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Research Article

INTRAGASTRIC FLOATING DRUG DELIVERY SYSTEM OF RANITIDINE HYDROCHLORIDE: FORMULATION AND EVALUATION

PUNITHA.K*, KHADHIR.S, RAVICHANDIRAN.V, UMADEVI.S.K, VAIJAYANTHI.V, PADMAPRIYA.S, SURESH KUMAR.S

VELS College of Pharmacy, Velan Nagar, Pallavaram, Chennai-600 117, Tamilnadu, India Email id: Punithasa26@gmail.com

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ABSTRACT

The present study involves preparation of floating microspheres of Ranitidine Hydrochloride with HPMC 15 cps and Eudragit E-100 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 both the polymers revealed HPMC to be a suitable candidate for sustained release.

Keywords: Ranitidine Hcl, Floating microspheres, HPMC 15 cps, Eudragit E 100, SEM, Dissolution and Kinetics.

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. 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%.

MATERIALS

Ranitidine Hcl (RH) was gifted from M/S.Tri-Star Ltd, Eudragit E-100 from M/S. Orchid Ltd, and HPMC 15 cps from M/S. CDH Ltd. All the other chemicals and reagents used were of analytical grade.

METHODS

Preparation of Microspheres

Six batches of microspheres were prepared by taking drug: polymer ratio as 1:1, 1:2 and 1:3 with same drug and two different polymers. The formulation batches were designated as A, B, C for HPMC(1:1,1:2,1:3 respectively) and D, E, F for Eudragit(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.

Assay

The percentage of Ranitidine hydrochloride in floating microspheres were analyzed by UV at 315nm.

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.

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.

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 12 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.

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.

RESULTS

The floating microspheres were prepared by solvent evaporation method (Table-1) and characterized for % entrapment, particle size and buoyancy (Table 2). % Yield of microspheres was high in HPMC batches over Eudragit 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 63.38%-75.58% which indicates that most of the microspheres were still floatable after 12 hours because of their low density and internal voids.

Table 1: Formulation batches of floating microspheres of ranitidine HCL

S. No.	Ingredients	Batches of Microspheres					
		A	B	C	D	E	F
1	Ranitidine Hydrochloride(g)	1	1	1	1	1	1
2	HPMC(g)	1	2	3	-	-	-
3	Eudragit E 100(g)	-	-	-	1	2	3
4	Heavy Liquid Paraffin(ml)	50	50	50	50	50	50
5	Dichloromethane(ml)	5	5	5	5	5	5
6	Ethanol(ml)	5	5	5	5	5	5
7	Span 80(%)	1.5	1.5	1.5	1.5	1.5	1.5
8	n-Hexane(ml)	180	180	180	180	180	180

Table 2: Characterization of floating microsphere

S. No.	Batches	% Yield	% Loading	% Entrapment	Particle Size (µm)	% Buoyancy
1	A	100.51 ± 1.76	21.84 ± 1.61	44.62 ± 0.99	63.87 ± 1.53	75.58 ± 1.02
2	B	82.81 ± 0.56	25.28 ± 1.06	63.38 ± 1.17	100.33 ± 0.80	78.95 ± 0.96
3	C	75.37 ± 0.54	30.35 ± 1.48	95.41 ± 0.75	99.82 ± 1.32	81.52 ± 0.81
4	D	72.38 ± 0.82	27.96 ± 1.84	37.58 ± 0.76	68.75 ± 1.27	53.32 ± 0.72
5	E	64.46 ± 1.07	31.58 ± 1.33	58.59 ± 1.11	103.70 ± 1.46	56.59 ± 0.63
6	F	55.26 ± 1.89	34.44 ± 1.27	75.79 ± 1.56	102.90 ± 1.78	63.38 ± 1.17

Mean ± Standard deviation (n = 3)

Fourier Transform Infrared Spectroscopy

The characteristics peaks of formulation batches at various brands were observed which were found to be identical in number of peaks, intensity and position with that of pure samples. (Fig.1)

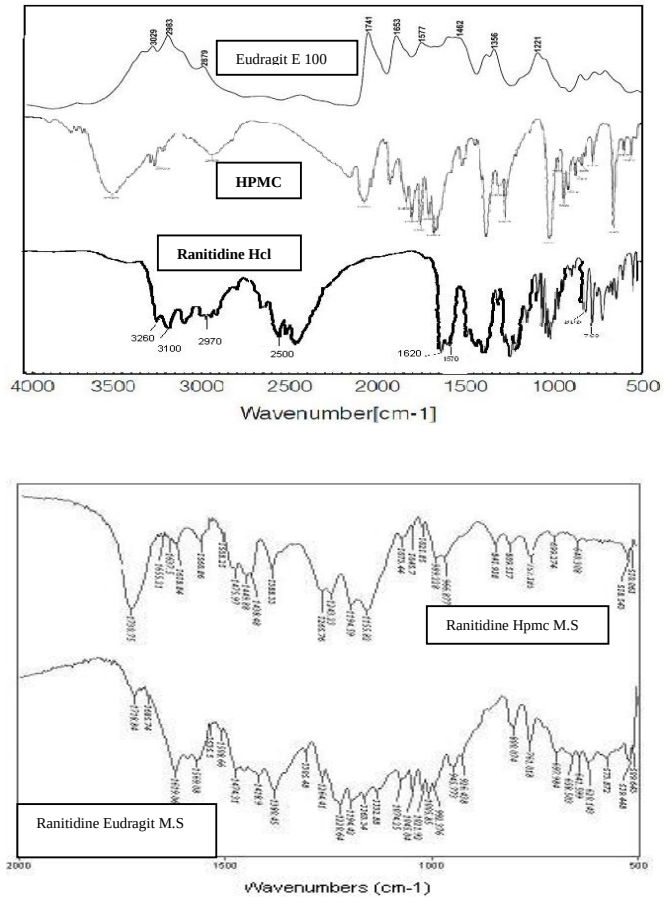

Fig. 1: FTIR spectra of ranitidine HCL, HPMC, Eudragit E 100, ranitidine HPMC M.S and Ranitidine Eudragit M.S.

Dissolution studies

Microspheres of Ranitidine with HPMC (Batches A, B, C) showed enhanced release rate when compared to Ranitidine with Eudragit-E100 (batches D, E, F). The % Cr at 12 th hrs for batch A was found to be 86.23 %, and 71.57 %, in batch D. The rates of dissolution of HPMC batches were much better than Eudragit batches due to hydrophilic nature of polymer. With increase in polymer concentration there was a decrease in drug release rate in both the batches. (Table 3, Fig 2)

Table 3: Cumulative % drug release of microspheres in 0.1 N HCL

S. No.	Time (hrs)	Cumulative % Drug Release					
		A	B	C	D	E	F
1	1	5.87 ± 0.49	4.44 ± 0.62	3.64 ± 0.60	3.81 ± 0.77	2.26 ± 0.73	2.38 ± 0.83
2	2	11.71 ± 0.51	9.72 ± 0.62	6.69 ± 0.62	4.67 ± 0.90	4.54 ± 0.57	3.22 ± 0.62
3	3	19.22 ± 1.12	13.69 ± 0.80	18.96 ± 0.67	9.87 ± 0.80	10.56 ± 1.16	9.73 ± 0.67
4	4	30.78 ± 0.53	28.59 ± 0.58	31.57 ± 1.28	21.69 ± 0.93	18.43 ± 1.12	18.39 ± 0.86
5	5	34.83 ± 0.85	36.73 ± 1.07	34.12 ± 0.70	37.58 ± 0.95	37.12 ± 0.87	34.45 ± 0.85
6	6	41.65 ± 0.81	45.56 ± 0.84	43.49 ± 0.90	44.73 ± 0.93	43.41 ± 0.97	41.72 ± 0.82
7	7	46.46 ± 1.17	54.28 ± 0.96	45.53 ± 0.83	48.46 ± 1.13	48.75 ± 0.58	47.29 ± 0.49
8	8	53.24 ± 0.97	60.38 ± 0.90	51.36 ± 0.88	54.58 ± 1.05	54.67 ± 0.75	52.69 ± 0.75
9	9	55.60 ± 1.26	67.28 ± 0.89	60.47 ± 0.83	59.43 ± 1.10	62.39 ± 1.17	54.42 ± 0.62
10	10	66.44 ± 0.71	72.83 ± 0.80	65.55 ± 0.93	64.29 ± 1.23	63.92 ± 0.95	58.60 ± 0.78
11	11	75.44 ± 0.69	77.07 ± 0.90	70.73 ± 1.54	67.58 ± 0.95	64.95 ± 0.75	60.60 ± 0.98
12	12	86.23 ± 0.79	80.58 ± 0.63	75.48 ± 0.99	71.57 ± 1.13	66.63 ± 0.77	62.25 ± 0.88

Mean ± Standard deviation (n = 3)

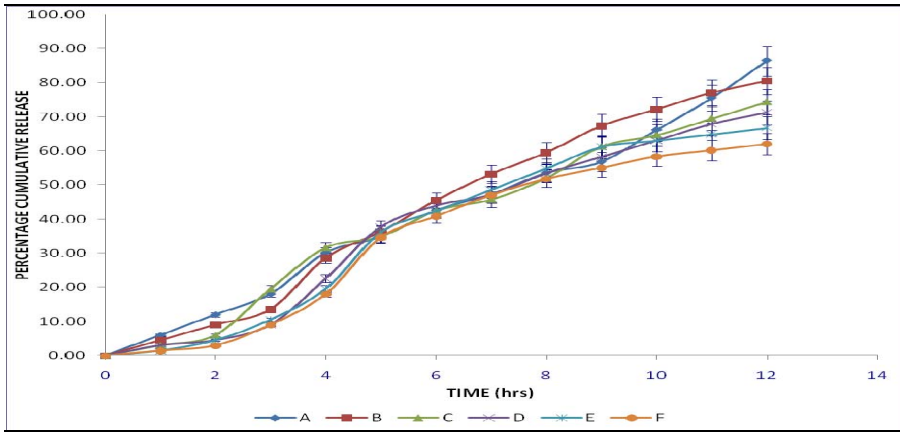

Fig. 2: Percentage cumulative release of ranitidine HCL microspheres in 0.1N HCL

SEM analysis

Surface topography revealed that the mean particle size various batches of microspheres were within the range of 63.87 to 102.90 µm .An increase in polymer ratio is found to have an increase in particle size due to coating of microsphere. Ranitidine microspheres were found to have rough and hollow surface and are slightly spherical. The hallow nature was responsible for the microspheres floatability. The release of the drug from the microspheres can be attributed to leaching and erosion mechanism (Fig 3).

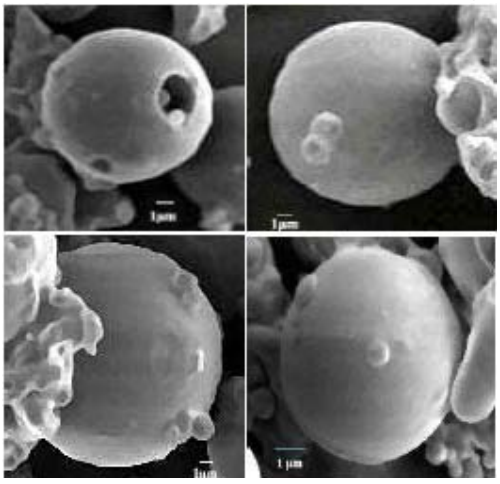

Fig. 3: SEM photograph of ranitidine HCL microsphere.

Release Kinetics

Different kinetics was applied to interpret the release rate of Ranitidine hydrochloride from the sustained release floating microspheres of formulations. From the co-efficient determination all the formulations showed the release was best fit in korsmeyer model with n>0.89.

DISCUSSION

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) 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.

The dissolution studies showed an enhanced rate of dissolution of Ranitidine from the microspheres (Fig.1). The dissolution rates of HPMC microspheres batches were higher than Eudragit E 100 batches. This may be attributed to the acrylic polymer property of Eudragit 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 GIT.

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