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Research Article

Formulation And In Vitro Evaluation Of Gastroretentive Ranitidine Floating Microsponges

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ABSTRACT

Ranitidine hydrochloride (BCS class III) is mainly used for the treatment of gastric ulcer and esophagitis, but its low bioavailability leads to shorter half-life. The aim of this research work is to formulate ranitidine floating micro sponges to improve the gastric residence time and sustained release action. Ranitidine floating micro sponges were prepared by quasi emulsion solvent diffusion method using the polymers ethyl cellulose, eudragit S and eudragit RS and their combination to produce six formulations (F1 – F6). FTIR reports confirmed the absence of incompatibilities between the drug and excipients. This formulation was evaluated for micromeritic properties, particle size, encapsulation efficiency, percent buoyancy and percentage cumulative drug release. The formulation F6 containing the combination of ethyl cellulose and eudragit RS was found to be the best formulation showing 86 ± 1.7% buoyancy, 62.58±0.71 % encapsulation efficiency and % cumulative drug release of 94.50±0.07% after 8 hrs. The kinetic data analysis showed that it follows zero order model by non fickian release mechanism. Therefore, this ranitidine floating micro sponges provides a promising novel approach for the treatment of gastric ulcer.

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INTRODUCTION

Ranitidine is a Histamine H2 receptor antagonist. Chemically N-[2-[[[5-[(dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-N'-methyl-2-nitro-1, 1-ethene diamine hydrochloride is used in the treatment of gastro esophageal reflux disease (150 mg twice daily), erosive esophagitis (150 mg 4 times a day), Zollinger-Ellison syndrome (oral-150 mg twice daily). Despite these promising biological effects of ranitidine, a major drawback with ranitidine is its extremely low solubility in aqueous solutions which leads to low bioavailability. Its low aqueous solubility, which impairs its dissolution in upper gastric fluid producing problems to prepared systems including short half-life. It is determined that ranitidine degrades in neutral, alkaline and photolytic condition but remains stable in acidic condition it would be advantageous to design a formulation which prolongs gastric residence time in stomach. Various strategies have been undertaken to deliver ranitidine in gastric cavity by oro-dispersible tablets. These systems have potential for targeting drug molecule to its targeted site but have low drug loading capacity [1].

Microsponge is one of the modern and new approach to deliver a drug for longer period of time in a sustained manner. Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The size of the microsponges can be varied, usually from 5 – 300 µm in diameter, although the microsponge size may vary, a typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. Microsponge polymers have the flexibility to load a wide range of actives providing the benefits of improved product efficacy, tolerability, mildness and extended wear to a wide range of skin therapies. Improved in formulation stability to ensuring long term product efficacy and extended shelf life [2,3].

In oral application, the microsponges system has been shown to increase the rate of solubilization of poorly water soluble drugs by entrapping drugs in pores of microsponges as these pores are very small, the drug in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increase the rate of solubilization[4-7].

The aim of this research is the successful development of ranitidine floating microsponges with high drug loading capacity using biocompatible, safe and inexpensive polymers ethyl cellulose, eudragit S and eudragit RS 100 polymers to target gastric ulcer as a site-specific targeted drug delivery system.

MATERIALS AND METHODOLOGY

All the materials used in the formulations, evaluation and other experiments are listed below. The chemicals used were of laboratory reagent grade and were used as they were procured. The distilled water was used in all experiments.

Table 1: List of chemicals and reagents used.

	Materials	**Suppliers**
Drug	Ranitidine Hydrochloride	Yarrow Chem, Mumbai

Polymer	Ethyl cellulose Eudragit S 100 Eudragit RS 100	Yarrow Chem, Mumbai
Chemicals	Polyvinyl chloride Calcium chloride Dichloromethane	Yarrow Chem, Mumbai

METHOD OF PREPARATION

Ranitidine floating microsponges were prepared by quasi emulsion solvent diffusion method using calcium chloride as the porogenic solution. Solution of polymer was prepared in dichloromethane (organic phase). The aqueous solution of the porogen was prepared. The porogen solution was uniformly emulsified in polymeric solution, to form a w/o emulsion. An aqueous polyvinyl alcohol solution (aqueous phase) was prepared separately and previously prepared w/o emulsion was emulsified in it. This w/o/w emulsion was stirred on magnetic stirrer for 8 h. The dispersed droplets were solidified in the aqueous phase by evaporation of the solvent. The floating microsponges were filtered, dried at 60°C in the hot air oven and stored in desiccator till use [8,9].

Table 2: Formulation ingredients

INGREDIENTS	F1	F2	F3	F4	F5	F6
Ranitidine hydrochloride	150	150	150	150	150	150
Eudrgit RS	-	-	800	-	400	400
Eudrgit S	-	800	-	400	400	-
Ethyl cellulose	800	-	-	400	-	400
Calcium Chloride	1000	1000	1000	1000	1000	1000
Polyvinyl Alcohol	0.75	0.75	0.75	0.75	0.75	0.75
Dichloromethane	10	10	10	10	10	10

(Dichloromethane in ml and other excipients are in mg)

EVALUATION

Organoleptic evaluation

Organoleptic properties of drug like Colour, appearance and Odour were observed [9].

Melting point determination

Melting point of drug sample was determined by melting point apparatus. The small quantity of drug was taken in a capillary tube sealed at one end and was placed in digital melting point apparatus and temperature range at which the drug melts is noted [10].

UV spectroscopy-determination of lambda max

The stock solution of Ranitidine hydrochloride was made in 0.1N methanolic hydrochloride. 100 mg of Ranitidine hydrochloride was accurately weighed and dissolved in 100 ml of 0.1N methanolic hydrochloride. The stock

solution was further diluted with phosphate buffer of pH 6.8 to obtain a working standard of 100µg/ml. By appropriate dilutions of standard solutions, Ranitidine hydrochloride was scanned in the range of 200-400 nm to determine the wavelength of maximum absorbance for the drug.

Preparation of standard calibration curve of ranitidine hydrochloride

100 mg of Ranitidine hydrochloride was dissolved in 20 ml phosphate buffer of pH 6.8 and volume was made up to 100 ml in a volumetric flask with phosphate buffer of pH 6.8. From this stock solution different dilutions were prepared in the concentration range of 20, 40, 60, 80 and 100 µg/ml in 10 ml volumetric flask and absorbance was taken at 313 nm. Standard curve was prepared by the observations recorded by taking concentration on X axis and absorbance on Y axis [11].

Solubility determination

Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other property assays, mask additional undesirable properties, influence both pharmacokinetic and pharmacodynamic properties of the compound, and finally may affect the potency of the compound [12].

Solubility test of ranitidine hydrochloride was performed by using various solvents. Water, methanol, ethanol, acetic acid, 0.1 N Hydrochloric acid, sodium hydroxide, dichloromethane was used as solvents [13].

FTIR study

The drug and excipients were prepared and scanned from 4000-400 cm-1 in FTIR spectrophotometer and evaluated using FTIR peak matching method and the shift in the major peaks are noted for any incompatibility detection [15].

EVALUATION OF RANITIDINE FLOATING MICROSPONGES

MICROMERITIC PROPERTIES

- **Bulk density**

  An accurately weighed 10 gm sample of powder was placed into 25 ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm^3)

$$\textbf{Bulk density} = \frac{\textbf{Weight of sample}}{\textbf{Volume of sample}}$$

- **Tapped density**

  An accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm^3)

$$\textbf{Tapped density} = \frac{\textbf{Weight of sample}}{\textbf{Tapped volume}}$$

- **Carr's index (%)**

  Flow property of blend depends upon Compressibility index. The Carr`s index is an indication of the compressibility of a powder.

$$\textbf{Carr's index (\%)} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \times \textbf{100}$$

- **Angle of repose (θ)**

  The angle of repose is indicative of flowability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by

$$\theta = \tan^{-1} h/r$$

  Where, θ is angle of repose, h is height of the pile, r is the radius of the pile.

- **Hausner's ratio**

  The Hausner`s ratio is an indication of the compressibility of a powder. It is calculated by the formula[16],

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}} \times \textbf{100}$$

Scanning electron microscopy (SEM)

Surface morphology of the formulation was visualized by scanning electron microscopy. The samples were coated with gold under argon atmosphere using gold sputter module VG microtech in high vacuum evaporator and observed under various magnifications (100-1000×) [17].

Particle Size

The particle size of the ranitidine floating microsponge was measured using optical microscopic method and mean floating microsponge size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Percentage Yield

Percentage yield of ranitidine floating microsponge was calculated by dividing actual weight of product to total amount of all nonvolatile components that are used in the preparation of floating microsponge [18].

Drug content

The prepared floating micro sponges of ranitidine were assayed spectrophotometrically for the drug content at the maximum wavelength with proper dilution of formulations taking suitable solvent as blank. Taking accurately weighted 50 mg of prepared micro sponges and crushed it and mixed in a beaker containing 100 ml 0.1 N HCL and stirred it at 75 rpm for 2 hrs. Filtered it taken supernant filtrate and observed at 313 nm using UV spectroscopy.

Drug Entrapment Efficiency (DEE)

The amount of drug entrapped was estimated by crushing the floating microsponge and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank [19,20].

***In Vitro* Buoyancy**

Floating behavior of microsponge was studied using a USP dissolution test apparatus II by spreading the microsponge (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microsponges were collected separately. The floating microsponges were filtered, dried and weighed [21].

Dissolution test (*in vitro* drug release) of Floating microsponge

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Floating microsponge equivalent to the drug dose are added to 900 ml of the dissolution medium and stirred at 50 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy [22].

Kinetic study

The drug release kinetic studies were done by various mathematical models like zero order, first order, higuchi model, Hixson crowell model and korsmeyer peppas model. The model that best fits the release data is selected based on the correlation coefficient (r^2) values in various models. The model that gives high 'r^2' value is considered as the best fit of the release data.

Stability Studies

Ranitidine floating microsponges equivalent to 50mg were filled in hard gelatin capsules size 0. The filled capsules were manually packed in blister and the samples were maintained in a stability chamber under accelerated storage conditions 25 ± 2ºC, 40 ± 2ºC and 75± 5% RH for three months with humidity and temperature control. The samples were analyzed for physical changes, buoyancy, % drug content and % Cumulative drug release at 0, 30, 60, and 90 days and results were noted [23-24].

RESULTS AND DISCUSSIONS

Organoleptic evaluation

Table 3: Organoleptic evaluation

Colour	White to off white
Odour	Odorless
Taste	Bitter Taste

Melting point determination

Melting point of Ranitidine was found to be 134° C which indicates the purity of the sample.

UV spectroscopy-determination of lambda max

The lambda max determination of ranitidine was done in phosphate buffer of p^H 6.8, which was scanned between 200-400 nm in the UV spectrophotometer. It was found to be 313 nm.

Standard calibration curve of ranitidine hydrochloride

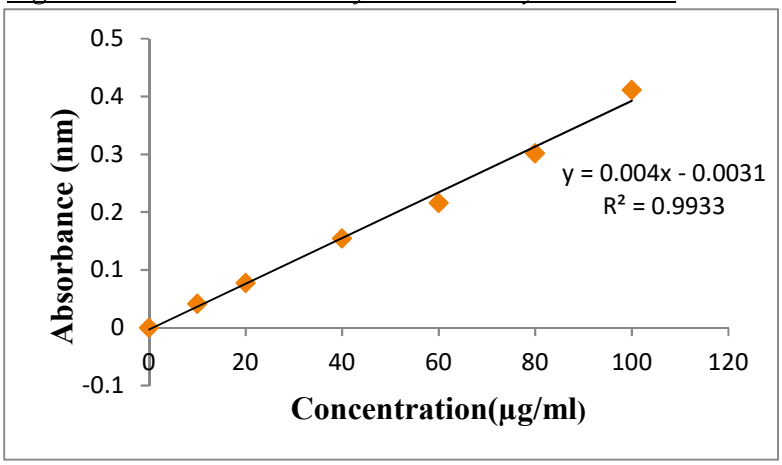
The absorbance of ranitidine HCL standard solutions containing 0-100µg/ml of drug was shown in table 4. Figure 1 shows a representative standard calibration curve with slope and regression coefficient of 0.004 and 0.993 respectively. The curve was found to be linear in the range of 0-100µg/ml at 313 nm. The calculation of the drug content and *in vitro* drug release is based on this calibration curve.

Table 4: Standard data of Ranitidine Hydrochloride

Concentration(µg/ml)	Absorbance(±SD)
0	0
10	0.042 ± 0.001
20	0.078 ± 0.001
40	0.155 ± 0.005
60	0.216 ± 0.004
80	0.302 ± 0.005
100	0.412 ± 0.004

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

Figure 1: Calibration curve of Ranitidine Hydrochloride



Solubility test

Solubility criteria of drug are important to check whether it is soluble or not. Ranitidine was freely soluble in water, Alcohol, acetic acid, distilled water, phosphate buffer p^H 6.8, slightly soluble in 0.1N HCL and dichloromethane.

FTIR spectroscopy

FTIR spectroscopy is a powerful technique, which is used for the identification of drug substances. The characteristic IR absorption peaks of ranitidine are 3035.96(C-H), 3317.56(N-H), 12691.16(C-N), 1373.32(N-O). It was shown in Figure 2.

The characteristic IR absorption peaks of prepared formulation at 3078.30(C-H),3344.57(N-H),1269.16(C-N),1327.07(N-O). All the characteristic peaks of ranitidine were present in spectra at within the respective wavelengths. Thus, indicating compatibility between drug and polymers. It shows that there was no significant change in the chemical integrity of the drug.

Figure 2: FTIR Spectrum of Ranitidine Hydrochloride Pure drug

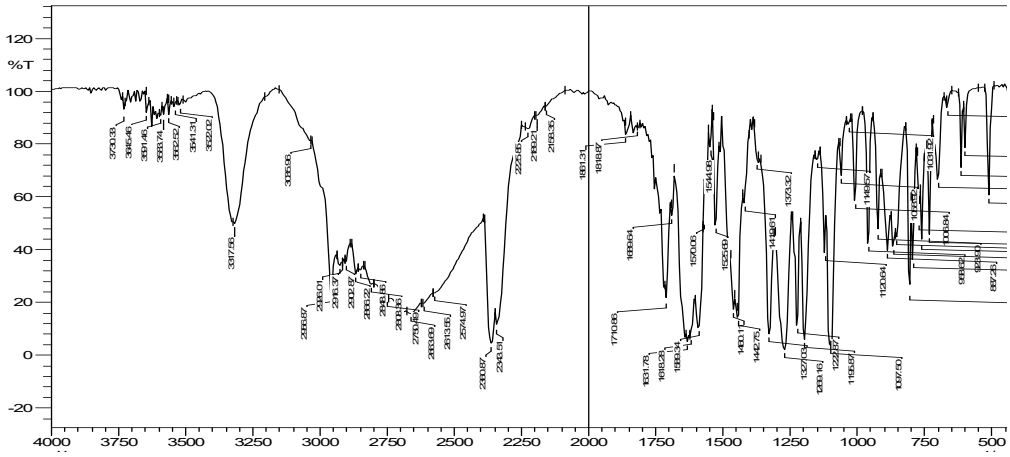


Figure 3: FTIR Spectrum of Ranitidine Hydrochloride + All excipients (Ethyl cellulose+ Eudragit S 100+ Eudragit RS 100+ Calcium chloride+ Polyvinyl chloride + Dichloromethane)

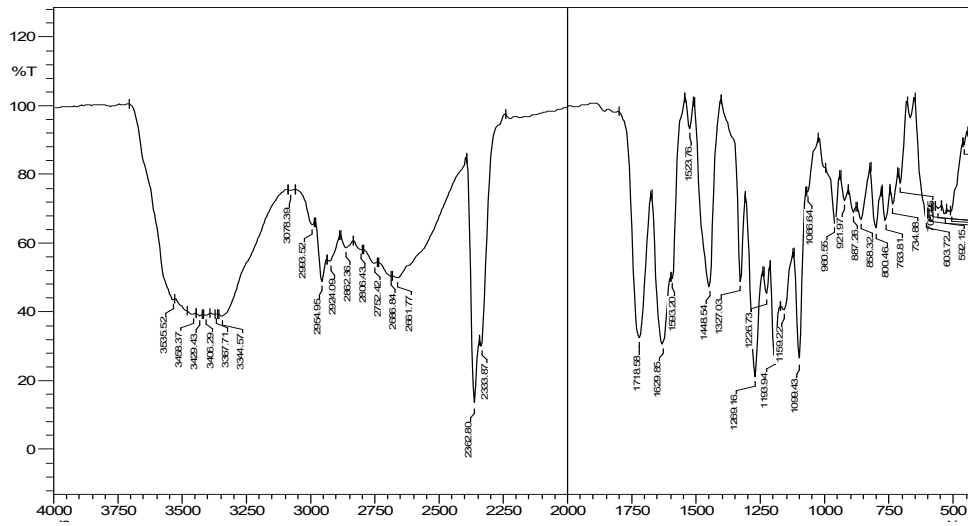


Figure 4: Ranitidine floating microsponges

Figure 5: Ranitidine floating microsponge capsules

Evaluation of Ranitidine Floating Microsponges

Micromeritic properties

The powder blend of microsponge were evaluated for their flow properties, the results were shown in the table 5 and the graph is plotted as the figure 6**,** 7. The bulk density were ranged between 0.24±0.010 to 0.37±0.28, tapped density between 0.31±0.45 to 0.45±0.32, carr's index between 16.66± 0.11 to 22.58± 0.31, hausner's ratio ranged in between 1.20±0.01 to 1.29±0.34, angle of repose between 20.5±0.06 to 28±0.61. These values indicate that the micrometric properties of microsponges are within the limits and they exhibit good flow properties.

Table 5: Micromeritic properties

Formulation code	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
F1	0.24±0.010	0.31± 0.45	25.4±0.61	22.58±0.31	1.29±0.34

F2	0.30±0.32	0.38±0.56	24.8±0.27	21.05±0.18	1.26±0.23
F3	0.36±0.21	0.44±0.1	21.5±0.34	18.18±0.14	1.22±0.02
F4	0.35±0.03	0.42±0.01	28±0.61	16.66±0.11	1.20±0.01
F5	0.35±0.37	0.42±0.34	25.5±0.34	16.66±0.23	1.20±0.01
F6	0.37±0.28	0.45±0.32	20.5±0.06	17.77±0.24	1.21±0.15

Each reading is an average of 3 determinations ± Standard deviation (SD)

Figure 6: Micromeritic properties (Angle of repose, Carr's index, Hausner's ratio)

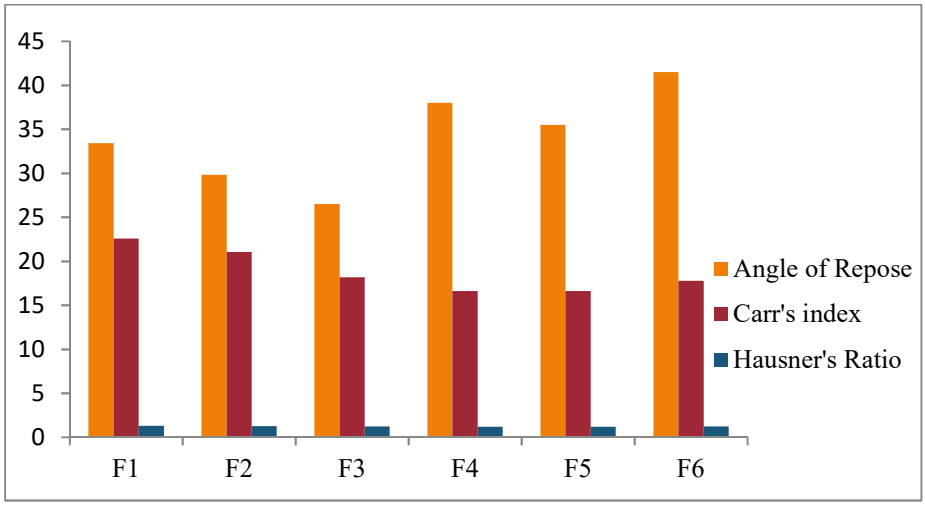


Figure 7: Micromeritic properties (Bulk density, Tapped density)

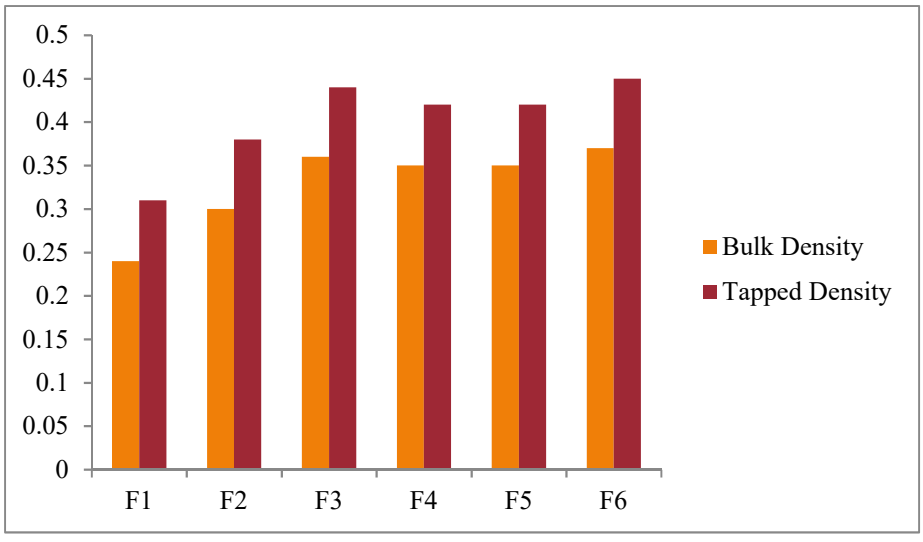


Figure 8: SEM image of floating microsponge

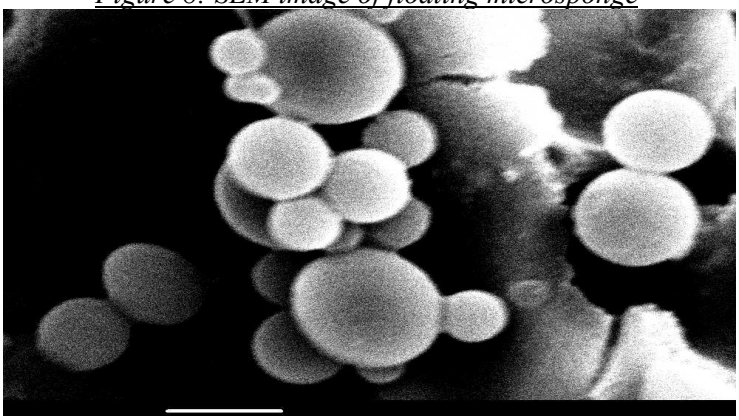
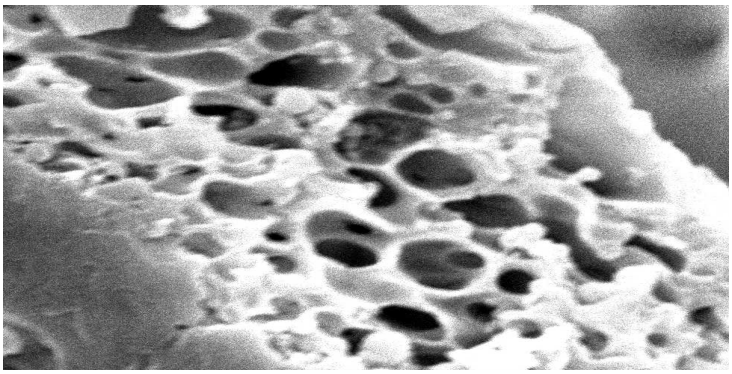


Figure 9: Floating microsponge with pore size



The external and internal morphology of floating microsponge were studied by SEM. SEM photograph of microsponge was shown in the figure 8, 9 in which the prepared floating microsponges were spherical with smooth surface and having porous structure containing void space.

Production yield

The production yield was found to be satisfactory in the range of 40.8±1.32% to 73.46±1.49% which is shown in the table 6 and the graph plotted as figure 10. The formulation F6 shows the highest value containing the polymers ethyl cellulose and eudragit RS 100.

Particle size

The particle size was found to be in the range 42.15±1.01% to 26.90±1.31%. The F1 exhibited the highest value of 42.15±1.01% and F6 shows the minimum value of 26.90±1.31%. The increase in the particle size is related to the increased viscosity due to the presence of ethyl cellulose, which results in the formation of larger sized droplets leading to larger floating microsponges. The results are shown in the table 6 and the graph is plotted as figure 11.

Drug content

The drug content was found to be in the range of 78.12±0011% to 93.87±0.044%. The highest value was found to be in F6 having 93.87±0.044%. The results were shown in the following table 6 and the graph plotted as figure 12.

Drug encapsulation efficiency

The encapsulation efficiency was found to be in the range of 52.08±0.04% to 62.58±0.71%. Among these the highest loading efficiency was found to be for F6 formulation which is 62.58±0.71%. The results were shown in the following table 6 and the graph plotted as figure 13.

Percentage buoyancy

The *In vitro* buoyancy test was carried out to investigate buoyancy of prepared floating microsponges and the results are shown in the table 6 and plotted graph as figure 14. It was found to be satisfactory in the range of 70±1.6% to 86±1.7%. The F6 shows the highest value of

86±1.4% which was prepared with the combination of ethyl cellulose and eudragit RS 100.

Table 6: Evaluation data of ranitidine floating microsponge

Formulation code	Production yield (%)	Particle size (µm)	Drug content (%)	Drug encapsulation efficiency (%)	Percent buoyancy (%)
F1	40.8±1.32	42.15±1.01	78.12±0011	52.08±0.04	84±1.4
F2	56.73±1.29	35.30±1.52	81.62±0.056	54.41±0.12	72±1.9
F3	71.24±1.43	33.60±1.22	91.5±0.063	61.0±0.31	70±1.6
F4	60.40±1.30	33.90±1.50	87.62±0.017	58.41±0.02	82±2.3
F5	64.89±1.20	31.20±1.44	85.125±0.033	56.75±0.09	74 ± 1.8
F6	73.46±1.49	26.90±1.31	93.87±0.044	62.58±0.71	86 ± 1.7

Each reading is an average of 3 determinations ± Standard deviation (SD)

Figure 10: Production yield

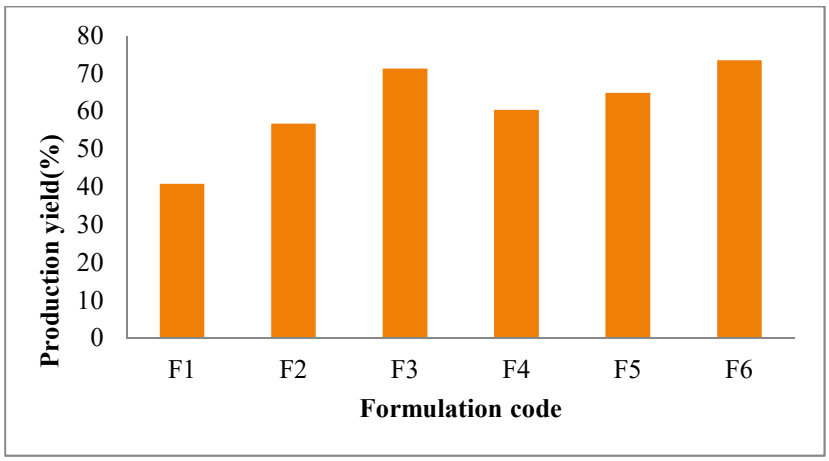


Figure 11: Particle size

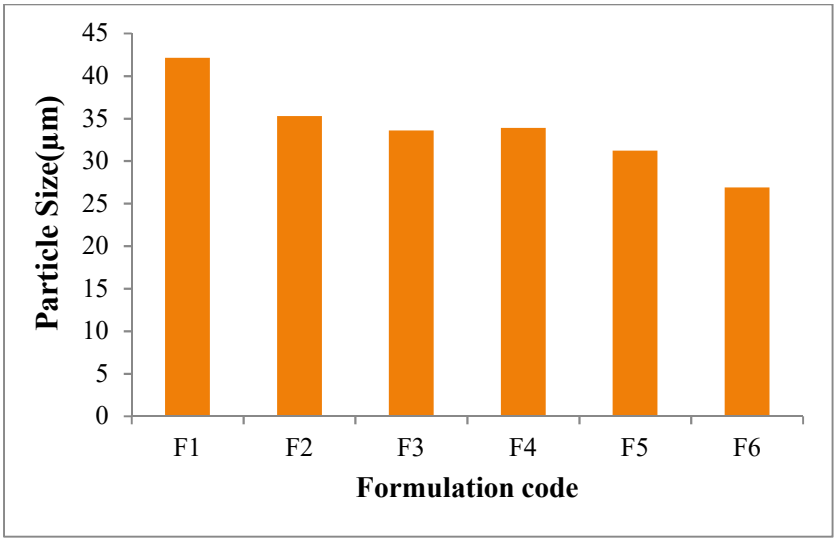


Figure 12: Drug content

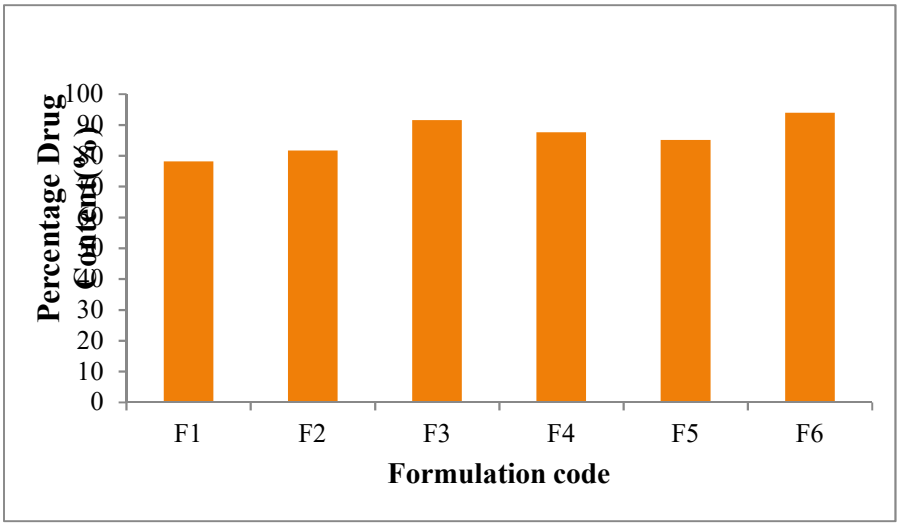


Figure 13: Encapsulation efficiency

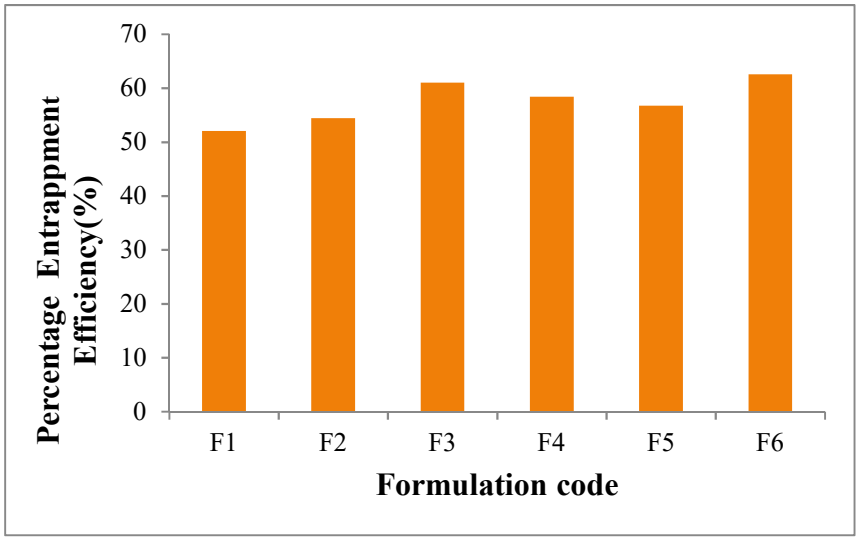
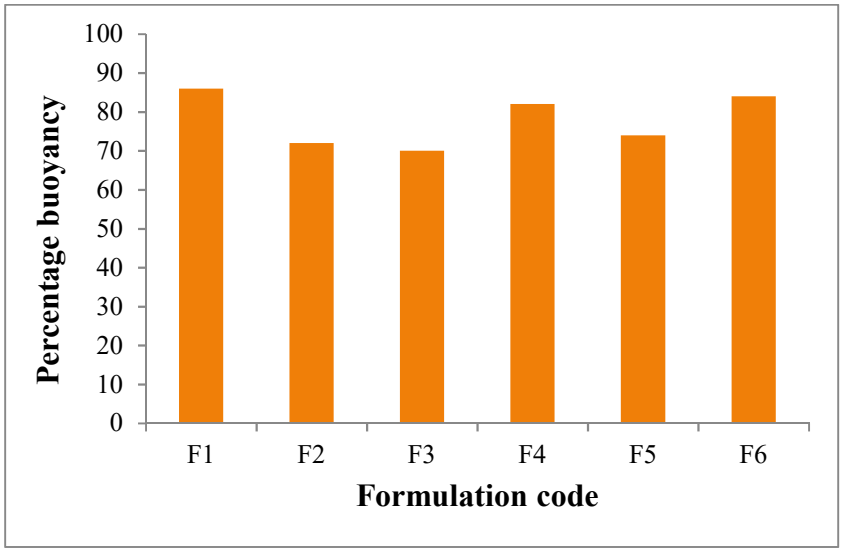


Figure 14 : Percentage buoyancy



***In vitro* dissolution studies of ranitidine floating microsponge capsules**

The *in vitro* drug release study of all formulations of ranitidine floating microsponges were carried out in 0.1N HCL using USP type-II apparatus and the results are shown in the table 7. The results were ranged in between 3±0.23% to 94.50±0.07. F6 shows the highest value of 94.50±0.07%. The plot of % Cumulative drug release (%) v/s time (hrs) was plotted and depicted as shown in figure number 12 and 13.

Table no 7: In vitro drug dissolution studies

Sl. No	Time (hr)	Cumulative Percentage of drug released (%)					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	12±0.02	1.5±0.13	9±0.14	6±0.47	3±0.23	10.50±0.47
3	2	18±0.08	12±0.45	24±0.78	9±0.56	15±0.22	22.50±0.32
4	3	28.5±0.05	15±0.23	33±0.14	15±0.03	25.5±0.24	46.50±0.24
5	4	33±0.03	24±0.58	43.5±0.24	34.5±0.14	30±0.21	63±0.45
6	5	43.5±0.12	28.5±0.24	49.5±0.28	43.5±0.36	36±0.45	75.0±0.63
7	6	52.5±0.15	33±0.63	63.33±0.21	46.5±0.17	54±0.63	82.50±0.14
8	7	58.5±0.01	37.5±0.52	61.5±0.85	52.5±0.32	61.5±0.41	91.50±0.02
9	8	61.5±0.07	46.5±0.44	73.5±0.21	60±0.74	88.5±0.06	94.50±0.07

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

Figure 14: In vitro drug profile of F1-F3

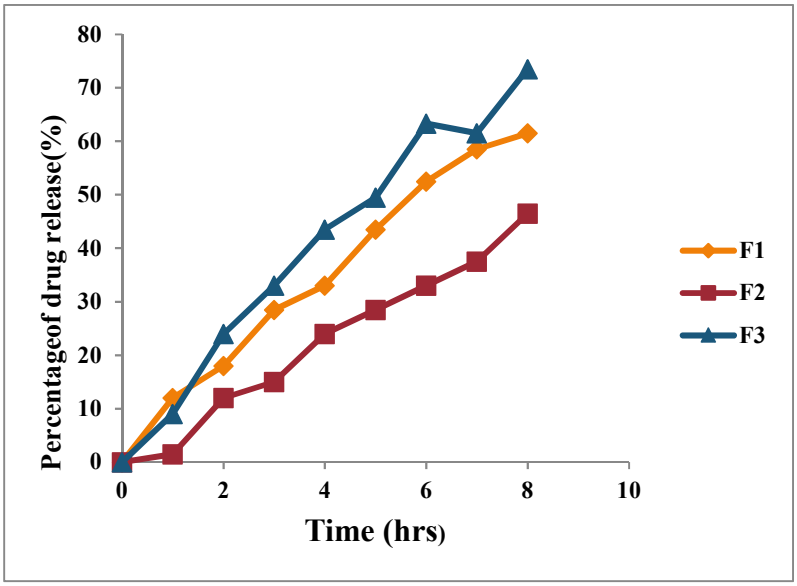
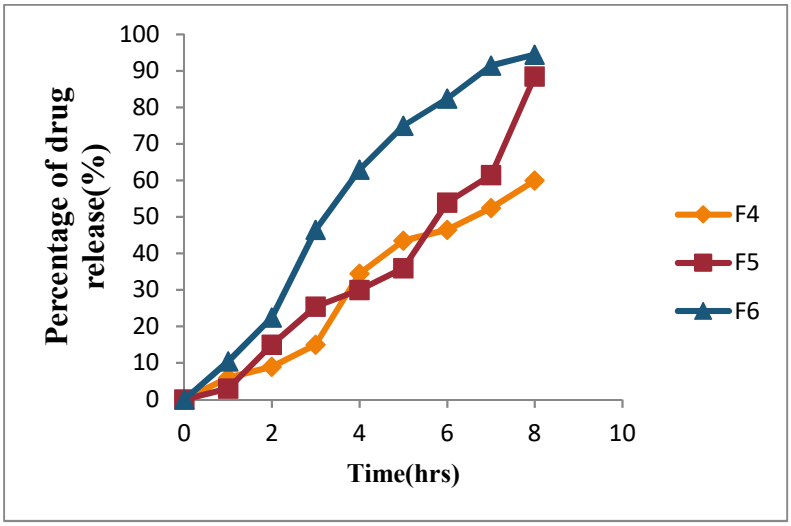


Figure 15: In vitro drug profile of F4-F6



Release kinetics of the optimized formulation

In the *in vitro* release study, F6 shows the highest value of drug release, 94.50±0.07% within 8 hrs which is formulated with the combination of ethyl cellulose and eudragit RS 100. The *in vitro* release kinetic data was applied to different kinetic models like zero-order rate kinetics, first-order, Higuchi's equations, Peppa's model to predict the drug release kinetic mechanism.

Figure 16: Zero model

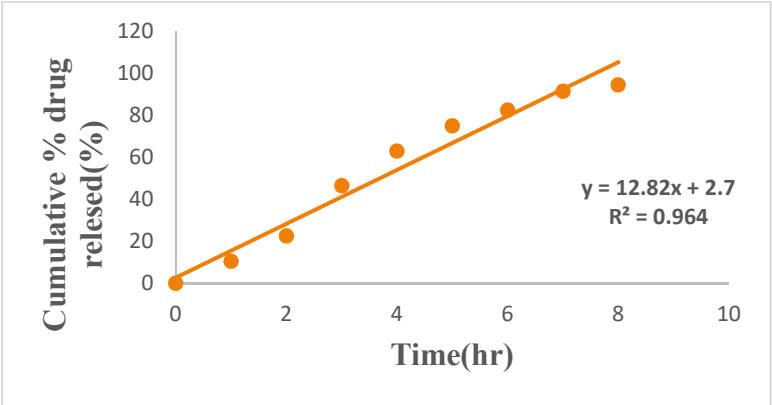


Figure 17: First order

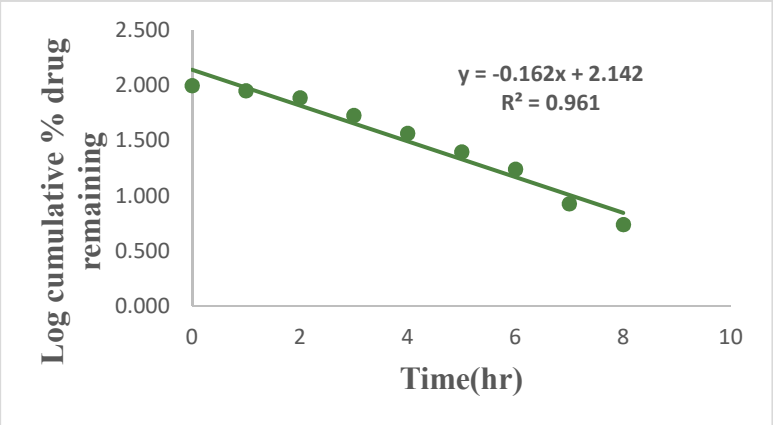


Figure 18: Korsmeyer peppas model

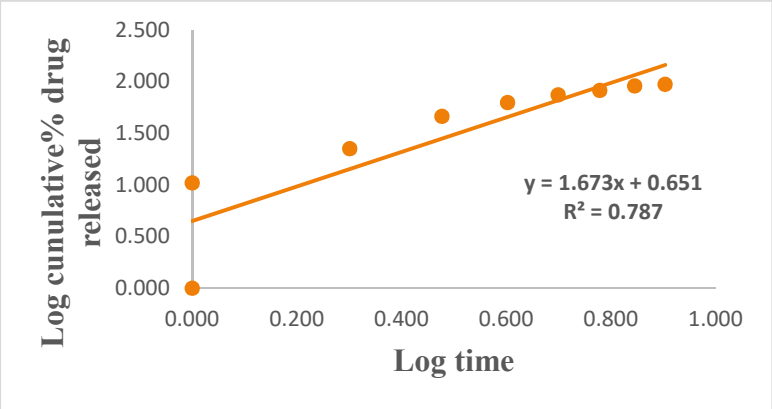


Figure 19: Higuchi model

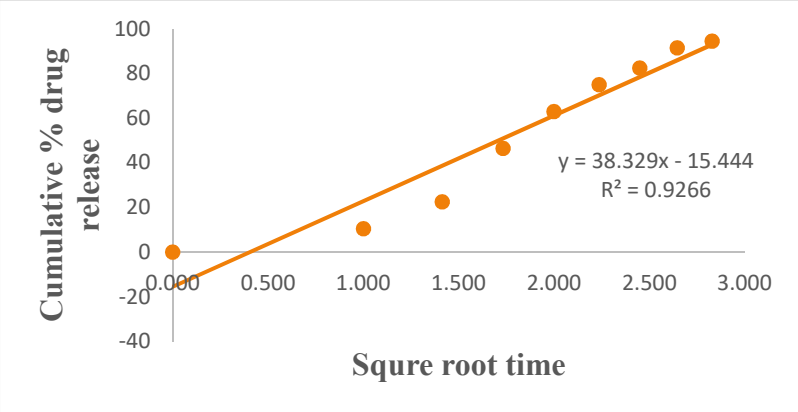


Figure 20: Hixson crowell model

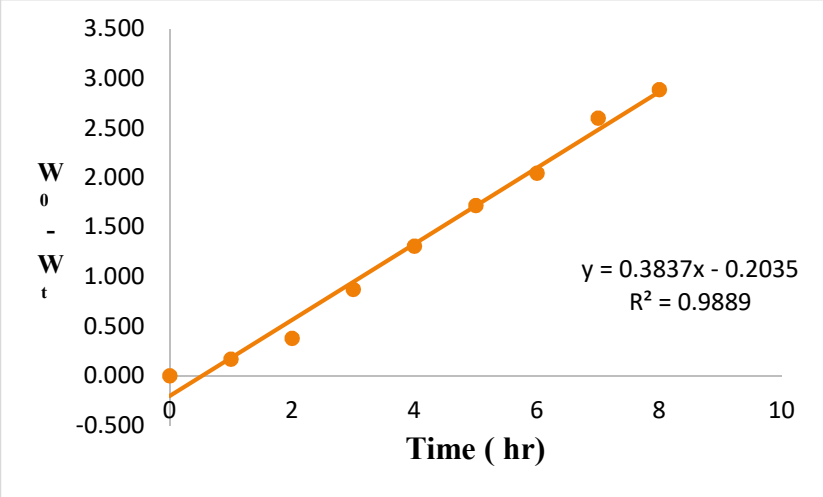


Table no 8: Kinetic profile of optimized ranitidine floating microsponges

Formulation code	Zero order	First order	Higuchi matrix	Hixson crowell	Korsmeyer peppas	N
F6	0.964	0.961	0.926	0.988	0.787	0.651

From the data (table no 8), it was shown that the drug release shows zero order model in which the rate of drug release is independent of concentration of drug and the drug release mechanism was found to be non fickian diffusion.

Stability studies

Stability study of the optimized formulation(F6) were carried out for 0 to 90 days. On physical observation of the stored samples there was found no change in Colour and shape of floating microsponges. The drug content, percentage buoyancy, *in vitro* dissolution data did not change significantly on storage at different periods. These studies suggest the physical and chemical stability of ranitidine floating microsponges. The results are shown in the table no 9.

Table no 9 : Stability study of ranitidine floating microsponges

Time (Days)	Physical changes	Percentage Buoyancy (%)	Percentage drug Content (%)	Cumulative percentage drug release (%)
0	-	86 ± 1.7	93.87±0.044	94.50±0.07
30	No change	85 ± 1.2	93.45 ± 0.012	93.12±0.31
60	No change	84 ± 1.0	92. 23± 0.023	93.12±0.04
90	No change	84 ± 1.3	91.05 ± 0.034	92.89±0.02

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

CONCLUSION

In this research work the suitability of ranitidine as the floating microsponge was studied. From all the above results, it clearly demonstrated the successful development of ranitidine floating microsponges which provides sustained release. The use of the inexpensive polymers like ethyl cellulose and eudragit RS make them safer and more biocompatible. So, this Gastroretentive floating microsponges have the potential for enhanced bioavailability and improved therapeutic response for the treatment of gastric ulcer.

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