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DEVELOPMENT AND EVALUATION OF RANITIDINE HYDROCHLORIDE FLOATING TABLET

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ABSTRACT: Floating matrix tablets of ranitidine hydrochloride were developed and evaluated to increase bioavailability by increasing gastric residence time and sustained release of drug in the upper part of gastrointestinal tract thereby diminishing side effects and enhanced patient compliance. The tablets were prepared by direct compression method, using polymers such as Hydroxy propyl methyl cellulose, carbopol 940, xanthum gum, oryza sativa husk, chitosan and cetyl alcohol. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released profile from all formulation batch F8 showed slow and sustained release of ranitidine hydrochloride over a period of 12 hours upto 95%. Optimized floating matrix tablets F8 showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40±2°C/75±5% for 90 days. It was concluded that formulation F8 shows the better buoyancy and drug release.

INTRODUCTION: Through current release technology, oral delivery for 24 h is possible for many drugs; however, the substance must be absorbed well throughout the whole gastrointestinal tract. A significant obstacle may arise if there is a narrow window for drug absorption in the gastrointestinal tract, if a stability problem exists in gastrointestinal fluids, or the drug is poorly soluble in the intestine or acts locally in the stomach. Thus, the real challenge in the development of oral controlled release dosage forms is not just to prolong the delivery of the drugs for more than 12 h, but to prolong the presence of the dosage forms in the stomach or somewhere in the upper small intestine until all the drug is released for the desired period of time [1].

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The gastro retentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drug that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [2, 3].

Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shaped systems, high density systems, and other delayed gastric emptying devices [4, 5].

Ranitidine hydrochloride is a histamine H2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger- Ellison syndrome, gastroesophageal reflux disease and erosive esophagitis [6, 7]. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily.

The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 h but not up to 10 h. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine hydrochloride is desirable [8]. The drug has a short biological half-life of approximately 2–3 h, an absolute bioavailability of only 50%, and it is absorbed only in the initial part of the small intestine also favors development of a sustained release formulation [9].

The objective of the present study was to develop and evaluate floating matrix tablets of ranitidine hydrochloride to achieve prolong gastric retention, enhance drug bioavailability and to sustained the release of ranitidine hydrochloride in the stomach, by using Hydroxymethylcellulose, carbopol 940, xanthum gum, chitosan, oryza sativa husk and cetyl alcohol.

MATERIALS AND METHODS:

Materials: Ranitidine hydrochloride was received as a gift sample from Hindustan Lab., Palghar, India. Hydroxypropyl methylcellulose, Chitosan, Xanthan gum, cetyl alcohol, Oryza sativa husk and Carbopol 940 were received as gift samples from Loba Chemical, Mumbai, India. All other ingredients were of laboratory grade.

Methods: Ranitidine floating tablets were prepared by direct compression technique. Drugs and polymers were accurately weighed and blended thoroughly using glass mortar and pestle manually in geometric proportion was mixed thoroughly. Lactose, talc, and magnesium stearate were added to the above blend. The powder blends were evaluated for the properties such as loose bulk density, tapped bulk density, compressibility index and angle of repose. The composition of different formulations of floating tablets is shown in **table 1**.

TABLE 1: COMPOSITION OF FLOATING MATRIX TABLETS OF RANITIDINE HYDROCHLORIDE

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Ranitidine HCL	150	150	150	150	150	150	150	150
HPMC K15M	20	-	20	20	20	20	-	-
HPMC K100M	100	100	100	100	100	100	200	100
Carbopol 940	20	20	20	20	20	20	20	20
XG	-	-	-	10	20	20	20	20
Chitosan	10	10	10	10		10	10	10
OSH	7	7	7	7	7	7	7	7
PVA	10	10	10	10	10	-	-	-
Cetostearyl Alcohol	-	-	3%	3%	3%	-	-	-
Cetyl alcohol	-	-	-	-	-	3%	3%	3%

Evaluation of Floating Matrix Tablet:

Hardness: Tablet was placed between two anvils of hardness tester; force was applied to the anvils and the crushing strength that just cause the tablet to break was recorded. Hardness was sometimes termed as tablet crushing strength.

Thickness and Diameter: It was determined for five tablets from a batch by using a calibrated Vernier Callipers and the result was given in mm.

Friability: The friability of uncoated tablets was determined by using Electrolab friabilator in the laboratory. This device subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each operation for 100 revolutions. The tablets was then dusted and reweighed. It is expressed as the loss of mass and it is calculated as a percentage of initial mass. The values for both Hardness & Friability can together indicate the mechanical strength of tablet.

Weight Variation Test: Weight variation of tablets was calculated by weighing 20 tablets individually and determining the average weight. Tablet meets the test if not more than two of the individual weights deviate from percentage limits [10].

Drug Content Uniformity: 10 tablets were weighed and triturated. The tablet triturate equivalent to 100 mg of the drug was weighed accurately, dissolved in pH 1.2 buffers and diluted to 100 ml with the same.

Further dilutions were done suitably to get a concentration of 10mcg/ml with simulated gastric fluid pH 1.2. Absorbance was read at 313nm against the blank [11].

Swelling Studies: Tablet were weighed individually (recorded as W1) and placed separately in Petri dish containing 5 mL of Hydrocloric acid (pH 1.2) solution. At regular intervals (1, 2, 3, 4 and 5 hours), the tablets was removed from the Petri dish and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W2), and swelling index (SI) was calculated using formula as [12];

Swelling Index =

$$SI = \frac{W_2 - W_1}{W_1}$$

***In vitro* Floating Study:** The *in vitro* floating behavior of the tablets was studied by placing them in 900 ml of plastic containers filled with 900 ml of 0.1 N HCl. (pH 1.2, 37 ± 0. 5^{o}C). The floating lag times (time period between placing the tablet in the medium and tablet floating) and floating durations of the tablets were determined by visual observation [13].

***In vitro* Dissolution Studies:** In-vitro drug release studies of Ranitidine hydrochloride were studies using dissolution apparatus USP type II paddle method with a stirring speed of 50 rpm at 37 ± 0.5^{o}C in 900 ml 0.1 N HCl for 12 hours. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution media. The collected samples were diluted and the absorbance was measured spectrophotometrically at 313 nm. The percentage of Ranitidine Hydrochloride released at various time intervals were calculated from the standard graph and the kinetic release model was fitted on dissolution data[14].

RESULT AND DISCUSSION:

Precompression Parameter: The prepared powder mixtures were evaluated for the blend property like an Angle of repose, Bulk density, Tapped density and compressibility index Hausner's ratio.

The results of bulk density & tapped density were showed good flow properties of powder. The results were showed in the **table 2.**

TABLE 2: EVALUATION OF PRE-COMPRESSION PARAMETERS OF FORMULATIONS F1-F8

Formulations	Bulk Density* (± SD)	Tapped Density* (± SD)	Angle of Repose (^{0})	Carr's Index	Hausner's Ratio
F1	0.595± 0.20	0.668±0.22	26.67±0.49	18.75±0.22	1.27±0.72
F2	0.620 ±0.38	0.670 ±0.38	28.89±0.39	20.47±0.46	1.12±0.51
F3	0.639 ±0.26	0.718 ±0.29	27.13±0.85	15.17±0.23	1.26±0.49
F4	0.652 ±0.15	0.730 ±0.19	29.67±0.45	16.39±0.61	1.19±0.68
F5	0.668±0.29	0.742 ±0.28	26.34±0.81	21.65±0.24	1.27±0.72
F6	0.679 ±0.36	0.756 ±0.28	25.90±0.39	19.87±0.47	1.17±0.67
F7	0.712 ±0.29	0.778 ±0.39	24.23±0.56	14.55±0.48	1.32±0.56
F8	0.690 ±0.35	0.764 ±0.26	30.45±0.85	16.10±0.63	1.23±0.79

Physicochemical Properties: The prepared formulations were evaluated for the physical characteristics like thickness, hardness, friability, weight uniformity. The results obtained are shown in **Table 3**. The deviation from the average weight was found to be within the prescribed official limits. Hardness of tablets was found to be in the range of 3.2 to 4.6 Kg given in the table 3. The friability of all tablets was found to be in range of 0.52-0.94 which is less than 1% that showed good mechanical strength.

TABLE 3: EVALUATION OF PHYSICOCHEMICAL PROPERTIES OF FORMULATIONS F1-F8

Formulations	Hardness (kg/cm^2)* (±SD)	Thickness (mm)* (± SD)	% Friability	% Wt Variation (mg) (n=20)	F_{lag} (second) ± SD	Floating Time (hr) ± SD
F1	3.2± 0.28	3.16±0.43	0.54±0.24	400.1±0.21	14±1.52	18.87±0.48
F2	3.1± 0.26	3.31±0.24	0.73±0.59	380.3±0.27	12±2.08	19.15±0.57
F3	4.3± 0.26	3.35±0.27	0.86±0.65	400.5±0.55	16±3.05	21.34±0.44
F4	3.8± 0.35	3.19±0.54	0.79±0.53	400.6±0.34	15±2.08	19.07±0.52
F5	3.2± 0.31	3.32±0.29	0.62±0.58	400.2±0.28	12±3.51	18.68±0.55
F6	4.5± 0.50	3.34±0.31	0.56±0.51	370.1±0.34	11±1.05	21.89±0.33
F7	3.1± 0.57	3.31±0.53	0.94±0.22	360.6±0.29	12±1.05	21.17±0.45
F8	4.6± 0.24	3.29±0.11	0.52±0.25	440.8±0.45	10±2.99	22.79±0.65

***In-vitro* buoyancy study:** The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time. The formulation (F8) shows better floating lag time (10 second) and it was floated 22 hrs. The floating behavior of prepared batches was showed in table 3.

Drug Interaction compatibility study: Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). FTIR absorption spectra of Ranitidine Hydrochloride, HPMC, Carbopol 940, chitosan, Oryza sativa husk, Xanthan gum, cetyl alcohol and the combination of drug and polymers were shows no significant interaction between Ranitidine hydrochloride and polymer (**figure 1 and 2**).

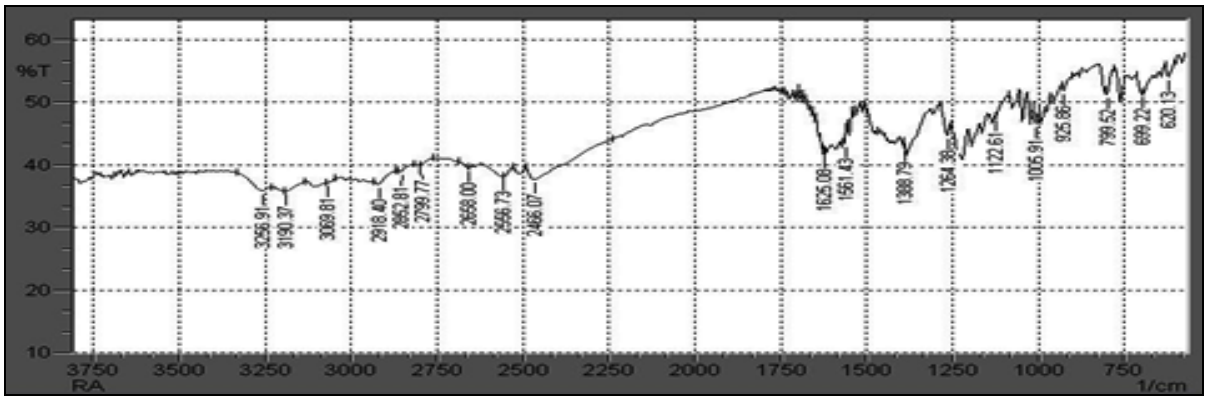

FIG. 1: FTIR SPECTRUM OF RANITIDINE HYDROCHLORIDE

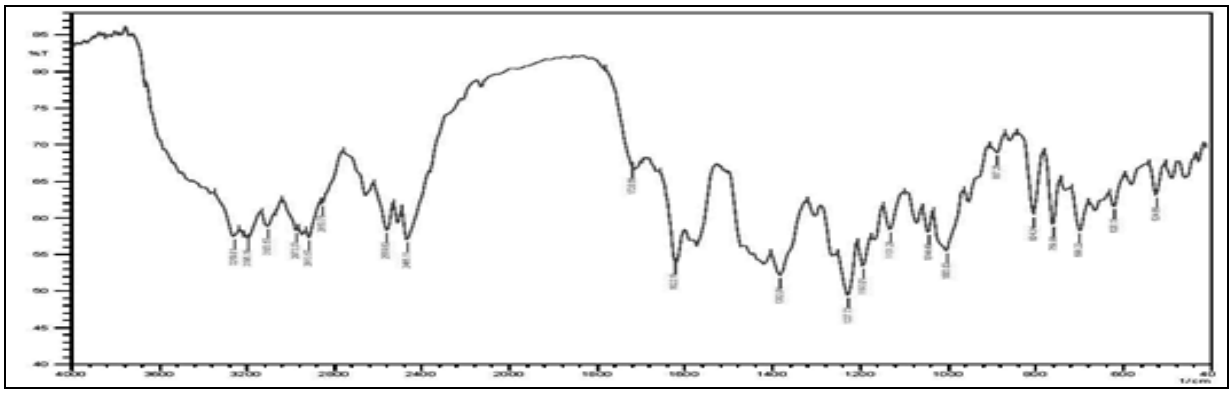

FIG. 2: FTIR SPECTRUM OF OPTIMIZED FORMULATION F8

***In-vitro* drug release study:** The data of *in vitro* release of ranitidine hydrochloride from different formulation combination are shown in table 3 and figure 1. The release behaviour was compared with marketed preparation. In Formulation F1, F2 and F4 showed 92.47%, 95.82% and 93.37% drug release at the end of 10 hours respectively.

The formulation F3, F5 and F6 were found to be 96.32%, 93.76% and 94.72% upto 11 hrs respectively. The Formulation F7 and F8 were showed 97.30%, 95.20 % drug release at the end of 12 hours respectively. The drug release from the marketed preparation was found to be 96.54 % in 12 hrs and it was nearer to optimized formulation F8. Hence, F8 was selected as optimized formulation because it gives sustained release of ranitidine hydrochloride over a period of 12 hours up to 95%. The percent drug release of all formulation was showed in **table 4 and figure 3.** *In vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism (**table 5**). The kinetic models used were zero order, first order, matrix and Hix. Crowel. The matrix model was fit to the formulation F8.

Stability Study: The stability study was carried out using the best batch. The Optimized batch was kept at condition of 40±2°C/75 ±5% RH and was analyzed at initial 30, 60 and 90 days. The optimized batch showed no significant effect on physical properties, drug content and drug release. It was concluded that tablets are stable after stability studies.

TABLE 4: % DRUG RELEASE OF FORMULATION F1 TO F8

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	MP
1	28.78±0.25	30.26±0.68	28.17±0.48	19.32±0.33	21.66±0.19	20.13±0.15	14.13±0.28	23.42±0.23	12.98±0.25
2	32.34±0.38	38.43±0.71	38.58±0.37	28.59±0.28	25.80±0.27	32.98±0.17	22.63±0.19	30.11±0.54	20.67±0.40
3	46.90±0.42	40.09±0.56	48.45±0.47	48.31±0.19	31.45±0.57	44.89±0.34	33.18±50	36.56±0.87	31.78±0.58
4	57.59±0.57	49.17±0.67	57.24±0.56	57.65±0.27	37.15±0.29	52.32±0.27	45.85±0.42	40.50±0.36	44.58±0.38
5	66.34±0.65	58.72±0.63	66.38±0.64	66.17±0.48	41.26±0.46	59.50±0.39	49.58±0.14	49.52±0.28	47.49±0.89
6	72.61±0.47	67.62±0.27	73.78±0.58	70.58±0.53	53.52±0.51	68.79±0.47	58.37±0.67	54.35±0.62	57.36±0.57
7	78.43±0.25	76.62±0.18	78.25±0.69	75.71±0.67	58.63±0.64	72.44±0.52	68.52±0.70	58.15±0.56	66.65±0.45
08	84.58±0.35	80.69±0.34	80.36±0.74	85.50±0.89	68.96±0.87	81.78±0.61	79.47±0.43	65.20±0.76	78.45±0.43
9	88.69±0.45	88.35±0.49	88.54±0.77	88.80±0.66	79.06±0.63	86.58±0.41	83.81±0.25	72.13±0.52	82.76±0.32
10	92.47±0.20	95.82±0.39	94.31±0.82	93.37±0.56	86.87±0.67	90.48±0.82	88.24±0.76	80.10±0.65	87.20±0.12
11	-	-	96.32±0.62	-	93.76±0.89	94.72±0.89	93.45±0.45	86.36±0.56	91.98±0.27
12	-	-	-	-	-	-	97.30±0.78	95.20±0.38	96.54±0.15

TABLE 5: KINETIC FITTING MODEL OF OPTIMIZED FORMULATION F8

Model Fitting (Average)		
Model	**R**	**K**
Zero order	0.9286	7.2000
1st order	0.9846	-0.1182
Matrix	0.9908	21.0068
Peppas	0.9883	19.6820
Hix. Crow.	0.9825	-0.0329

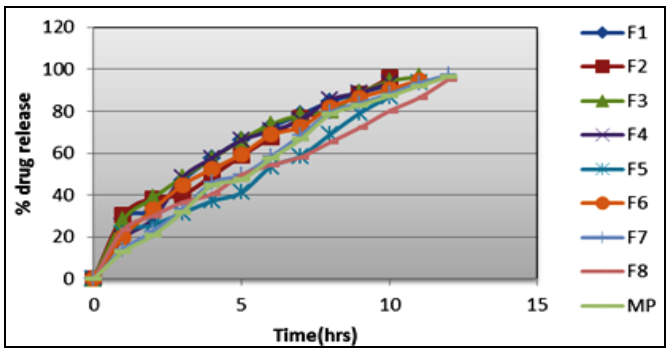

FIG. 3: % DRUG RELEASE OF RANITIDINE HYDROCHLORIDE

CONCLUSION: The present study was aimed at developing an oral floating system for Ranitidine HCL using combination of polymers like HPMC, carbopol 940,chitosan, oryza sativa husk, cetyl alcohol and Xanthan gum the floating tablets were prepared by using direct compression technique. The floating tablets of Ranitidine HCL were evaluated for physicochemical characteristics like thickness, hardness, weight variation, friability, floating lag time and swelling index. The *in-vitro* buoyancy studies, *in-vitro* drug release studies and the results were found that the optimized formulation F8 showed slow and sustained release of ranitidine hydrochloride over a period of 12 hours up to 95%.

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