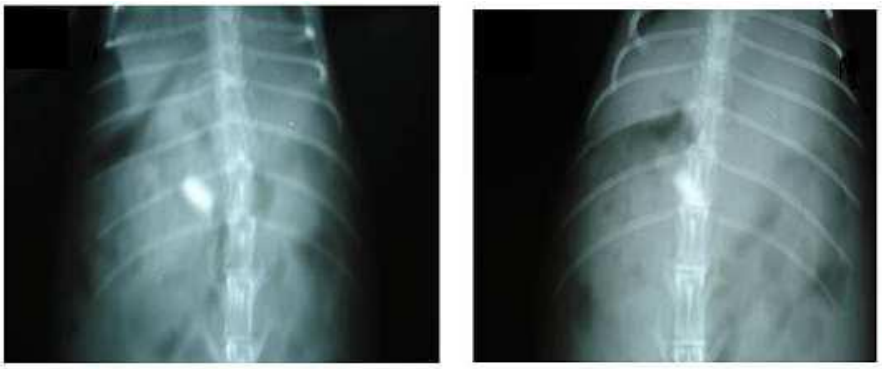
Figure 5: SEM images of RHCL floating tablet surface (F3)

Evaluation of gastric retention using X-Ray imaging

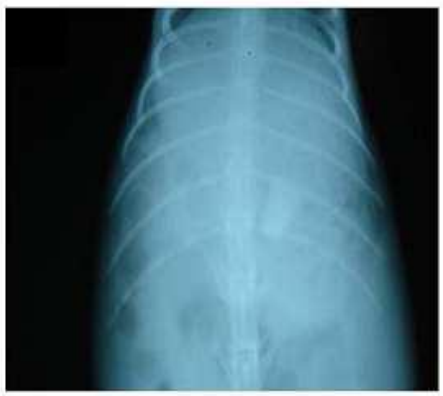
The selected tablet formula (F3) for *in vivo* investigation was reformulated with 15% $BaS0_4$ as opaque agent. *In vivo* study was performed in rabbits by using X ray imaging technique. Rabbit was placed upright posture for checking the position of tablet in gastric region by using X-ray machine. X-rays were taken at different time intervals like 1hr, 2 hr, 4hr, 8hr and 12hr. X ray imaging studies results showed that tablet was float more than 12 h in gastric region of the Albino rabbits. The X- ray images of optimized RHCL floating tablet (F3) at different time intervals is presented in figure 6.

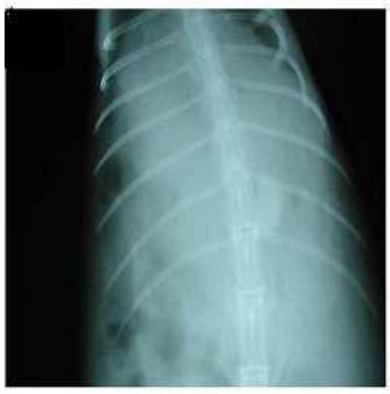


Without tablet **After 1 hr of tablet administration**



After 2 hr of tablet administration **After 4 hr of tablet administration**





After 8 hr of tablet administration **After 12 hr of tablet administration**

Figure 6: X-ray images of RHCL floating tablet (F3) in rabbit at different time intervals

Stability studies

The optimized floating tablet of RHCL (F3) was subjected for stability study. The tablets was investigated at 40°C/75%RH in both opened and closed high density polyethylene bottles for 3 months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters. The comparison of dissolution profile before and after stability studies of the best batch, the data indicated a good similarity between both the dissolution profiles. Similarly, no significant variation in all the parameters under the test period at 40°C/75%RH. Thus, it was found that the floating tablets of RHCL tablets (F3) were stable under these storage conditions for at least 3 months. The results of stability studies are presented in figure 7.

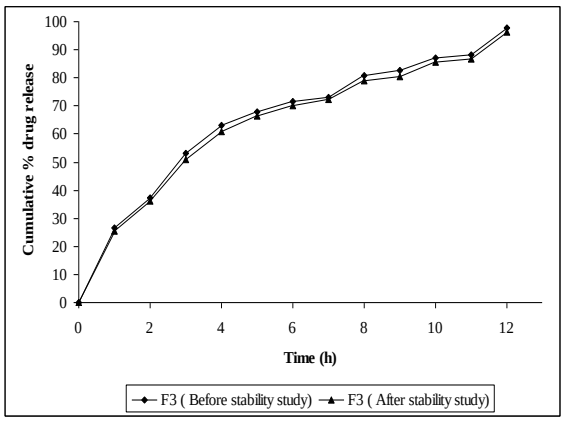


Figure 7: Comparison of *in vitro* release profile of RHCL floating tablet (F3)

CONCLUSION

The results from the physicochemical parameters of the mucilage manifested all the characteristics of a good pharmaceutical excipient that can be used for the formulation of floating tablets. In addition, the swelling ratio of the mucilage is optimum which aids in the floatation of

the tablet in the gastric fluids. From the present investigation, it is quite evident that incorporation of *Borassus flabellifer* fruit mucilage as one of the pharmaceutical excipients facilitates controlled release of the drug for prolonged time by maintaining the tablet in a floating condition in the gastric fluids due to the matrix forming capability of the mucilage. *Borassus flabellifer* fruit mucilage has swellable property; hence it can be used as a polymer in the development of a floating drug delivery system either singly or in combination with polymers like HPMC. But, the formulation with only *Borassus flabellifer* fruit mucilage is very much acceptable for formulating floating matrix tablets since it showed a sustained release effect for more period of time. This further helps to decrease the frequency of dosing; thus minimizing the side effects caused due to ranitidine HCl. In addition, since *Borassus flabellifer* fruit mucilage is easily available and the extraction includes very fewer steps, it is comparatively economical for bulk production of the drug.

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REFERENCES

1. Chien YW. Novel Drug Delivery Systems. 2nd Edn., New York: Marcel Dekker Inc; 1992.
2. Robinson JR and Lee VHL. Controlled Drug delivery. 2nd Edn., New York: Marcel Dekker Inc;1987.
3. Jain NK. Controlled and Novel Drug Delivery. 1st Edn. Delhi: CBS Publishers; 2004.
4. Ateshkadi A, Lam. N, Johnson CA. Helicobacter pylori and peptic ulcer disease. Cli Pharm 1993; 12: 34-48.
5. Menon A, Wolfgang A, Ritschel A, Sakr A. Development of and evaluation of monolithic floating dosage form for furosemide. J Pharm Sci 1994; 83: 239-245.
6. Talukder R and Fassinir R. Gastroretentive Delivery System: Hollow beads. Drug Dev Ind Pharm 2004; 4: 405-12.
7. Klausner EA, Lavy E, Friedmon M and Hoffman A. Expandable gastroretenstive dosage forms. J Control Release 2003; 90: 143-62.
8. Singh BN and Kim KH. Floating drug delivery system: approach to oral controlled drug delivery via gastric retention. J Control Release 2000; 63: 235-59.

9. Yeola PG, Khan S, Patel VF. Floating Drug Delivery System: Need and development. Indian J Pharm Sci 2005; 67(5): 265-72.
10. Histamine H2 antagonists. In: *Drug Facts and Comparisons*. 16th ed. St Louis, MO: Wolters Kluwer Co; 1996:1862-1876.
11. Somade S, Singh K. Comparative evaluation of wet granulation and direct compression methods for preparation of controlled release Ranitidine HCL tablets. Indian J Pharm Sci 2002;64:285.
12. Kapoor LD. Hand Book of Ayurvedic Medicinal Plants. 1st ed., Newyork: CRC Press; 2005:320-322.
13. Kokate CK. Practical Pharmacognosy. 4th ed., New Delhi: Vallabh Publication; 2006:120-123.
14. Government of India. Ministry of health and family welfare. Indian Pharmacopoeia Vol. I & II. The Controller of Publication, New Delhi; 1996: 762-10.
15. Martin A. Physical Pharmacy. 4th ed., Maryland USA: Lippincott Williams; 1991:205-208.
16. Knudsen LF, Curtiss JM. The use of the angular formulation in biological assays. J Am Stat Soc 1947; 42:282-96.
17. Cobby J, Mayersohn M, Walker GC. Influence of shape factors on kinetics of drug release from matrix tablets. Experimental J Pharm Sci 1974; 63:732-37.
18. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of sustained release gastro retentive drug delivery system for ofloxacin: *In vitro* and *in vivo* evaluation. Int J Pharm 2005; 304(1-2):178-84.
19. Rahman Z, Mushir A, Khar RK. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm 2006; 56:49-57.
20. Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195: 125-135.
21. Harries D, Sharma HL. GI transit of potential bio adhesive formulations in man: A scintigraphic study. J Control Release 1990; 12: 45-53.
22. Timmermans J, Gansbeke VB, Moes AJ. Assessing by gamma scintigraphy the *In vivo* buoyancy of dosage forms having known size and floating force profiles as a function of time. Vol I. Proceedings of the 5th International Conference on Pharmacy Technology, Paris, France, APGI, 1989: 42-51.

23. Girish S, Devendra KJ, Dhananjay M. Preparation and *in vitro* evaluation of bilayer and floating bioadhesive tablets of rosiglitazone maleate. Asian Journal of Pharmaceutical Sciences 2007; 2 (4): 161- 169.
24. Saroj KR, Prabhakar B. Bioadhesive Polymeric Platforms for Transmucosal Drug Delivery Systems. Trop J Pharm Res 2010; 09:91-104.
25. Peh KK, Wong CF. Polymeric Films as vehicle for buccal drug delivery: Swelling, Mechanical and bioadhesive properties. J Pharm Pharmaceutics Sci 1999; 2:53-61.