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Development and Evaluation of Gastro-retentive Floating Microspheres Containing Ranitidine Hydrochloride with Natural Polymers Tamarindus indica and Trigonella foenum-graecum

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ABSTRACT

The aim of this study was to formulate and evaluate floating microspheres of Ranitidine Hydrochloride. This formulation mainly used for inhibition of Gastric acid secretion. In the present study, preparation of ranitidine floating microspheres, evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of stirring speed and polymers ratio to match target release profile was investigated. Floating microspheres were prepared by Cross- linking emulsification method using Tamarind indica, Eudragit RS 100, Trigonella foenum graecum for mucoadhesive and as rate controlling polymer targeted drug delivery or to create protective barriers within the stomach. Floating drug delivery is considered as the most effective amongst the several approaches of gastro retentive drug delivery systems. The short gastric residence times (GRT) and unpredictable gastric emptying times (GET) are the two most important parameters that play a vital role in improving the bioavailability of drugs those are having an absorption window at the stomach. The gastric contents and remain buoyant in the stomach without affecting the stomachic emptying rate for a prolonged duration. The developed floating microspheres of ranitidine may be used in clinic for prolonged drug release in stomach there by improving the bioavailability.

Keywords: *Floating microsphere, Gastric retention time, Bioavailability, Sustained release, Absorption, Microsphere, Drug delivery , Floating drug delivery, Gastric acid.*

1. INTRODUCTION

Floating microspheres are gastro-retentive drug delivery system. If System is floating on gastric environment then its increases residence & fluctuation in plasma peak level and the drug is release slowly at the esteem rate. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Ranitidine Hydrochloride is competitive, reversible inhibiter of action histamine at the histamine H_2- receptor found in the gastric parietal cell and the meal-stimulated secretion of acid. It is widely prescribed in gastric ulcers, duodenal ulcers, zollinger-Ellison syndrome and gastro-esophageal reflux disease. Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by lesions in the lining of the stomach or duodenum, primarily caused by excessive gastric acid secretion, Helicobacter pylori infection, and prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs). Ranitidine Hydrochloride, a histamine H_2-receptor antagonist, is widely used in the treatment of peptic ulcers due to its ability to reduce gastric acid secretion and promote ulcer healing. However, its short biological half-life and the need for frequent dosing limit its therapeutic efficiency and patient compliance.

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. The Floating drug delivery system (FDDS) is improving the bioavailability of drugs that are poorly soluble or unstable at higher pH of the intestinal or colonic environment. In order to obtain local and sustained drug delivery in the stomach and proximal parts of

the small intestine, it is desired to have prolonged gastric retention of the drug. This helps to have improved bioavailability and therapeutic efficacy which may also results in the reduction in dosing frequency of the dosage form 2-6. The diminished efficacy of the administered dose may be observed due to inter-subject variability and short time of gastric emptying which may results because of incomplete drug release from the drug delivery system above the absorption zone (stomach ,upper part of small intestine).

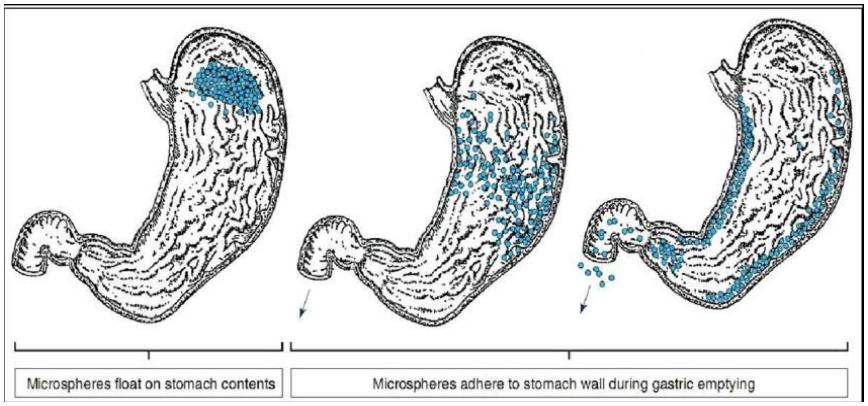

Figure 1: Floating Microsphere in Stomach

Moreover, it has been reported that drug delivery system is one of the commercial system which is attributed to obtain the higher bioavailability than that of the non floating system. The FDDS system is widely useful for the drugs which effectively act in the stomach and have absorption window in stomach.

2. MATERIAL AND METHODS

Materials

Ranitidine Hydrochloride was obtained Hetero drugs, Hyderabad, (India). Eudragit RS 100 was received from Evonik, (Mumbai, India). Span 80 Loba Chemie Pvt. Ltd, Mumbai, India. Epichlorhydrin A. B. Entreprises, Mumbai, India. The dried seeds of Tamarindus indica, Trigonella foenum graecum were purchased from the local market of Dehardun , India.

Table 1. Materials in the experiment.

S.No.	Drug
1.	Ranitidine HCl
2.	Fenugreek seeds
3.	Tamarind seeds
4.	Eudragit RS 100
5.	Tween 80
6.	Acetone
7.	Dichloromethane
8.	Isopropyl alcohol
9.	Hydrochloric acid
10.	Sodium bicarbonate
11.	Castor oil
12.	Span 80
13.	Epichlorohydrin
14.	Potassium bromide

15.	Liquid paraffin
16.	Phenol
17.	Conc H2SO4

Preparation of Floating Microsphere

The dried seeds of Tamarindus indica, Trigonella foenum graecum were heated in a hot air oven at 140˚C, for 45 minutes, cooled, and cracked, to separate their outside brown layer. Only the brown–red seed coat was collected and ground into fine powder. Then they were defatted with petroleum ether. After defatting with petroleum ether, the seed coat powder was extracted with methanol for 48 hours and filtered through Whatman No. 4 filter paper. The residues were re-extracted with an additional 100 ml of methanol. The solvent of the combined extract was evaporated under reduced pressure (34 – 36 kPa) using a rotary vacuum evaporator at 40˚C and the contents were air dried.

Preparation of Floating microspheres Floating microspheres containing Ranitidine Hydrochloride were prepared by using Cross-linking emulsification solvent evaporation technique. In this technique, floating microspheres prepared by taking drug and polymers ratio as:

1:0	3:1	1:1	1:3	1:4	1:5	1:9.

Aqueous phase was prepared by dissolving Ranitidine hydrochloride

into required amount of distilled water to get 20mg/ml drug solution. Varied amount of polysaccharide (as mucoadhesive polymer) and Eudragit RS 100 (as rate controlling polymer) were dispersed into drug solution to make 2% w/v dispersion containing both (Tamarind ,Trigonella foenum graecum polysaccharide and Eudragit RS 100) (Table2). Sodium bicarbonate (0.1:1with polysaccharide) was dissolved into aqueous phase. In this technique, floating microspheres prepared by taking drug and polymers ratio as :

1:0	3:1	1:1	1:3	1:4	1:5	1:9

Aqueous phase was placed for 4 h under magnetic stirring at 500 rpm for entire hydration of polysaccharide. Hydrated Aqueous phase was dispersed into castor oil by use of span 80 (1.0% v/v) as an emulsifying agent. The aqueous and oil phase ratio was placed in the ratio of 1:10 throughout the whole experiment. The emulsion was homogenized with an addition of 0.2 mL H_2SO_4 using high speed mechanical stirrer at 2000 rpm. Epichlorohydrin (4% v/v) was added as a crosslinking agent. Stirring was continued for 18 h at 45ºC. Finally, microspheres were collected by centrifugation followed by its washing using isopropyl alcohol and dried at 60ºC Air dry or vacuum dry the microspheres overnight. The percentage yield of was found to be 9.85 ± 0.01% w/w.

Table-2 Formulation of floating- microspheres.

Formulation Code	Tamarind indica/ Trigonella foenum graecum(%w/w)	Eudragit RS 100 (%w/w)	Tween 80(%w/w)	Epichlorohydrin (%w/w)	Dichloromethane (%w/w)
F1	100	-	0.5	0.5	2.0
F2	75	25	0.6	0.6	2.2
F3	50	55	0.8	0.8	2.5
F4	25	75	1.0	1.0	2.7
F5	20	80	1.2	1.0	2.9
F6	15	85	1.4	1.1	3.0
F7	10	90	1.6	1.2	3.2

Evaluation of Floating microspheres

Organoleptic property

Floating microspheres are designed to improve the pharmacokinetic profile of drugs by enhancing gastric retention and providing controlled release. Their organoleptic properties, such as appearance, colour, odour, taste, and mouthfeel, are influenced by the drug and excipients used in their formulation.

Particle Size Determination

The particle size can be determined by using an optical microscope (Radical Instrument, RXL.5T Amabala Cant, India) under regular polarized light, and mean particle size was calculated by measuring 100particles with the help of a calibrated ocular micrometer.

The average of particle size was determined by using Edmondson's equation, $D=\sum nd/\sum n$

Where, n=Number of microspheres checked;

D=Mean of size range.

Micro-meriticsproperties

Micromeritic properties have significant importance in pharmaceutical industry. The study of bulk and tapped density of a powdered material is utilized for selection of the suitable storage container, packaging substances and various process equipments in the manufacture of dosage form. Angle of repose, hausner ratio and carr's index are the parameters which are calculated in order to forecast flow properties of powders or granules.

Angle of Repose

The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as, **$\tan \theta = 2H/D$**

Where, 2H/D is the surface area of the free standing height of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

Bulk Density

Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined.

Bulk density = Weight of microspheres in g/Bulk Volume

Tapped Density

The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100 taps as well as1000 taps using tapped density apparatus such as OSC, India.

Tapped density = Mass of microspheres/Volume of microspheres after tapping

Percentage Compressibility Index/Carr's Index

The same tapping method was used to determined percentage compressibility index was calculated according to following formula,

%Compressibility Index = Tapped density-Bulk density

Hausner's ratio

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation .

Hausner's Ratio = Tapped density/Bulk density

Percentage Yield of Microspheres

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product /Total weight of excipients and drug) x 100

Determination of Drug Entrapment Efficiency

To determine the incorporation efficiency, 40 mg of microspheres were taken, thoroughly triturated and suspended in a minimal amount of dichloromethane. The suspension was filtered to separate shell fragments. Drug contents were analysed spectrophotometrically at 313.5 nm.

DEE= (Amount of drug actually present/Theoretical drug load expected)× 100

Accelerated stability studies

The optimized RH-loaded TI microsphere formulations under a sealed condition were kept at refrigerated temperature (5 ± 3°C) and in stability chamber maintained at 25 ± 2 °C/60 ± 5% Ranitidine hydrochloride tests. The samples were analyzed periodically for any change in average particle size and drug content.

3. RESULT AND DISCUSSION

Micromeritics properties

Micromeritic characteristics play a role in the pharmaceutical industry, particularly in determining the appropriate packaging materials, storage conditions, and processing equipment for dosage forms. Bulk density & tapped density are assessed to aid these decisions. Additionally, flow-related characteristics of powders are predicted by calculating the angle, Hausner ratio & Carr's index. The micromeritic analysis results for tamarind polysaccharide are given in Table 3. A similar assessment was achieved for fenugreek polysaccharide, with the outcomes abridged in Table 4.

Table 3: Micromeritics characterization of Tamarind indica

Micromeritics characterization	Tamarind
Bulk density	0.497±0.02g/cc
Tapped density	0.709±0.012g/cc
Angle of repose*(θ)	26.56±0.12
Carr's index (%)	21.88±1.2
Hausner's ratio	1.12±0.052

Table 4 :Micromeritric characterization of Trigonella foenum - graecum

Micromeritic characterization	Fenugreek
Bulk density	0.519±.004 g/cc
Tapped density	0.706±0.016 g/cc
Angle of repose*(θ)	33.91±1.21
Carr's index (%)	22.42±2.37
Hausner's ratio	1.25±0.021

Surface features by SEM

The surface morphology of the extracted polysaccharides was analyzed using SEM, a reliable method for examining particle structure at the micro- to nanoscale. This technique delivers vision into the texture, including the occurrence of surface roughness and pores. SEM images of Tamarind indica and Trigonella foenum- graecum are revealed in Figures 1 and 2. The tamarind powder appeared to have an uneven, coarse surface with particles of varying shapes and sizes (Figure 2), while the Trigonella foenum- graecum sample revealed irregularly shaped particles featuring visible pores and surface indentations (Figure 3).

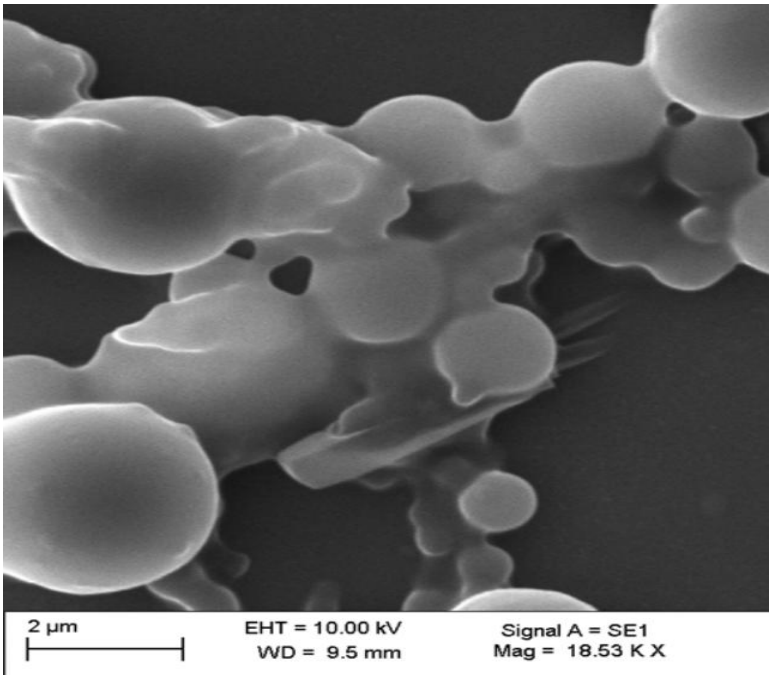

Figure 2 : SEM images of Tamarind Indica

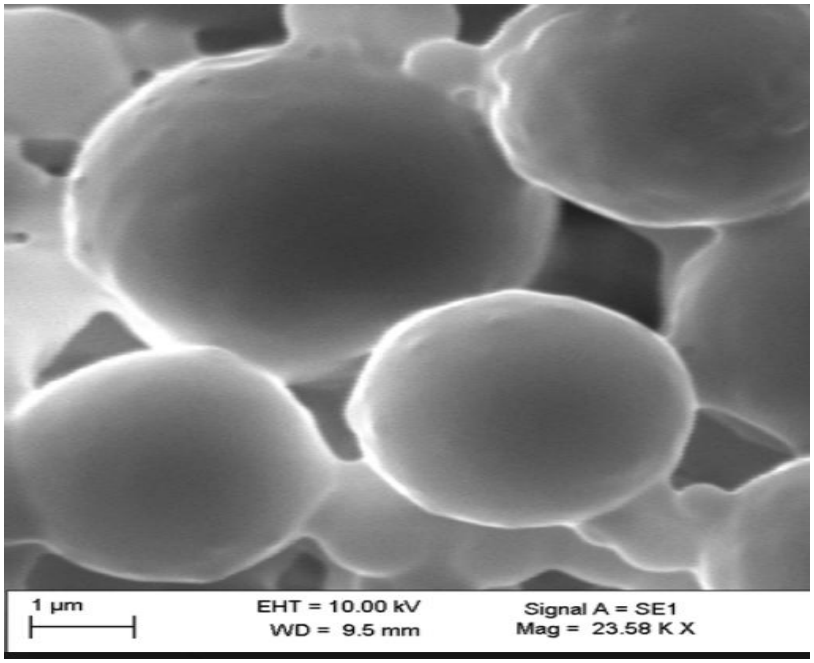

Figure 3 : SEM images of Trigonella foenum- graecum

Standard Calibration curve of Ranitidine hydrochloride

The standard calibration curve for ranitidine demonstrated a linear relationship, indicating that the drug follows Beer-Lambert's law within the concentration of 10 to 125 µg/ml (Figure 3). The calibration curve was created by intrigue the concentration of ranitidine hydrochloride (RH) on the X-axis and the corresponding absorbance values on the Y-axis. The absorbance for numerous concentrations in 0.1 M HCl (pH 1.2) is provided in Table 5 and the resulting calibration plot is presented in Figure 4.

Table 5: The absorbance standards for numerous concentrations in 0.1 M HCl (pH 1.2)

Concentration (µg/ml)	Absorbance at 313 nm
25	0.114
50	0.224
75	0.316
100	0.424
125	0.54

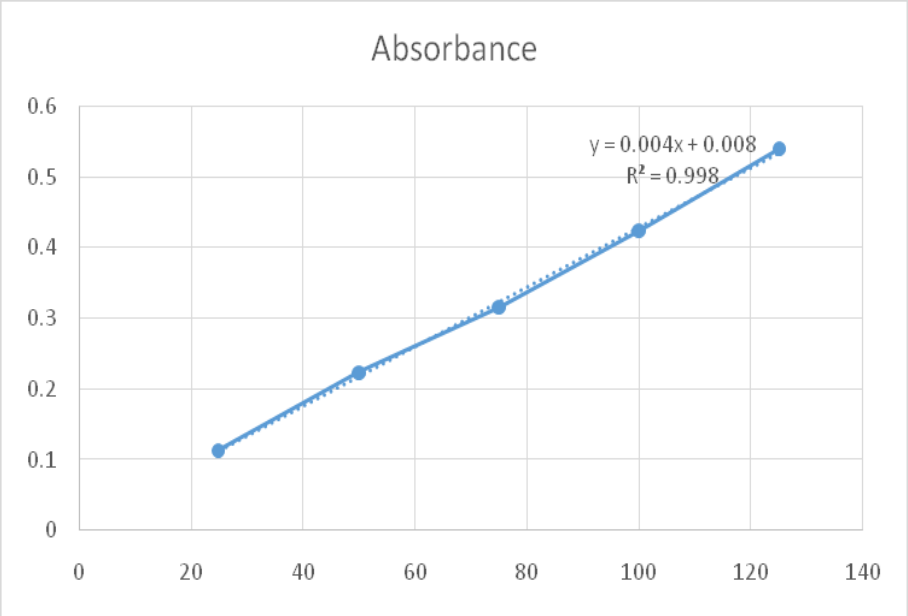

Figure 4: Standard Graph of RH in 0.1M HCl (pH 1.2)

FT-IR study Tamarind- Indica

The FT-IR spectra of RH, extracted Tamarind indica polysaccharide and prepared RH loaded microspheres were shown in figure 5. The characteristic peaks of RH and extracted polysaccharide were examined by using the previous reported literature. The FTIR spectra of RH showed the C-H out of plane vibration at 695 cm^{-1}, C-O stretching at 1200 cm^{-1} C-N stretching at 1121 cm^{-1}(Fig. 4a). The peak at 1370 cm^{-1} for S=O, at 1550 cm^{-1} for C=C stretching vibrations and the drug was found to be present in crystalline form.

The FTIR spectra of TI showed major peaks at 1052 cm^{-1}, 1457.22 cm^{-1}, 1655.25 cm^{-1}, 3403.48 cm^{-1} and 3718 cm^{-1}(Fig. 5b). The FT-IR spectra of RH were compared with the FTIR spectra of RH loaded TI microspheres. The study indicated that all the characteristic peaks of RH were present in the spectra of microspheres, which revealed that the drug was unchanged during the preparation of microspheres (Fig. 5 c). On the other hand, few new emerged peaks were observed in the spectra of microspheres at frequencies 1164 and 867 cm^{-1}, which can because of the formation of mono and di-ether linkage as the outcome of chemical cross- linking between extracted polysaccharide and epichlorohydrin. Absence of any new emerging peak in the FT-IR spectra of microspheres also confirmed the absence of any byproduct through epichlorohydrin mediated polysaccharide crosslinking.

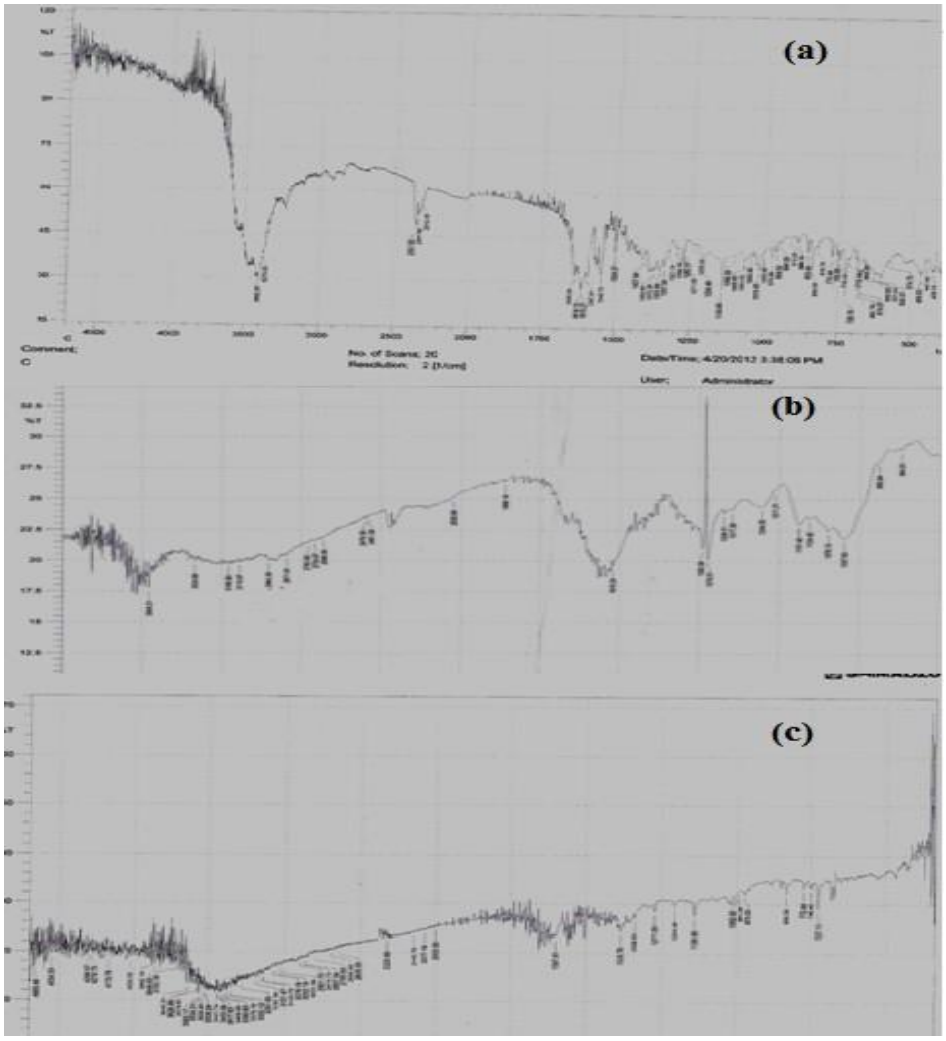

Figure 5: FTIR spectra of drug Ranitidine hydrochloride (a) Tamarind Indica polysaccharide (b) RH loaded floating-mucoadhesive TI microspheres(c).

FT-IR study Trigonella foenum graecum

FT-IR spectra of drug, polysaccharide and prepared RH loaded Trigonella foenum graecum microspheres are illustrated in figure 6. Similarly, the FTIR spectra also shows that all characteristic peaks of RH were present in the spectra of microspheres, which indicate that there was no chemical interaction occurred between the pure drug and the extracted Trigonella foenum graecum polysaccharide. Moreover, the drug remained stable during the preparation of microspheres. However, some new peaks at frequencies 1196 and 834 cm^{-1} were found in the spectra of RH loaded microspheres, which may be due to the formation of mono and diether linkage due to chemical crosslinking between TFG polysaccharide and epichlorohydrin. Moreover, absence of new peak in the spectra of microspheres also confirmed the absence of any byproduct of crosslinking process.

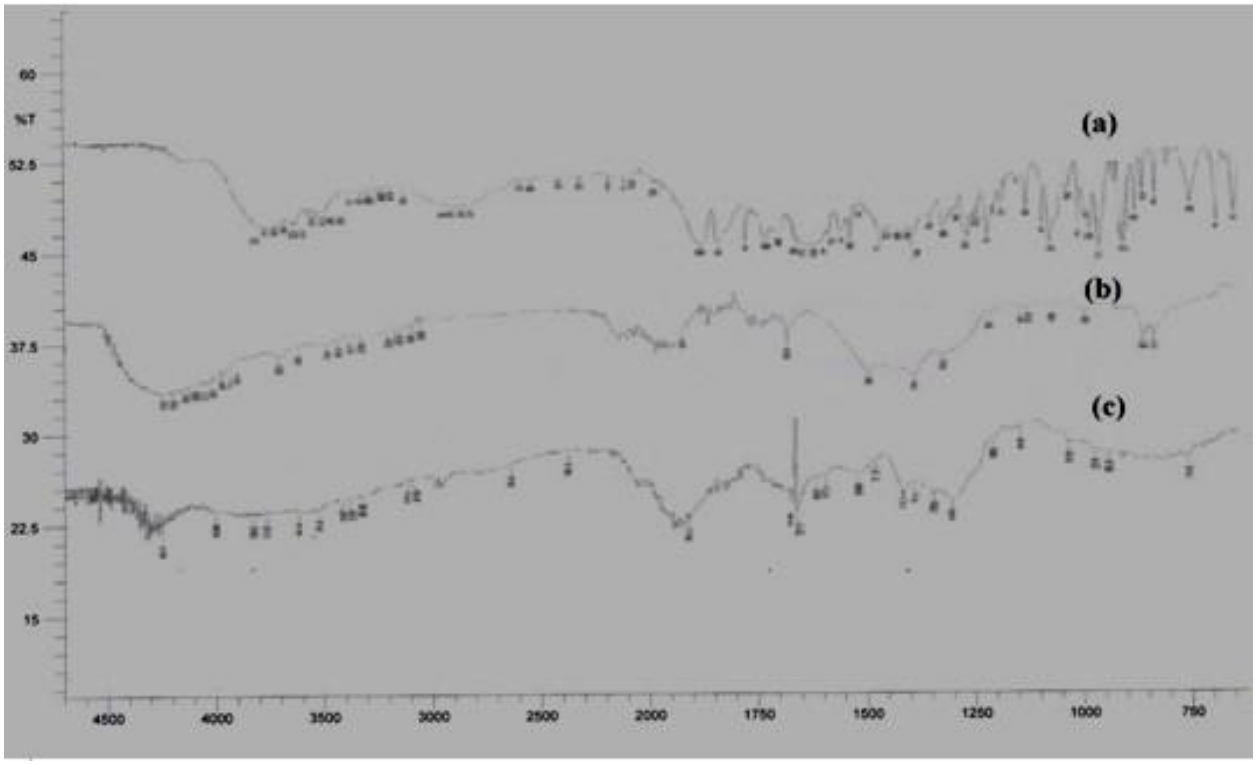

Figure 6: FTIR spectra of drug Ranitidine hydrochloride (a)Trigonella foenum graecum polysaccharide (b) and prepared microspheres (c).

Particle size analysis

The size of particles for all batches of Ranitidine hydrochloride-loaded Tamarind indica/ Trigonella foenum – graecum based microspheres was evaluated using straightforward microscopic techniques. The microspheres prepared with Ranitidine hydrochloride and Tamarind indica and Trigonella foenum graecum appeared spherical, discrete, and exhibited good flow properties. The average arithmetic diameter of these microspheres ranged from 5.38 to 7.84 µm, as shown in Table 6. Microspheres formulated without Eudragit RS 100 tended to have the largest particle size. The results from this learning suggest that variations in excipient concentration do not significantly distress the particle size of the prepared microspheres.

Table 6: Batch data and characterization of Particle size of different formulation based floating-microspheres.

Formulation Code	Tamarind indica/ Trigonella foenum - graecum (%w/w)	Eudragit RS 100 (%w/w)	Particle size (µm)
F1	100	-	4.56 ±1.44
F2	75	25	3.98±2.04
F3	50	50	2.76±0.84
F4	25	75	1.23± 0.71

Accelerated stability studies

The optimized Ranitidine hydrochloride (RH)-loaded Tamarind indica and trigonella foenum -graecum microsphere formulations were stowed in sealed containers at refrigerated temperature (5 ± 3°C) and also in a stability chamber maintained at 25 ± 2°C with 60 ± 5% relative humidity. The samples were periodically tested over a period of six months to

monitor any variations in average particle size and drug content.

The outcomes of the stability study for the microspheres stored at both room temp. & refrigerated conditions are summarized in Table 7. Throughout the storage period, no significant changes in particle size were observed; however, a slight increase in the particle size occurred under both storage environments.

Table 7: Mean Particle Size and Encapsulation efficiency of Ranitidine hydrochloride loaded microspheres

Storage conditions	Formulation code	Mean Particle Size (µm) Months			Encapsulation Efficiency (%) Months		
		0	3	6	0	3	6
5± 3 °C	F1	6.82±0.31	6.93±0.58	7.16±0.76	78.47±0.54	76.43±0.75	75.37±0.66
	F2	2.51±0.14	2.84±0.29	3.12±0.84	76.57±0.41	73.85±0.22	71.32±0.13
	F3	5.49±0.56	6.55±0.52	7.02±0.89	85.49±0.78	82.91±0.52	80.88±0.89
	F4	4.39±0.66	5.76±0.76	5.37±0.79	81.77±0.69	77.33±1.22	77.43±3.59
25±2 °C	F1	5.56±0.22	5.72±0.55	6.86±0.49	81.38±0.88	79.76±1.97	76.38±0.69
	F2	3.78±0.88	4.14±0.19	5.49±0.87	88.48±0.29	88.14±0.38	82.92±0.49
	F3	2.96±0.43	3.15±0.55	4.58±0.11	84.52±2.67	82.23±0.35	81.26±1.52
	F4	1.53±0.95	2.11±0.78	3.15±0.08	84.81±0.22	82.89±0.91	79.77±1.98

4. CONCLUSION

The present study successfully demonstrated the formulation and evaluation of floating microspheres of Ranitidine Hydrochloride using natural polymers, specifically fenugreek and tamarind gum, as gastroretentive drug delivery systems for the treatment of peptic ulcer disease. The microspheres were prepared using the Cross-linking Emulsification Method technique and exhibited satisfactory physicochemical properties, including good flowability, buoyancy, drug loading, and entrapment efficiency.

The natural polymers showed excellent potential as release-modifying agents. Among the formulations, the microspheres containing a higher concentration of fenugreek and tamarind gum displayed prolonged floating time (more than 12 hours) and sustained drug release over an extended period, up to 12 hours, which is desirable for effective ulcer therapy. In-vitro drug release followed a controlled release profile, suggesting the ability to maintain therapeutic drug levels in the gastric environment for a longer duration.

Thus, the study concludes that fenugreek and tamarind gums are effective natural polymers for developing floating microspheres of Ranitidine Hydrochloride. These microspheres offer a promising approach for improving gastric retention, enhancing bioavailability, and providing sustained release of the drug, which may ultimately improve patient compliance and therapeutic outcomes in the management of peptic ulcer disease.

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