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# Development and Evaluations of Natural Gums-based Ranitidine HCL-loaded Floating Mucoadhesive Microspheres

**Rupali B. Patil[1], Amol P. Patil[2], Parag T. Bakshe[3], Rajesh Y. Chaudhari[4]**

*[1]Department of Quality Assurance, TVES HLMC College of Pharmacy, Faizpur, Maharashtra, India, [2]Department of Pharmacology, TVES HLMC College of Pharmacy, Faizpur, Maharashtra, India, [3]Department of Quality Assurance, TVES HLMC College of Pharmacy, Faizpur, Maharashtra, India, [4]Department of Pharmaceutical Chemistry, TVES HLMC College of Pharmacy, Faizpur, Maharashtra, India*

## Abstract

**Objective:** Ranitidine hydrochloride (RH) is a commonly used antacid as an $H_2$ receptor antagonist, which shows the maximum absorption at the initial part of the small intestine. Moreover, colonic metabolism is also responsible for poor oral drug bioavailability, which leads to a poor patient compliance. To improve therapeutic action and patient compliance, it is required to design a formulation which can increase the retention of the drug into the upper part of along with sustain release action. Thus, the aim of the present work was to investigate the role of novel polysaccharides in combination in the development of floating mucoadhesive microspheres for localized drug delivery of RH specifically into the upper parts of gastrointestinal tract. **Materials and Methods:** Ranitidine HCl floating, mucoadhesive microspheres, were successfully developed by ionic gelation method. **Results:** The RBG3 was found to be best as it releases Ranitidine HCl 99.98 ± 0.25% at the end of 14 h in a sustained manner. It was stable at 40°C/75% RH during accelerated stability studies carried out as per the International Council for Harmonization guidelines. **Conclusion:** The floating mucoadhesive microspheres for localized drug delivery of RH were developed.

**Key words:** Drug delivery system, mucoadhesive microspheres, ranitidine hydrochloride

## INTRODUCTION

Ranitidine hydrochloride (RH) is a commonly used antacid as $H_2$ receptor antagonist which shows maximum absorption at the initial part of small intestine. Oral route is the most widely used route of administration.[1] The major drawback of oral drug delivery is drug absorbed in a particular section of gastrointestinal tract (GIT) only or is absorbed to a different extent in various sections of GIT. This phenomenon drastically diminishes the time available for drug absorption after it, which is then followed by lesser bioavailability. The other difficulties are related with physiological differences like short gastric residence time and unpredictable gastric emptying time. Many difficulties are faced in designing controlled release systems for improved absorption and enhanced bioavailability. One of such difficulties is the failure to restrict the dosage form in the desired area of the GIT. An ability to prolong and control gastric emptying time is a valuable asset for drugs which reside in stomach for a longer period of time. To overcome this, gastro retentive systems were introduced.[2]

Thus, the aim of the present work was to investigate the role of novel polysaccharides in combination in the development of floating mucoadhesive microspheres for localized drug delivery of RH specifically into the upper parts of GIT.

## MATERIALS AND METHODS

RH was obtained as generous gift sample from Samrudh Pharma Pvt. Ltd, Tarapur, Mumbai. India. The Bhara gum (BG) and Guar Gum (GG) were purchased from Yarrow

**Address for correspondence:**
Dr. Amol P. Patil, Department of Pharmacology,
TVES HLMC College of Pharmacy, Faizpur,
Maharashtra, India.
E-mail: amolpatil311@gmail.com

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Chem Pharmaceuticals, Mumbai. All other materials, such as Sodium alginate (SA), Calcium chloride, Sodium bicarbonate, and Glacial acetic acid, were of analytical grade and were procured from commercial sources.

## Preparation of microspheres

The final batches of floating mucoadhesive Ranitidine HCl microspheres were prepared by ionic gelation method, which involved a reaction between SA and polycationic ions like calcium chloride ($CaCl_2$) to produce a hydrogel network of calcium alginate. Floating mucoadhesive microspheres were prepared using sodium bicarbonate as gas forming agent, BG as mucoadhesive polymer. GG and SA as drug release modifier. SA in the fixed (3% w/v) ratios was dissolved in purified water in one beaker then drug (Ranitidine HCl) was added into it with stirring into the same beaker. Natural gums in different polymer to polymer ratios selected on the basis of previously preliminary performed studies, like 2:1, 2:2, 2:3, 2:4 (prepared by placing the GG in fix quantity and BG invariable quantities), were added and stirred vigorously. After that gas form in G-agent Sodium bicarbonate in the ratio of (4% of alginate) was also mixed in alginate solution. The prepared slurry was added with 26 G syringe needle into the gelation medium into 5% w/v $CaCl_2$ solution contained in a 500 mL beaker at a stirring speed of 1200 rpm. 10% v/v glacial acetic acid was then added slowly while stirring for ionic gelation reaction. Stirring was continued for 1 h to complete the reaction and to generate spherical microspheres. Afterward, microspheres were recovered by filtration through a sintered glass filter under vacuum, dried in a hot air oven at 60° for 1 h. Different prepared floating mucoadhesive Ranitidine HCl microspheres formulations are represented in Table 1. The ionic gelation methods used the concept of cross-linking of polyelectrolyte in the presence of counter ions.[3-6]

## Characterization of microspheres

### *Fourier transform infrared (FT-IR) study*

The IR spectra of Ranitidine HCl were recorded by the potassium bromide dispersion technique. 2–3 mg of a sample of Ranitidine HCl was mixed with previously dried potassium bromide and kept in a sample cell. The cell was then fitted on a sample holder, and spectra were recorded by using FTIR spectrophotometer. Natural gum and prepared microspheres were recorded to determine any possible chemical changes of drug during microspheres preparation. Samples were scanned over the range of 4000–400 $cm^{-1}$ by using FT-IR (IRAffinity-1) (Shimadzu Co, Japan).

### *Surface topography of microspheres optimized formulation (RGB3) by scanning electron microscopy (SEM)*

Shape and surface morphology of the microspheres optimized formulation (RBG3) was examined and photographed using SEM (LEO 435 VP, LEO Electron Microscopy Ltd., England). Before scanning, film-coated pellets were uniformly coated with gold (Agar SputterCoater, UK) after fixing the sample on the stubs.[7]

### *Particle size analysis*

The particle size of the prepared microspheres was determined by a laboratory-scale optical microscope. Calibration of the instrument was done first and make sure that 1 unit of eyepiece micrometer was equal to 12.5 µm. Approximately 100 microspheres were calculated under 45 × magnifications. The average particle size of the prepared microspheres was determined using Edmondson's equation.[8]

$$D\ mean = nd/n$$

Where n = Number of microspheres observed and d = Mean size range

### *Swelling measurement*

A swelling study was performed in a dissolution test apparatus Type II. 100 mg of prepared microspheres were placed in the vessels containing 500 mL 0.1 NHCl (pH1.2) and allowed to rotate at 50 rpm and swell throughout 12 h. The microspheres were withdrawn at a fix time intervals and placed on blotting paper to remove an excess amount of water. The changes in weight of microspheres were determined at different time intervals until a constant weight was obtained. The swelling index was calculated using the following equation.[9]

**Table 1:** Formulations of floating mucoadhesive Ranitidine HCl Microspheres using Guar gum and Bhara gum

| Formulation Ingredients | Ranitidine: Gaur gum: Bhara gum | Stirring Rate (RPM) | NaHCO3 | Sodium Alginate |
|---|---|---|---|---|
| RGB1 | 1:2:1 | 1200 | 5 | 3 |
| RGB2 | 1:2:2 | 1200 | 5 | 3 |
| RGB3 | 1:2:3 | 1200 | 5 | 3 |
| RGB4 | 1:2:4 | 1200 | 5 | 3 |

$$\text{Swelling index (S)} = \frac{\text{Weight of microspheres after swelling} - \text{Initial weight of microspheres}}{\text{Initial weight of microspheres}} \times 100$$

### *In vitro* mucoadhesion study

The mucoadhesive behavior of the prepared microspheres was performed by *in vitro* wash-off test. In this test, a 4 cm × 4 cm piece of goat intestinal mucosa was taken and tied onto the paddle bottom of a USP dissolution test apparatus-II using a thread. A specified amount of microspheres, that is, 100 mg were spread onto the wet tissue specimen. The dissolution test apparatus was operated such that the tissue specimen was rotated at a speed of 25 rpm in 0.1 N HCl (pH1.2). At the end of h and 12 h, the weight of microspheres still adhering onto the tissue was calculated by using formula.[10]

$$\% \text{ Mucoadhesion} = \frac{\text{Amount of microspheres still adhering}}{\text{Amount of microspheres applied}} \times 100$$

### *Encapsulation efficiency*

100 mg of prepared microsphere were crushed carefully and incorporate in 100 mL of simulated gastric fluid (0.1N HCl pH 1.2 without pepsin). The prepared suspension was kept on a magnetic stirrer overnight, and after that, filtered through a 0.22 mm filter to separate shell fragments. The contents of drug were analyzed by spectrophotometer at 313 nm. The drug entrapment efficiency of each sample was determined in triplicate by using the formula.[8]

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical amount of drugs}} \times 100$$

### *In vitro* drug release study

An *in vitro* drug release study was performed in USP type-II dissolution test apparatus. An accurately weighed amount of microspheres equivalent to 100 mg of Ranitidine HCl was placed in the basket of dissolution vessel containing 900 mL of 0.1N HCl pH 1.2 stirred at 50 rpm and maintained at 37 ± 10°C for first 2 h and after that 900 mL phosphate buffer pH 7.4 was used as the dissolution media for next 12 h as a dissolution media. At 1 h interval, the appropriate quantity of samples was withdrawn from the dissolution basket, and the same volume was replaced by the dissolution media used at the time of dissolution was carried out, and the samples were sent to measure absorbance by using ultraviolet (UV) spectroscopy technique, and rate of dissolution of microspheres were determined.[9]

## RESULTS AND DISCUSSION

In the present work, the natural gum-based RH-loaded floating mucoadhesive microspheres were developed to improve the residential time of RH into upper GIT. The GG and BG plant polysaccharides in combination were investigated for their application in the mucoadhesive delivery system.

### FT-IR study

Ranitidine HCl, GG, BG, and other excipients compatibility testing was performed by mixing drug with excipients in equal proportion, then the mixture was kept under accelerated stability condition (i.e., 40°C and 75 ± 5% RH) for a period of 21 days in a glass vial. The IR spectrum was noted for the mixture after 21 days. The obtained FTIR spectrums were showed in Figures 1-4.

### Surface topography of microspheres optimized formulation (RGB3) by SEM

Shape and surface morphology of the microspheres optimized formulation (RBG3) was examined and photographed using SEM (LEO 435 VP, LEO Electron Microscopy Ltd., England). Before scanning, film-coated pellets were uniformly coated with gold (Agar SputterCoater, UK) after fixing the sample on the stubs. The obtained SEM Photographs are shown in the following Figure 5. The SEM


**Figure 1:** Fourier-transform infrared spectrum of ranitidine HCl

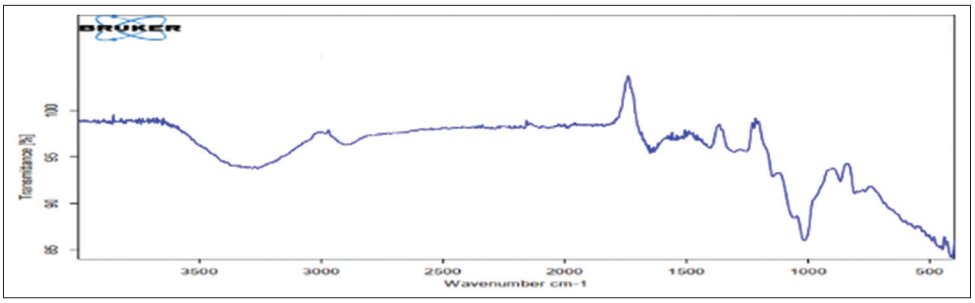


**Figure 2:** Fourier-transform infrared spectrum of guar gum

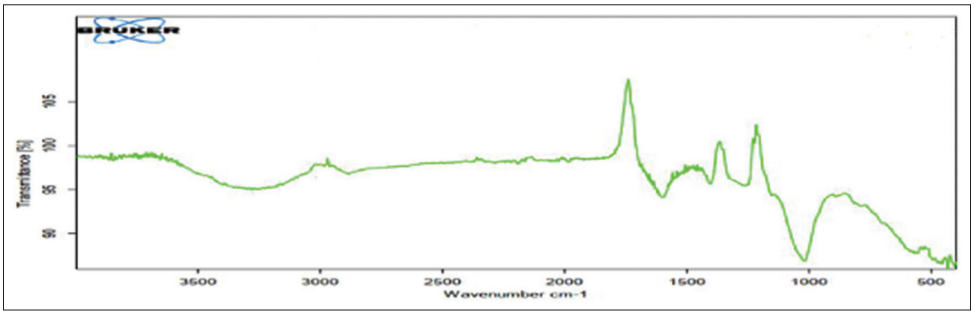


**Figure 3:** Fourier-transform infrared spectrum of bhara gum

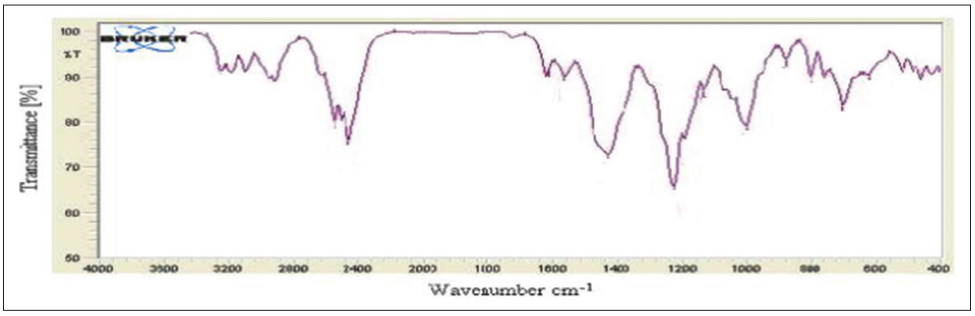


**Figure 4:** Fourier-transform infrared spectrum of ranitidine HCl with guar gum and bhara gum

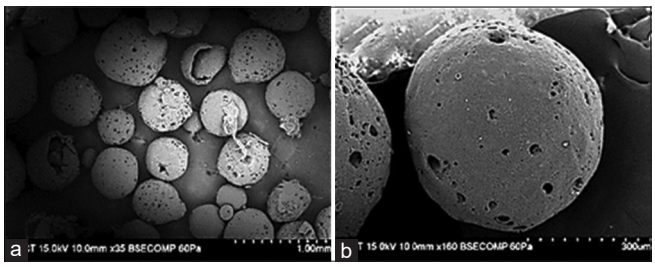


**Figure 5:** (a) Scanning electron microscopy (SEM) photograph of ranitidine HCl-loaded group of microspheres at ×35 magnification; (b) SEM photograph of ranitidine HCl-loaded single microspheres at ×160 magnification

analysis results showed the prepared floating mucoadhesive Ranitidine HCl microspheres were discrete and spherical. The SEM photographs indicated that microspheres were completely covered the coat polymer.

### *In vitro* mucoadhesion study

The mucoadhesive behavior of the prepared microspheres was determined by *in vitro* wash-off test. A specified amount of microspheres, that is, 100 mg were spread onto the wet tissue specimen. The dissolution test apparatus was operated such that the tissue specimen was rotated in 0.1 N HCl, pH 1.2. At the end of h and 12 h, the weight of microspheres still adhering onto the tissue was calculated using a formula, and mucoadhesive behavior was determined. The obtained results of the same are shown in Table 3.

The wash-off results indicated that all the formulations having a good percentage of mucoadhesion that were ranging from 80% to 88% for formulations RBG1–RBG4. The formulation RBG4 had showed the highest mucoadhesion of 88% as shown in the results at the end of 12 h. It was due

**Table 2:** Evaluation parameters of Ranitidine HCl floating mucoadhesive Microspheres

| Batch Code | Yield (%) | Particle Size (μm) | Encpsulation efficiency (%) | Swelling Rate (%) | In vitro Buoyancy (%) |
|---|---|---|---|---|---|
| RGB1 | 80.30±0.3 | 410±0.42 | 73.12±0.19 | 81.45 | 84±0.27 |
| RGB2 | 84.40±0.1 | 435±0.53 | 78.32±0.33 | 84.22 | 87±0.56 |
| RGB3 | 88.67±0.2 | 456±0.86 | 84.11±0.38 | 87.39 | 92±0.23 |
| RGB4 | 89.97±0.4 | 478±0.78 | 86.32±0.48 | 89.94 | 93±0.42 |

**Table 3:** Percentage Mucoadhesion of *In vitro* wash-off test for allmicrospheres formulations

| Time (Hrs) | Initial amount of microsphere attached (mg) | Microsphere remaining (in %) | | | |
|---|---|---|---|---|---|
| | | RBG1 | RBG2 | RBG3 | RBG4 |
| 0 | 100 | 100 | 100 | 100 | 100 |
| 6 | | 84 | 85 | 87 | 89 |
| 12 | | 80 | 82 | 86 | 88 |

**Table 4:** *In vitro* drug release data of floating mucoadhesive microspheres (mean + SD in parenthesis; n = 3)

| Sr. No. | Time in Hrs. | RBG1 | RBG2 | RBG3 | RBG4 |
|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 24.2±0.18 | 21.18±0.23 | 19.06±0.55 | 16.77±0.76 |
| 3 | 2 | 33.12±0.10 | 29.09±0.33 | 24.25±0.08 | 20.21±0.27 |
| 4 | 3 | 42.46±0.55 | 35.12±0.41 | 30.36±0.66 | 26.41±0.15 |
| 5 | 4 | 50.64±0.22 | 41.35±0.09 | 35.04±0.82 | 31.28±0.13 |
| 6 | 5 | 58.06±0.11 | 48.78±0.33 | 40.89±0.56 | 37.12±0.67 |
| 7 | 6 | 64.33±0.42 | 55.85±0.18 | 47.7±0.29 | 42.25±0.30 |
| 8 | 7 | 73.15±0.40 | 62.95±0.28 | 53.35±0.08 | 48.17±0.48 |
| 9 | 8 | 80.2±0.22 | 68.82±0.36 | 59.26±0.47 | 54.01±0.70 |
| 10 | 9 | 87.11±0.48 | 74.81±0.58 | 65.48±0.63 | 59.04±0.28 |
| 11 | 10 | 94.55±0.33 | 80.72±0.10 | 72.56±0.57 | 64.07±0.90 |
| 12 | 11 | 99.4±0.48 | 87.9±0.60 | 79.28±0.75 | 69.91±0.83 |
| 13 | 12 | | 94.98±0.46 | 85.3±0.20 | 75.45±0.50 |
| 14 | 13 | | 99.79±0.26 | 93.4±0.10 | 81.43±0.47 |
| 15 | 14 | | | 99.98±0.25 | 86.97±0.68 |

**Table 5:** Accelerated stability study of microspheres optimized formulation (RGB3)

| Parameters | Days | | | |
|---|---|---|---|---|
| | 7 | 14 | 21 | 28 |
| Appearance | No change | No change | No change | No change |
| Entrapment Efficiency | 84.11±0.38 | 84.10±0.29 | 84.08±0.23 | 84.08±0.12 |
| Particle size | 456±0.86 | 455±0.55 | 455±0.46 | 455±0.13 |

to the presence of a higher proportion of BG and due to the nature of the gum.

### *In vitro* drug release study

An *in vitro* drug release study was performed. An accurately weighed amount of microspheres equivalent to 100 mg of Ranitidine HCl was placed in the basket of dissolution vessel containing 900 mL of 0.1N HCl pH 1.2 stirred at 50 rpm and maintained at 37 ± 10C. for first 2 h and after that 900 mL phosphate buffer pH 7.4 was used as the dissolution media for next 12 h as a dissolution media. At 1 h interval, the appropriate quantity of samples was withdrawn from the dissolution basket, and the same volume was replaced by the dissolution media used at the time of dissolution was carried out, and the samples were sent to measure absorbance using the UV spectroscopy technique, and the rate of dissolution of microspheres was determined.[11]

From the evaluation of Ranitidine HCl floating mucoadhesive microspheres prepared [Table 2] using the GG and BG for various parameters like micromeritic evaluation, percentage yield, encapsulation efficiency, particle size analysis, *in vitro* buoyancy test, swelling study, *in vitro* mucoadhesion study, the formulation RGB3 had given the comparable results as compared to RBG4 [Table 4] but in case of *in vitro* drug release studies contains GG: BG ratio, that is, 2:3 gives the overall best results that's why the formulation RGB3 was selected as an optimized formulation of microspheres and subjected to the accelerated stability studies according to the ICH guidelines.

### Accelerated stability study of microspheres optimized formulation (RGB3)

The optimized formulation of microspheres RBG3 in accelerated stability studies, which were carried out in accordance of ICH guidelines, did not show any significant change in appearance, particle size, and entrapment efficiency when kept at different temperature and humidity condition and periods. This indicated that the RBG3 was stable at 40°C/75% RH as per the ICH guidelines [Table 5].

## CONCLUSION

The present study concludes that the natural gum that is GG and BG can be considered as excipients for the development of floating-mucoadhesive drug delivery. BG possesses an optimized value of viscosity. Prepared microspheres found suitable in buoyancy study with high encapsulation efficiency. The *in vitro* release study indicates that microspheres were able to release the RH up to 12 h into acidic media. Further investigations, such as stability studies, scale-up studies, and *in vivo* pharmacokinetic studies, are needed for the establishment of GG and BG as pharmaceutical excipients for microspheres drug delivery systems.

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