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FORMULATION AND EVALUATION OF FLOATING MICROSPHERE H_2 RECEPTOR BLOCKER RANITIDINE HCl BY IONIC GELATION METHOD

Ajaykumar Tiwari*, Gaurang Patel and Nirav Rabadia

Department of Pharmaceutics, School of Pharmaceutical Science, Jaipur National University, Jaipur, Rajasthan, India

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Sodium alginate,
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calcium chloride

Correspondence to Author:

Ajaykumar Tiwari
Assistant Professor, Department of Pharmaceutics, School of Pharmaceutical Science, Jaipur National University, Jaipur, Rajasthan, India

E-mail: gaurang.pharma@yahoo.com

ABSTRACT

The present study involves preparation of floating microspheres of Ranitidine Hydrochloride with Sodium alginate, Guargum and Xanthan using ionic gelation method. Floating microspheres were aimed to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability. The formulations were evaluated for FTIR, drug loading, % entrapment, particle size, SEM, buoyancy, dissolution study and the drug release kinetics. The enhanced floatability of the formulation and its retention in GIT may attribute for the increased bioavailability and decrease in frequency of administration. Comparison of three polymers revealed HPMC to be a suitable candidate for sustained release.

INTRODUCTION: A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and will have the whole surface area of the small intestine available for absorption [1]. These considerations have lead to the development of oral controlled gastro retentive dosage forms possessing gastric retention capabilities. Thus Gastroretentive dosage forms, i.e. those designed to exhibit a prolonged gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery [2, 3, 4].

The multiple unit system has been developed to identify the merit over a single unit dosage form because the single unit floating systems are more popular but have a disadvantage owing to their "all-or-nothing" emptying process, leading to high variability of the gastrointestinal transit time.

The synthetic polymer has been used to prepare floating microspheres. The Present study was based on floating microspheres of both hydrophilic and acrylic polymers using Ranitidine hydrochloride (RH) as a model drug. It is an anti-ulcer drug that has been widely used in treating gastric and duodenal ulceration and also in Zollinger Ellison syndrome. It is poorly absorbed from the lower GIT and has a short elimination half life of 2-3 hours and bioavailability of 50%.

The drugs used in the treatment of ulcer include receptor blockers, proton pump inhibitors, drugs affecting mucosal barrier and act on the central nervous system[5]. Even though, wide range of drugs available for the treatment of ulcer, many do not fulfill the requirements and have many side effects such as arrhythmias, impotence and hemopoietic changes are noted [6]. H_2 antagonists unlike anticholinergics they do

not cause side effects like dry mouth, urinary retention etc. They do not delay gastric emptying time which may reflexly stimulate gastric secretion because of food remaining in the stomach for long time. Also it does not cause abdominal colic and diarrhea caused by proton pump inhibitors [7]. Out of the available category of drugs for the treatment of ulcer, H_2 antagonists class of drugs like Famotidine, Ranitidine are considered to be the safest drugs available, and hence, this drug has promising future if controlled release formulations are made.

MATERIAL: Ranitidine HCl was gifted from J.B. Chemical and Pharmaceutical LTD. Sodium alginate, guargum and xanthan gum was gifted from Hindustan Gum and Corporation. All other material used was analytical grade.

METHOD:

Preparation of Floating Microsphere: Floating microsphere of Ranitidine Hydrochloride was prepared by ionotropic gelation technique using different proportion of polymers as shown in table 8.4.1. Sodium alginate was dissolved in distilled water at a concentration of 2% (w/v), the solution was stirred thoroughly after Ranitidine HCl of different ratio (Drug: Polymer = 1:1, 1:2, 1:3) and calcium carbonate (Polymer: $CaCO_3$ = 1:1) were added. The gelation medium was prepared by dissolving calcium chloride (3% w/v) in 2% glacial acetic acid. The homogenous alginate solution was extruded using 21G syringe needle into the gelation medium. The distance between the edge of the needle and surface of gelation medium was about 10cms. The gel microspheres formed were left in the solution with gentle stirring for 30 min at room temperature to improve mechanic strength. After that, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr and stored in desiccators.

Evaluation parameters:

IR Spectroscopy: FT-IR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drug and polymers. The IR spectra of physical mixtures were studied using KBr disc method.

Particle Size Analysis: The particle size of floating microspheres in all samples was analyzed using optical microscopy method.

Determination of yield of Microsphere: Percentage yield of each batch of prepared floating microsphere was calculated by dividing actual weight of product to total weight of all non-volatile components that were used in preparation of floating microsphere and is respected by following formula:

$$\% \text{ Yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100$$

Determination of % Drug Loading and Entrapment Efficiency: The Ranitidine HCl content in prepared floating microsphere was determined by dissolving 10mg of ranitidine hydrochloride loaded floating microsphere in 100 ml of simulated gastric fluid with agitating at room temperature for 12 hr. After 12 hr, filter it through 0.45micrometer membrane filter. The rug concentration was determined spectrophoto-metrically at wavelength of 313nm. Now % drug loading and entrapment efficiency was calculated using following equation.

$$\% \text{ Drug Loading} = \frac{\text{Weight of drug present in microspheres in gms}}{\text{Weight of quantity of microspheres in gms}} \times 100$$

$$\text{Entrapment Efficiency} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

***In vitro* evaluation of Floating Ability of Floating Microsphere:** *In vitro* floating ability of prepared floating microsphere was determined by placing 1 gms of each formulation in USP type 2 dissolution test apparatus containing simulated gastric fluid of pH 1.2. The medium was stirred at 100 rpm at 37±0.5^{o}C. After 12hr, both fraction of microsphere (floating and settled microsphere) were collected, dried and weighed separately. Now, % buoyancy was calculated using following formula:

$$\% \text{ Buoyancy} = \frac{Q_f}{Q_f + Q_s}$$

Where, Q_f = Quantity in weight of floating microsphere, Q_s = Quantity in weight of settled microsphere

***In vitro* Drug Release Study:** The *in vitro* release of Ranitidine HCl from different formulation was examined by using USP dissolution apparatus type 2 at 37±0.5°C. The amount of floating microsphere equivalent to 100mg of drug was placed in the basket. Simulated gastric fluid without enzyme used as a dissolution medium and temperature was maintained at 37±0.5°C and rotation speed at 100rpm.

An aliquot of 5ml solution was withdrawn at specific time interval and replaced it with dissolution medium. The sample was analyzed by spectrophotometrically at 236nm after filtration through 0.45 µm membrane filter.

Data Analysis of Release Studies: The *in vitro* release data obtained was treated to Zero order, First order, Higuchi, Hoffenberg and Korsemeyer – Peppas to know precisely the mechanism of drug release of the floating microspheres.

Stability Studies: A study of stability of pharmaceutical product is essential. These studiers were designed to increase the rate of chemical and physical degradation of the drug substance or product by using exaggerated storage condition. Optimized formulations were packed in amber colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40°C/ 75%RH for 3 months and evaluated for the physical appearance and drug content, %buoyancy and entrapment efficiency at specific interval of time. Finally, at the end of 3 months and *in vitro* release studies were also conducted.

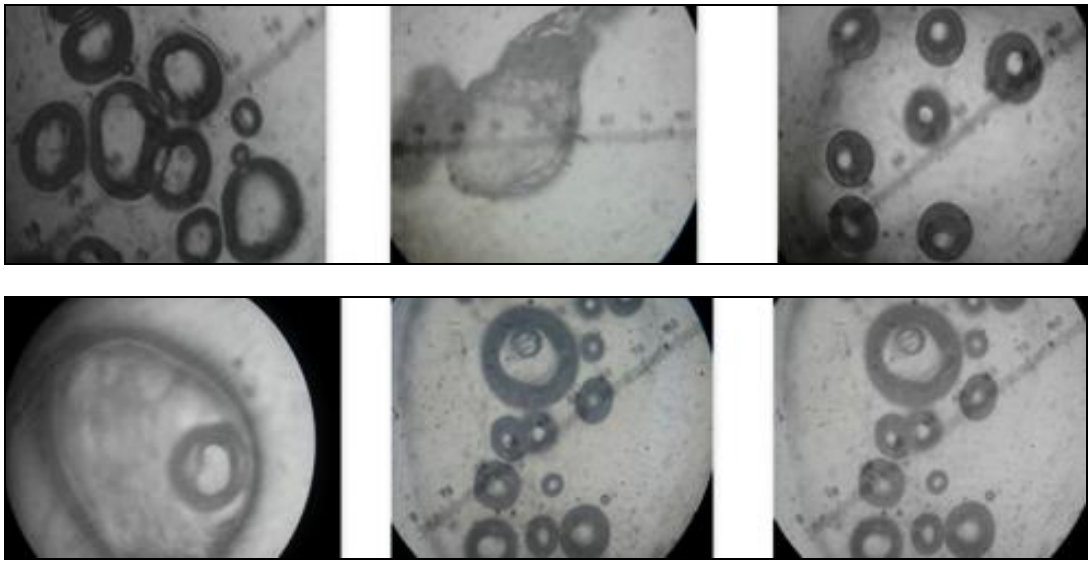

FIG. 1 MICROSCOPIC SNAP OF PREPARED FLOATING MICROSPHERE

TABLE 1 COMPOSITION OF FLOATING MICROSPHERE OF RANITIDINE HCl

Composition of Floating Microsphere of Ranitidine HCl									
Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranitidine Hydrochloride (gm)	500	500	500	500	500	500	500	500	500
Sodium Alginate (gm)	500	1000	1500	375	750	1125	375	750	1125
Guar gum (gm)	-	-	-	125	250	375	-	-	-
Xanthan gum (gm)	-	-	-	-	-	-	125	250	375
Drug: Polymer	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
Concentration of Polymeric Solution (%)	2	2	2	2	2	2	2	2	2
Calcium Chloride (%)	3	3	3	3	3	3	3	3	3
Acetic Acid (%)	2	2	2	2	2	2	2	2	2

RESULT AND DISCUSSION:

IR Spectroscopy:

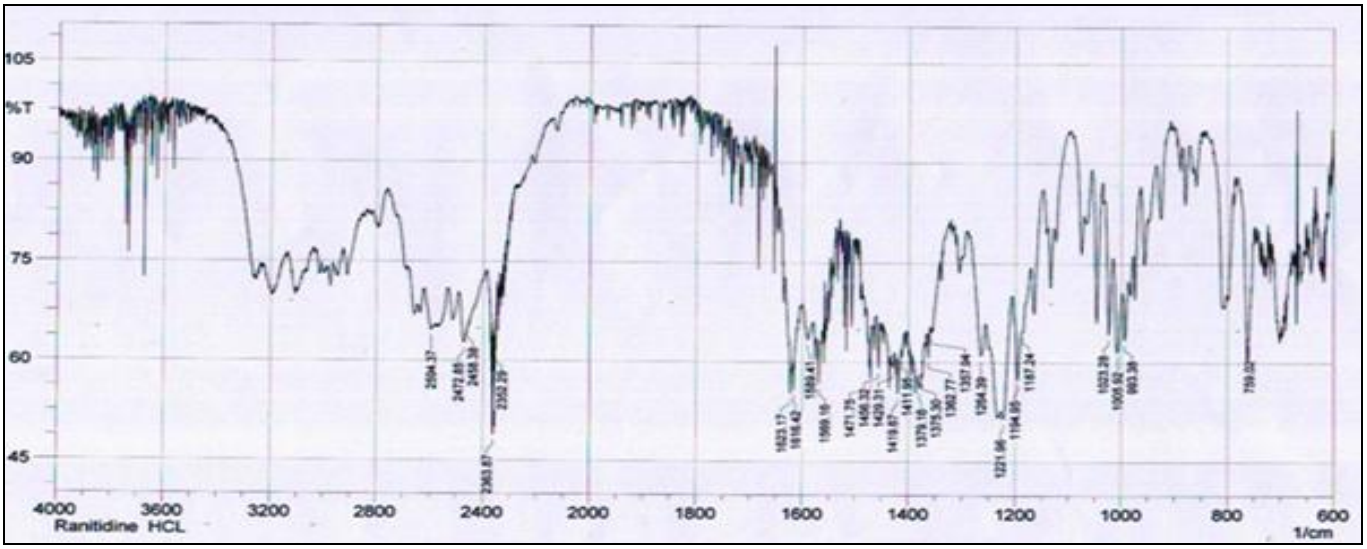

FIG. 2: FTIR SPECTRA OF PURE DRUG e.g. RANITIDINE HCl

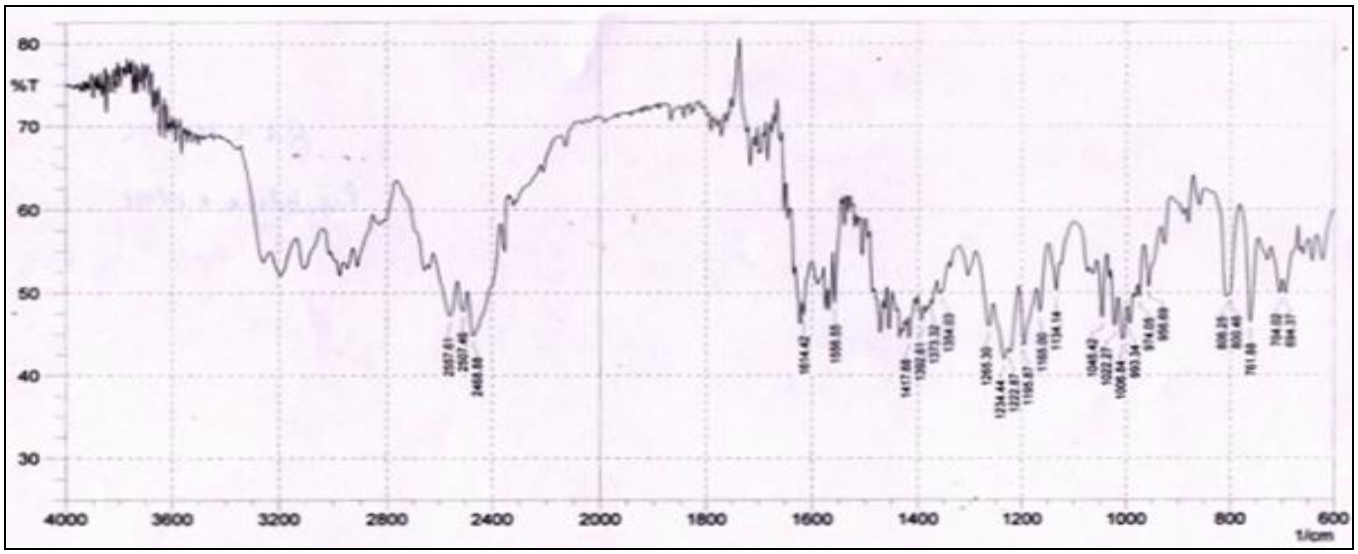

FIG. 3: FTIR SPECTRA OF RANITIDINE HCl WITH SODIUM ALGINATE

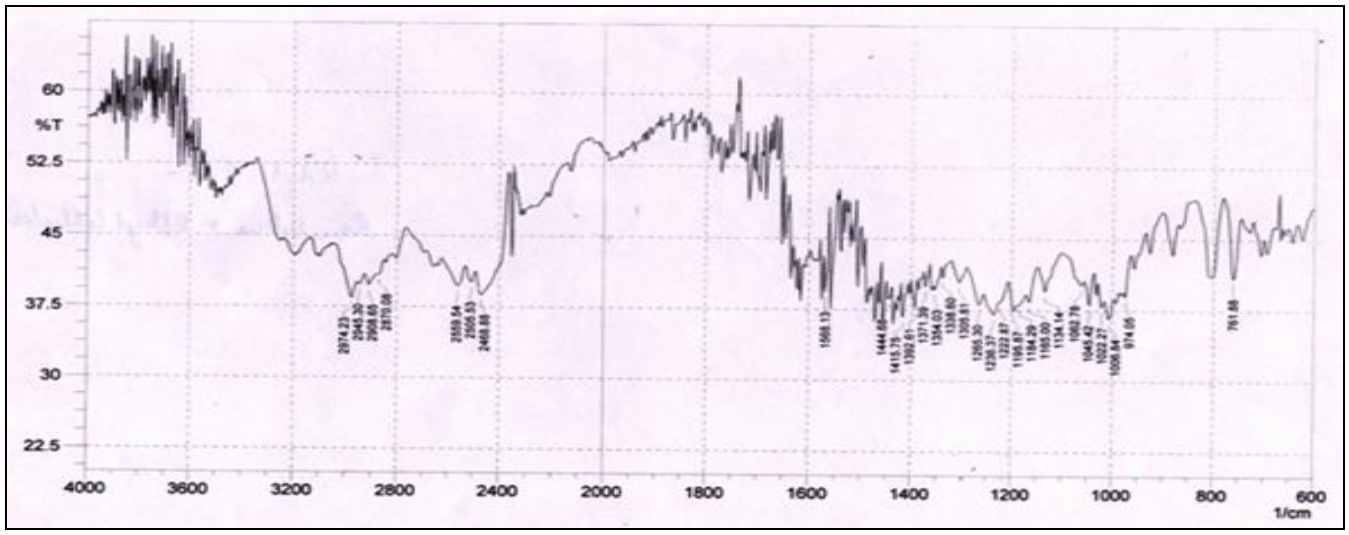

FIG. 4: FTIR SPECTRA OF RANITIDINE HCl USP WITH GUAR GUM

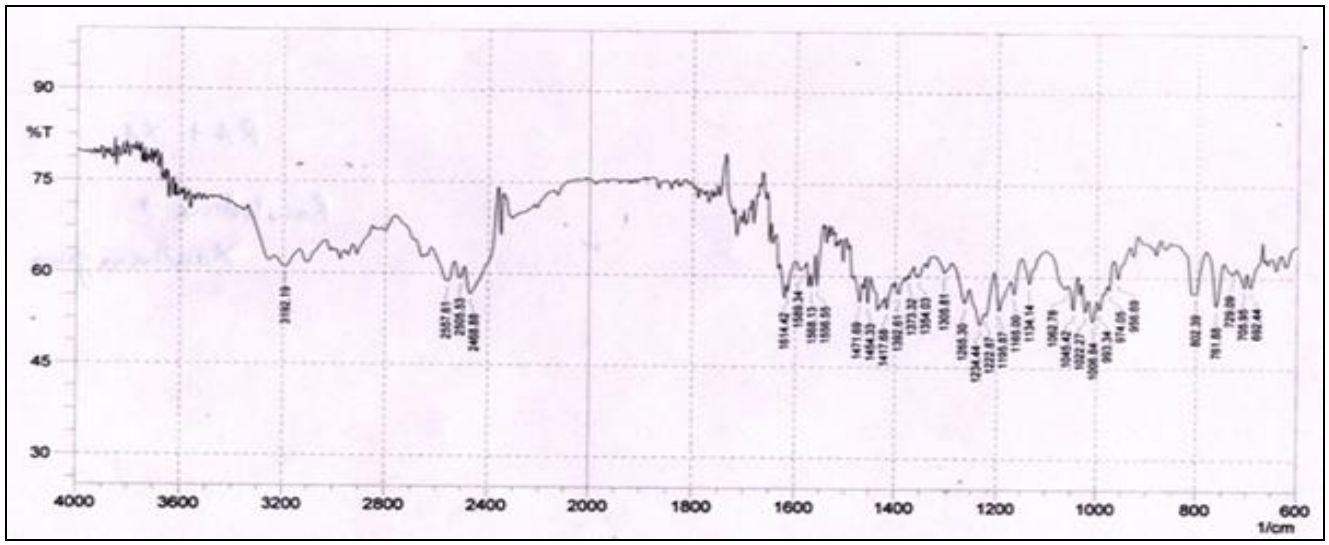

FIG. 5: FTIR SPECTRA OF RANITIDINE HCl WITH XANTHAN GUM

Micromeritic properties:

TABLE 2: MICROMERITIC PROPERTIES AND SHAPE OF PARTICLE OF DIFFERENT PREPARED FORMULATION

Formulation Number	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr`s Index	Hausner's Ration	Angle of repose (^{o})	Shape of Particle
F1	0.403	0.469	14.074	1.164	25.20^0	Spherical
F2	0.341	0.401	14.964	1.176	25.25^0	Spherical
F3	0.441	0.521	15.364	1.182	27.89^0	Slightly Irregular
F4	0.400	0.468	14.528	1.170	27.26^0	Spherical
F5	0.318	0.364	12.643	1.145	26.22^0	Slightly Irregular
F6	0.412	0.484	14.857	1.175	25.75^0	Slightly Irregular
F7	0.405	0.512	20.897	1.264	36.56^0	Spherical
F8	0.352	0.410	14.137	1.164	26.80^0	Slightly Irregular
F9	0.457	0.531	13.931	1.162	29.39^0	Slightly Irregular

The values were found in the range of 25.20 to 36.56 which are within the normal acceptable range of 20^0 to 40^o. Thus porous microspheres showed reasonable good flow potential. This is further substantiated by the value of Compressibility Index which was in the range 12.64 to 20.89, indication good flow characteristics of microsphere. This also implies that the microspheres are non-aggregated. The improved micrometric properties of the prepared microspheres when compared to that pure drug alone, suggest that they can be easily handled and filled into a capsule.

% Yield, Loading and Entrapment efficiency and Particle size:

TABLE 3: % YIELD, % DRUG LOADING, % ENTRAPMENT EFFICIENCY OF PREPARED DIFFERENT FORMULATION

Formulation Number	% Yield (%)	% Drug Loading (%)	% Entrapment efficiency (%)	Particle Size (µm)
F1	84.67	20.10 ± 0.10	60.30 ± 0.03	75.276
F2	79.20	17.65 ± 0.21	88.25 ± 0.14	102.67
F3	75.43	12.88 ± 0.18	90.18 ± 0.02	150.23
F4	76.67	14.87 ± 0.13	44.60 ± 0.17	123.44
F5	70.80	12.77 ± 0.32	63.83 ± 0.26	129.65
F6	64.29	9.77 ± 0.28	68.37 ± 0.29	158.04
F7	84.67	17.10 ± 0.21	51.30 ± 0.25	119.90
F8	84.00	15.55 ± 0.03	77.75 ± 0.45	125.74
F9	80.00	13.20 ± 0.52	92.40 ± 0.56	148.11

± Mean standard deviation where n=3

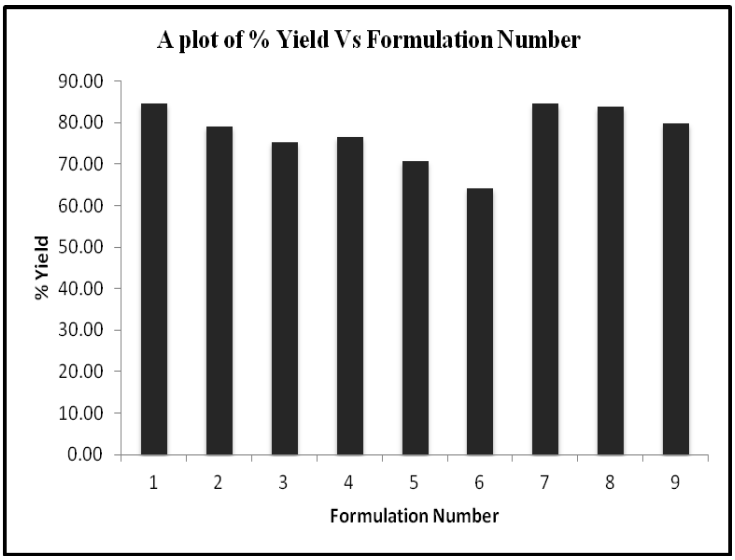

FIG. 6: PLOT OF % YIELD VS FORMULATION NUMBER

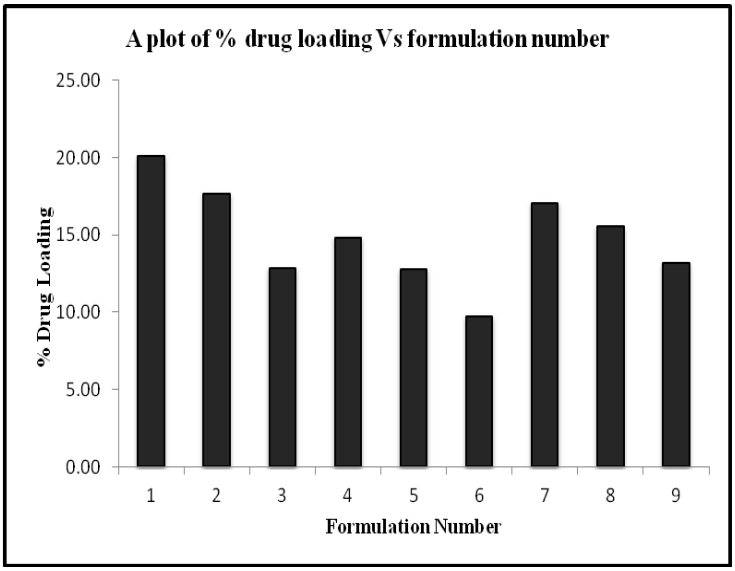

FIG. 7: PLOT OF % DRUG LOADING VS FORMULATION NUMBER

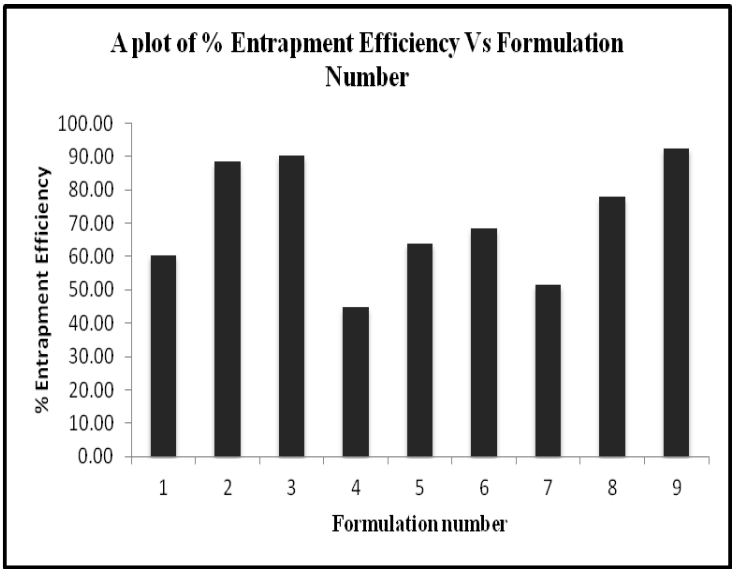

FIG. 8: PLOT OF ENTRAPMENT EFFICIENCY VS FORMULATION NUMBER

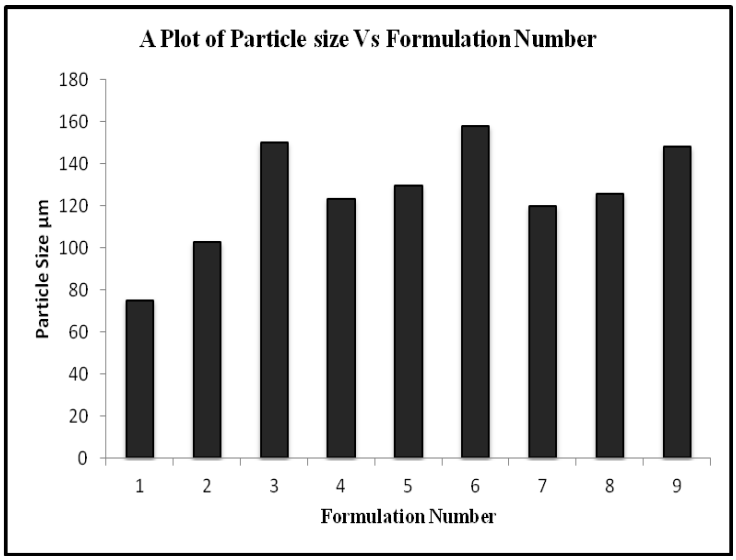

FIG. 9: PLOT OF PARTICLE SIZE VS FORMULATION NUMBER

High % drug loading are seen with lower concentration of polymer. As the concentration of polymer increased, the % drug loading decreased. High % entrapment efficiency is seen with higher concentration of polymer. As the concentration of polymer increased, % entrapment efficiency increased. It is also concluded that as the concentration of polymer increased, particle size of formulation also increased. Particle size range of prepared floating microsphere was found to be in the range of 75 to 150 µm.

% Buoyancy:

TABLE 4: FLOATING CAPACITY OF FLOATING MICROSPHERE

Floating capacity of Floating microsphere	
Formulation Number	**% Buoyancy (%)**
1	75.39
2	70.50
3	67.12
4	89.39
5	85.90
6	79.34
7	84.22
8	81.66
9	76.40

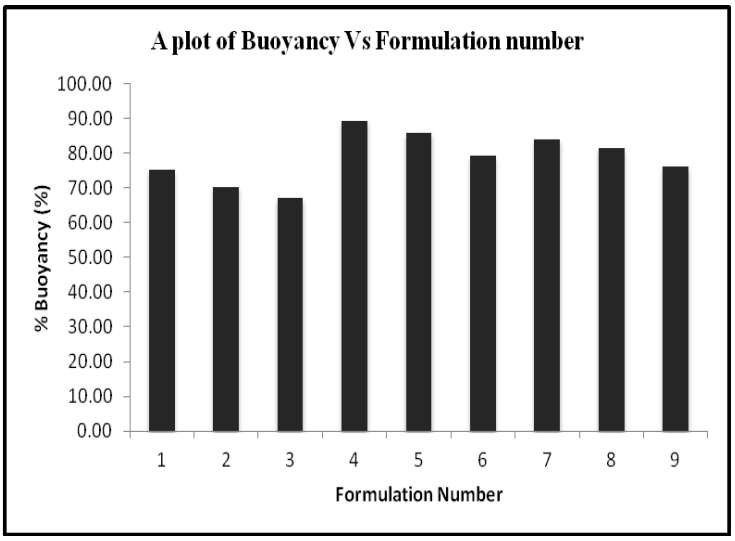

FIG. 10: PLOT OF BUOYANCY VS FORMULATION NUMBER

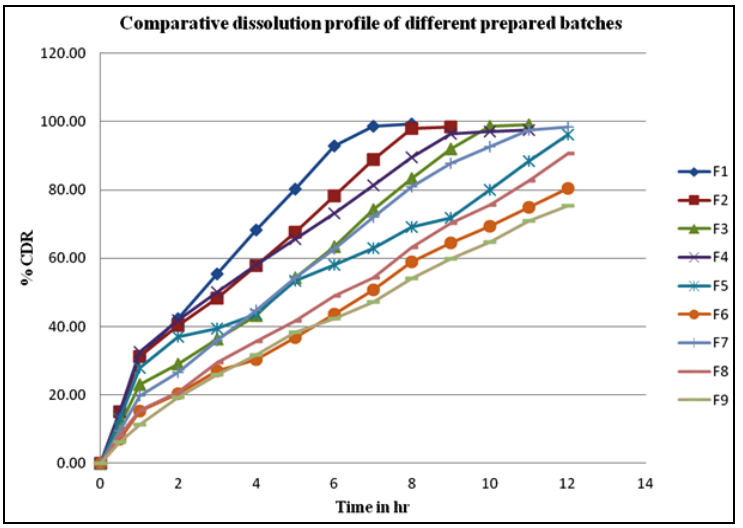

FIG. 11: COMPARATIVE DISSOLUTION PROFILE OF DIFFERENT PREPARED BATCHES

The % buoyancy was found in range of 67% to 89%. In formulation F1 to F3, as the concentration of polymer increased, % buoyancy is decreased from 75.39% to 67.12%. Same as in formulation F4 to F6, % buoyancy decreased from 89.39% to 79.34% and in formulation F5 to F6, % buoyancy decreased from 84.33% to 76.40%. The floating microsphere prepared using guar gum and sodium alginate shows better % buoyancy then the floating microsphere prepared using xanthan gum and sodium alginate and sodium alginate alone.

***In vitro* Drug Release:** Formulations F_1, F_2, and F_3 containing drug and Sodium alginate prepared at a drug-polymer ratio of 1:1, 1:2 and 1:3 released 99.21%, 99.03% and 99.04% of Ranitidine Hydrochloride in 8, 9, 11 hrs respectively. We could not extend release upto 12 hrs because sodium alginate is hydrophilic in nature and ranitidine hydrochloride is also in hydrophilic in nature.

Formulations F_4, F_5, and F_6 containing drug and Sodium alginate and Guar gum prepared at a drug-polymer ratio of 1:1, 1:2 and 1:3 and where sodium alginate and guar gum was used in 1:3 ration which released 97.50%, 96.30% and 80.44% of Ranitidine Hydrochloride in 11, 12, 12 hrs respectively. In F5 formulation, drug release was around 96.30% in 12 hr

Formulations F_7, F_8, and F_9 containing drug and Sodium alginate plus Xanthan gum prepared at a drug-polymer ratio of 1:1, 1:2 and 1:3 released 98.44%, 90.56% and 75.37% of Ranitidine Hydrochloride in 12hrs.

Data Analysis of Kinetic Release:

TABLE 5: MECHANISM OF DRUG RELEASE

Formulation	Regression coefficient of Higuchi Model (Diffusion)	Regression coefficient of Hoffenberg model (Erosion)	Korsemeyer and Peppas model		Order of drug release
			Regression coefficient (R^2)	("n")	
F_7	0.974	0.972	0.993	0.731	Both Diffusion and erosion or Non fickian are involved

DISCUSSION: The present novel drug floating microsphere approach for Ranitidine HCl proposes that with hydrophilic polymers the GI retention can be enhanced and the frequency of administration can be decreased. This gives a signal to extending this approach to similar combinations of drugs used in clinical practice so as to improve bioavailability of poorly absorbed drugs in GI.

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