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Formulation And *In-Vitro* Evaluation of Gastroretensive Floating Microspheres of Ranitidine Hydrochloride

Kumar Darapu B N*, K Sundaramoorthy and T Vetrichelvan

*****Adhiparasakthi College of pharmacy, Melmaruvathur-603 319, Tamilnadu, India.

ABSTRACT

The present study involves preparation of floating microspheres of Ranitidine Hydrochloride with HPMC K 100, Xanthan gum and Eudragit S-100 and in various ratios of 1: 1, 1: 2, and 1: 3. 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.

Keywords: Ranitidine HCl, Floating microspheres, HPMC K 100, Eudragit S 100, Xanthan gum.

Corresponding author
Email: dbindunaveen@gmail.com

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INTRODUCTION

Drug absorption from oral controlled release (CR) dosage forms is often limited by the short gastrointestinal retention time, available for absorption. Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms [1]. 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 [2] .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%.

MATERIALS

Ranitidine HCl obtained from Aurobindo Pharmaceutical (Hyderabad, India). Eudragit S-100 from M/S. Orchid Pharmaceutical (Tamilnadu, India), HPMC K 100 and Xanthan gum from Nickon Laboratories Pvt.Ltd (Pondicherry India). All the other chemicals and reagents used were of analytical grade.

METHODS

Preparation of Microspheres

Nine batches of microspheres were prepared by taking drug: polymer ratio as 1:1, 1:2 and 1:3 with same drug and three different polymers. The formulation batches were designated as F1,F2,F3 for HPMC(1:1,1:2,1:3 respectively); F4,F5,F6 for Xanthan gum(1:1,1:2,1:3); and F7,F8,F9 for Eudragit S 100(1:1,1:2,1:3 respectively). Drug and polymer in different proportions were weighed and co-dissolved at room temperature into a mixture of ethanol and dichloromethane (1:1% v/v) with vigorous agitation to form uniform drug polymer dispersion. This was slowly poured into the dispersion medium consisting of heavy liquid paraffin (50ml) containing 1.5% span 80. The system was stirred using over head propeller agitator at a speed of 700-800 rpm at room temperature over a period of 4-5 hrs, to ensure complete evaporation of the solvent. Liquid paraffin was decanted and the microspheres were separated by filtration through a whatmann filter paper, washed thrice with 180 ml of n-Hexane and air dried for 24 hrs [3].

Assay

The percentages of Ranitidine hydrochloride in floating microspheres were analyzed by UV at 315nm [4].

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 [5].

Differential scanning calorimetry (DSC)

The DSC analysis of pure drug, drug+ HPMC K100M, drug+ Xanthan gum and drug+ Eudragit S 100 were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 40-300ºc at heating rate of 10ºc /min under nitrogen flow of 20ml/min [6].

Yield of microspheres and Entrapment Efficiency

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds which were used for preparation of microspheres [7].

$$\% \text{ Yield} = \frac{\text{Weight of microspheres}}{\text{Weight of solid starting material}} \times 100$$

Drug entrapment efficiency for each batch was calculated in terms of percentage drug entrapment (PDE) as per the following formula [8]:

$$\text{PDE} = \frac{\text{Practical yield}}{\text{Theoretical Drug Loading}} \times 100$$

Particle size analysis

The particle size of floating microspheres in all samples was analyzed using optical microscopy method [9].

***In vitro* Buoyancy studies**

The floating microspheres (300 mg) were spread over the surface of the dissolution medium (simulated gastric fluid, SGF, pH (1.2) containing 0.02%w/v of Tween 20 that was agitated by a basket rotated at 100 rpm. After agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of

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the flask were recovered separately. After drying, each fraction of the micro particles was weighed and their buoyancy was calculated by the following equation [10]:

$$\text{Buoyancy \%} = \frac{Q_f}{(Q_f + Q_s)} X \quad 100$$

Where Qf and Qs are the weight of the floating and the settled microspheres, respectively.

Scanning Electron Microscopy

The surface morphology and particle size was confirmed by Scanning Electron Microscopy and the Picture of microspheres was taken by random scanning of the stub [11].

Dissolution study

Drug loaded microspheres equivalent to 100 mg of drug was introduced into the 900 ml of 0.1N HCl, containing Tween 80 (0.5%).The medium was maintained at 37±0.5ºC at 100 rpm. Aliquots (5ml) were withdrawn at regular intervals for 10 hours and analyzed spectrophotometrically at 315nm. The dissolution studies were carried out in triplicate in 0.1N HCl (pH 1.2). Sink condition was maintained throughout the study by replacing equal volume of fresh dissolution medium [12].

Data Analysis of Release Studies

The *in vitro* release data obtained was treated to Zero order, First order, Higuchi and Korsemeyer – Peppas to know precisely the mechanism of drug release of the floating microspheres [13].

RESULTS AND DISCUSSION

Table 1: Formulation batches of floating microspheres of Ranitidine HCl

S.NO	INGREDIENS	BATCHES OF MICROSPHERES PREPARED								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ranitidine Hydrochloride	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm
2	HPMC	1gm	2gm	3gm	-	-	-	-	-	-
3	Xanthan gum	-	-	-	1gm	2gm	3gm	-	-	-
4	Eudragit S 100	-	-	-	-	-	-	1gm	2gm	3gm
5	Heavy Liquid Paraffin	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml

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6	Dichloromethane	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
7	Ethanol	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
8	Span 80	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%
9	n-Hexane	180 ml	180 ml	180 ml	180 ml	180 ml	180 ml	180 ml	180 ml	180 ml

Table 2: Percentage Yield

S.NO	FORMULATION	% YIELD
1	F1	96.00±0.13
2	F2	80.00±0.32
3	F3	73.00±0.64
4	F4	74.50±0.36
5	F5	66.34±0.69
6	F6	59.50±0.26
7	F7	81.50±0.38
8	F8	72.67±0.62
9	F9	63.50±0.34

The floating microspheres were prepared by solvent evaporation method (Table 1) and characterized for % entrapment (Table 3), % buoyancy (Table 4), and particle size (Table 5). % Yield of microspheres was high in HPMC batches over Xanthan gum and Eudragit S 100 batches. The particle sizes of microspheres were found to increase by increasing the polymer concentration. Buoyancy of microspheres was found to be in the range of 54.36% - 83.50% which indicates that most of the microspheres were still floatable after 12 hours because of their low density and internal voids.

Table 3: Percentage entrapment

S.NO	FORMULATION	% ENTRAPMENT
1	F1	52.08±1.12
2	F2	41.66±0.64
3	F3	34.29±0.78
4	F4	67.11±1.34
5	F5	61.72±0.52
6	F6	51.54±0.34
7	F7	61.34±0.84
8	F8	45.87±1.06
9	F9	39.37±0.76

Mean ± Standard deviation (n = 3)

Table 4: Percentage buoyancy

S.NO	FORMULATION	% OF BUOYANCY
1	F1	75.52±1.02
2	F2	78.33±0.94
3	F3	83.50±0.62
4	F4	72.39±0.48

5	F5	74.31±1.16
6	F6	79.92±1.26
7	F7	54.36±0.64
8	F8	56.79±0.82
9	F9	62.37±1.28

Mean ± Standard deviation (n = 3)

Table 5: Mean particle size

S.NO	FORMULATION	MEAN PARTICLE SIZE (µm)
1	F1	68.87 ± 0.59
2	F2	87.53 ± 0.80
3	F3	99.12 ± 1.62
4	F4	70.35 ± 1.24
5	F5	91.70 ± 1.46
6	F6	101.40 ± 1.26
7	F7	60.46 ± 0.38
8	F8	72.84 ± 1.42
9	F9	86.27 ± 1.64

Mean ± Standard deviation (n = 3)

Earlier studies reveal that researchers adopted polymers with extended release for designing floating microspheres to improve the gastrointestinal tract absorption. In the present study a novel floating drug delivery was attempted to investigate the dissolution characteristics of microspheres of hydrophilic polymer (HPMC), Xanthan gum and an acrylic polymer (Eudragit E 100). Ranitidine HCl has 50% bioavailability, low half life of 2.2 hours, exhibits poor bioavailability when given in conventional dosage form due to degradation in lower GIT. The floating microspheres of Ranitidine HCl were prepared by solvent evaporation technique, with different ratios of the polymers. IR spectral analysis indicated absence of chemical interaction between drug and polymers.

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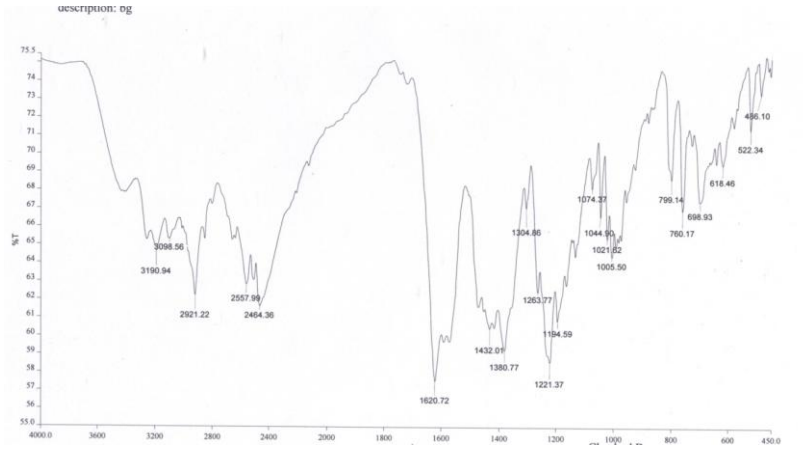

Figure 1: FTIR spectrum of Ranitidine HCl

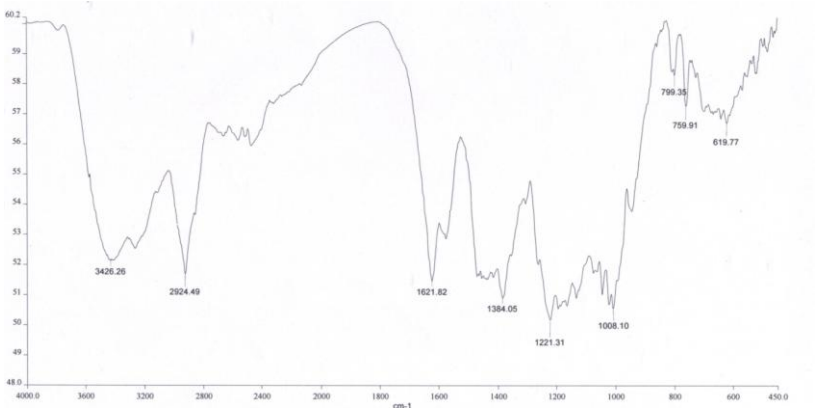

Figure 2: FTIR spectrum of mixture of Ranitidine HCl and HPMC K 100

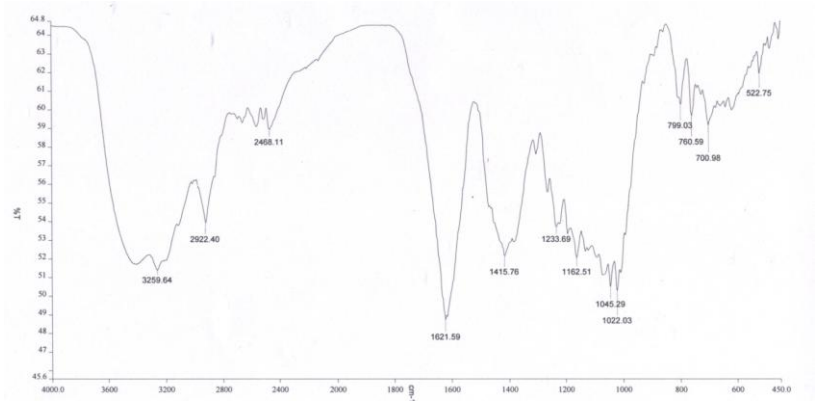

Figure 3: FTIR spectrum of mixture of Ranitidine HCl and Xanthan gum

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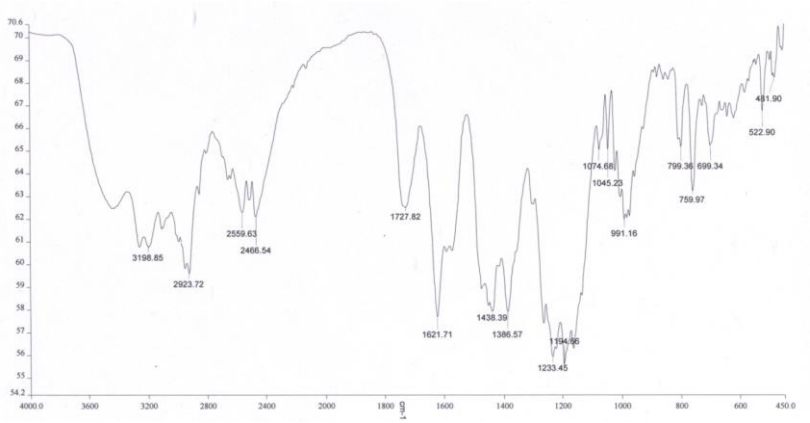

Figure 4: FTIR spectrum of mixture of Ranitidine HCl and Eudragit S100

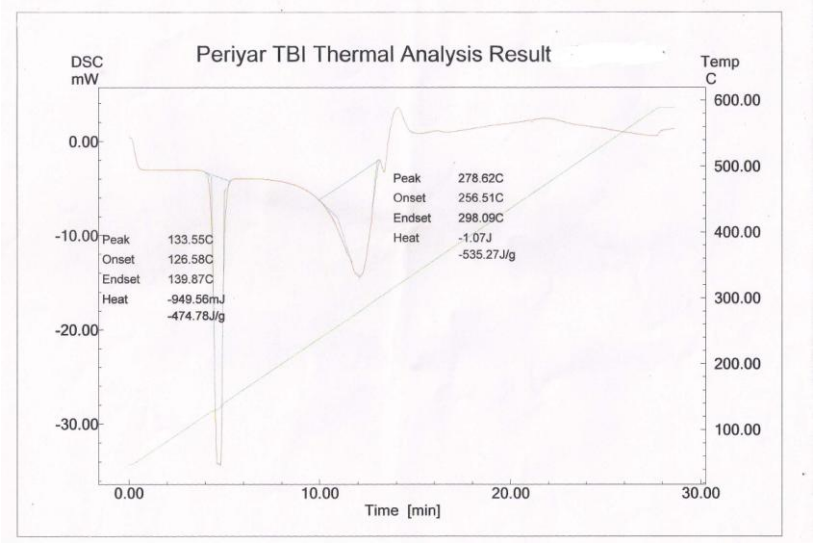

Figure 5: DSC thermal analysis of pure Ranitidine Hydrochloride

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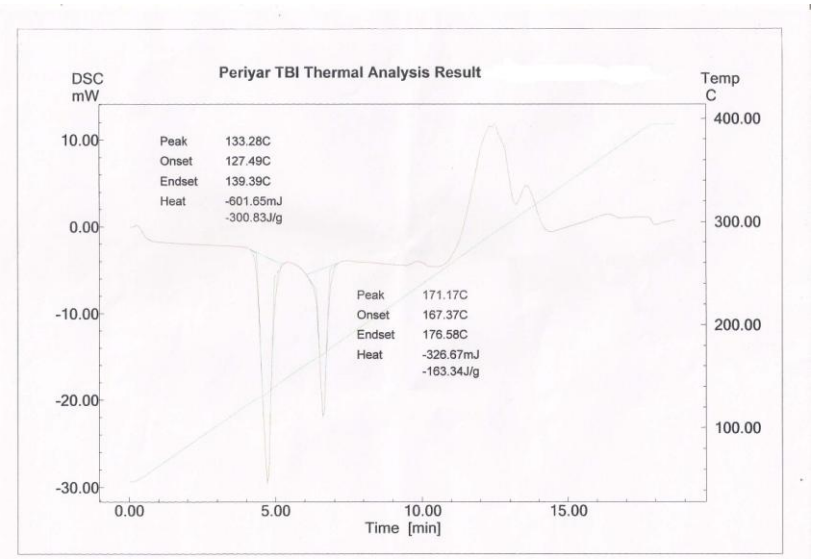

Figure 6: DSC thermal analysis of Ranitidine HCl + HPMC K 100

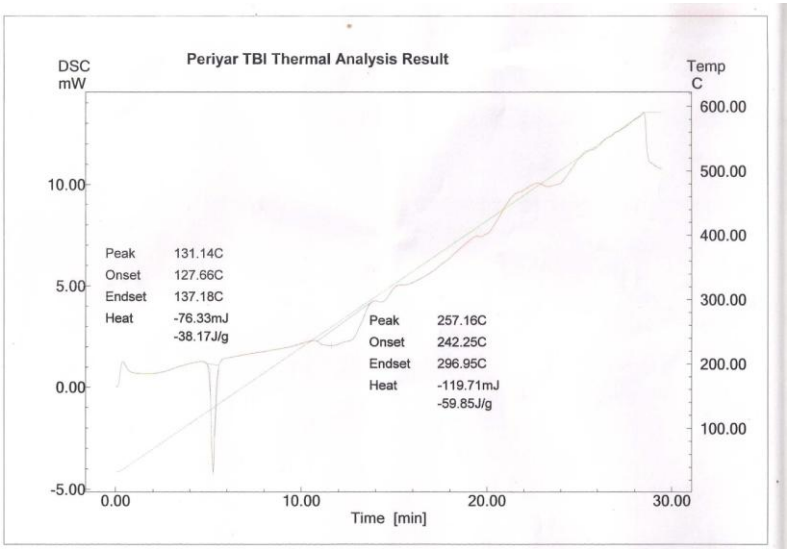

Figure 7: DSC thermal analysis of Ranitidine HCl + Xanthan gum

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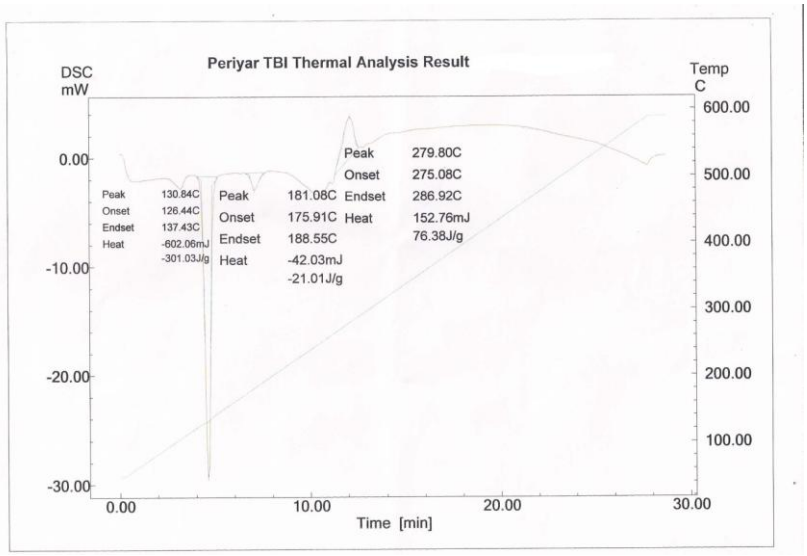

Figure 8: DSC thermal analysis of Ranitidine HCl + Eudragit S 100

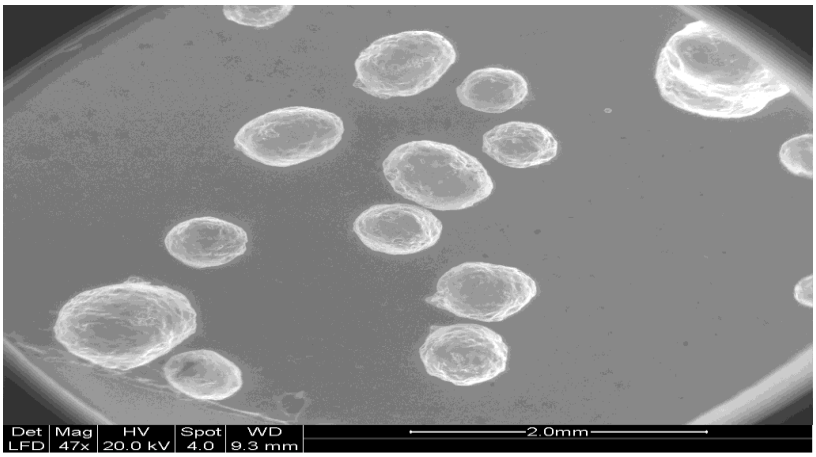

Figure 9: Scanning electron microphotograph of formulation F1 at lower magnification

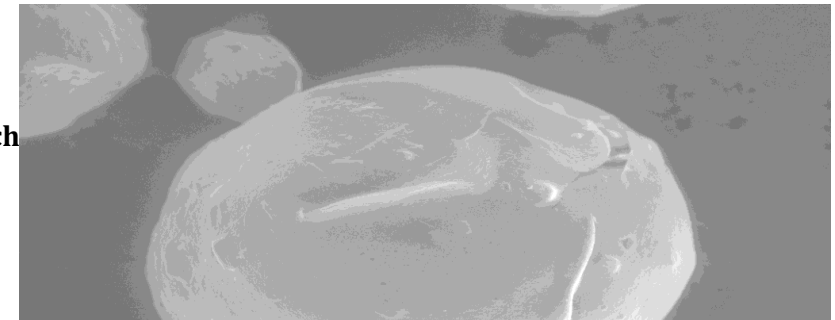

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Figure 10: Scanning electron microphotograph of formulation F1 at higher magnification

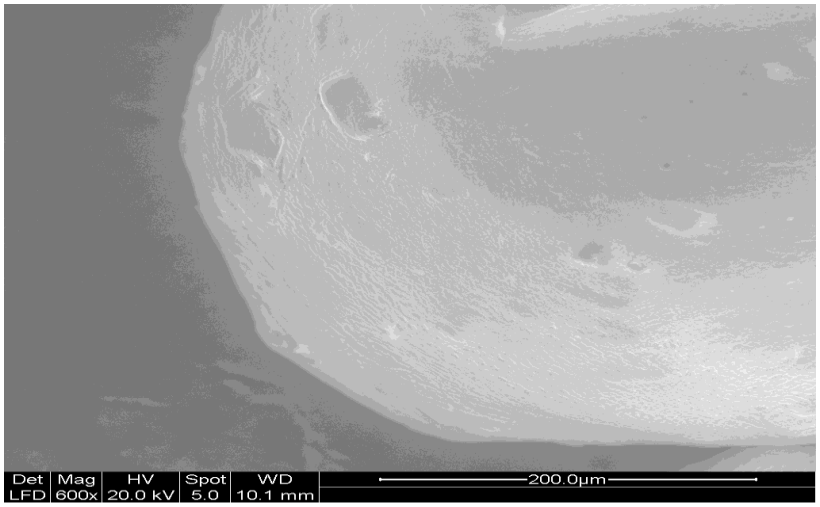

Figure 11: Scanning electron microphotograph of formulation F1 surface morphology

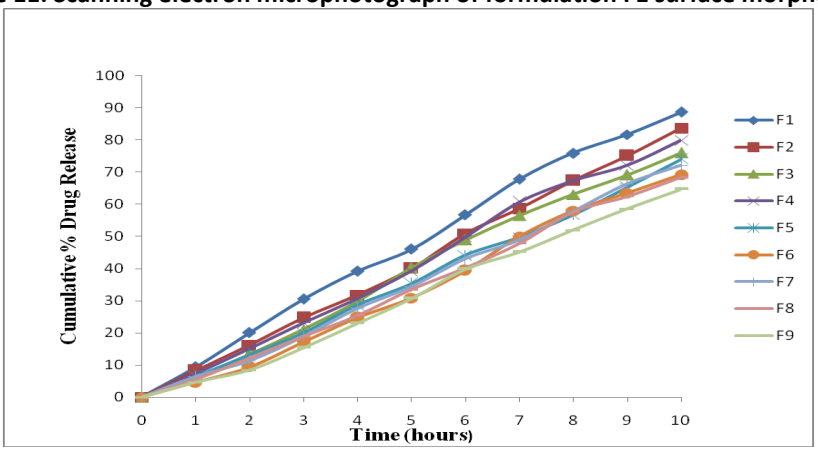

Figure 12: *IN-VITRO* Dissolution studies of formulations (F1-F9)

Table *6: In-vitro* dissolution studies

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S.NO	TIME (hrs)	CUMULATIVE % DRUG RELEASE								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	9.44± 0.35	8.27± 0.19	6.27± 0.21	7.43± 0.40	6.54± 0.32	4.59± 0.34	6.38± 0.34	5.47± 0.31	4.64± 0.42
2	2	20.03± 0.31	16.20± 0.28	13.35± 0.35	15.15± 0.25	13.18± 0.32	9.36± 0.31	11.28± 0.44	12.28± 0.45	8.46± 0.45
3	3	30.54± 0.24	24.71± 0.30	21.05± 0.25	23.01± 0.17	19.93± 0.28	17.20± 0.29	18.85± 0.30	18.98± 0.30	15.38± 0.56
4	4	39.19± 0.34	31.72± 0.24	29.68± 0.26	30.67± 0.37	28.62± 0.39	24.75± 0.27	27.66± 0.43	25.45± 0.23	22.96± 0.38
5	5	46.02± 0.34	40.06± 0.30	40.27± 0.31	39.29± 0.28	35.41± 0.30	30.83± 0.25	34.42± 0.22	33.48± 0.34	30.78± 0.27
6	6	56.70± 0.32	50.87± 0.32	49.00± 0.40	49.81± 0.32	44.20± 0.31	39.37± 0.24	43.01± 0.33	40.26± 0.39	39.84± 0.63
7	7	67.79± 0.74	58.57± 0.30	56.51± 0.36	60.70± 0.25	49.77± 0.31	49.98± 0.28	49.00± 0.25	47.88± 0.21	45.15± 0.24
8	8	75.96± 0.35	67.41± 0.36	63.06± 0.27	67.34± 0.33	56.76± 0.27	57.94± 0.44	57.74± 0.35	57.66± 0.29	51.93± 0.41
9	9	81.77± 0.32	75.16± 0.47	69.11± 0.31	72.11± 0.31	65.39± 0.43	63.52± 0.46	66.41± 0.32	62.49± 0.37	58.61± 0.36
10	10	88.73± 0.34	83.73± 0.28	76.07± 0.31	79.97± 0.45	74.07± 0.37	69.28± 0.37	72.14± 0.31	68.34± 0.39	64.73± 0.52

Mean ± Standard deviation (n = 3)

The dissolution studies showed an enhanced rate of dissolution of Ranitidine from the microspheres. The dissolution rates of HPMC microspheres batches were higher than Xanthan gum and Eudragit S 100 batches. This may be attributed to the acrylic polymer property of Eudragit S 100 which gave lower release and hydrophilic nature of HPMC showed higher release. It was found that with increase in polymer ratio there was an increase in the particle size range and due to lower density of microspheres buoyancy was 80% till 12 hours for both the polymers. The release kinetics of Ranitidine HCl microspheres followed supercase II transport diffusion. The microspheres prepared with both the polymers were spherical with rough, hollow surface and slightly aggregated. The presences of pores were detected on the surface of microspheres, which indicated leaching of the drug during the dissolution without gelation of the polymeric surface.

CONCLUSION

The present novel drug floating microsphere approach for Ranitidine HCl proposes that with both acrylic and 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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