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Sustained Delivery of Ranitidine HCl from Floating Matrix Tablets: Formulation and *in vitro* Evaluation

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The objective of this study was the preparation of floating matrix tablets of ranitidine HCl, a novel H2-recepter antagonist used in ulcerative condition of upper part of gastro intestinal tract. Various formulations were prepared using rate controlling hydrophilic matrix materials (HPMC K100M), effervescent agents (sodium bicarbonate, citric acid) by the wet granulation method. The granules were evaluated for angle of repose, bulk density. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, lag floating time, total floating time and *in vitro* release studies. *In vitro* dissolution tests were performed in 0.1 N HCl for up to 12 h. The release kinetics of ranitidine HCl was evaluated using regression coefficient analysis. Among the prepared formulations, F7 & F8 showed satisfactory *in vitro* lag floating time as well as *in vitro* release in the initial hours and controlled release up to 12 h. FTIR and XRD studies further confirmed the integrity of the formulation. Most of the formulations exhibited diffusion dominated drug release. The results suggest that the floating matrix tablets could perform better than the conventional sustained release dosage forms, leading to improved efficacy and better patient compliance.

Key Words: Ranitidine HCl, Floating matrix system, Sustained release, Effervescent.

INTRODUCTION

Sustained release (SR) floating delivery systems for oral dosing are very effective in achieving ideal therapy with drugs that are intended for local action or have a narrow window for absorption or drugs that are degraded in lower part of intestine, as in conventional sustain release dosage form[1-4]. Polymers of hydroxypropyl methyl cellulose (HPMC), are often used to prepare SR floating matrix tablets because these are low density, easy to handle, non toxic and do not require any special manufacturing technology for the production of SR tablets[5-7]. Reviews of the use of HPMC of different grades, carbopol, sodium bicarbonate in SR floating dosage forms have been published earlier[8-10].

Ranitidine HCl, a histamine H2-receptor antagonist is the first line drug used in the treatment of gastro-esophageal reflux disease, zoollinger-ellison syndrome and gastric ulcers. Ranitidine HCl was selected as a model drug due to its local action in stomach and upper part of gastro-intestinal. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 h. Again a traditional oral sustained release formulation releases most of the drug at the colon. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine HCl from the colon. These properties of ranitidine HCl do not favour the traditional approach to sustained release delivery. Hence, a floating drug delivery system of ranitidine HCl is desirable to increase the gastric residence time (GRT), which in turn producing local action and enhances its bioavailability. These systems helps in continuously releasing the drug before it reaches the absorption window. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficiency of drugs to reduce acid secretion.

Thus, the main aim of this study was to develop sustained release floating matrix tablets for ranitidine HCl. To achieve good floating ability and effective drug release up to 12 h, a hydrophilic polymer like HPMC K-100M was selected among different grades of HPMC and was used with various concentrations along with different binders.

EXPERIMENTAL

Ranitidine HCl was obtained as a gift sample from Albert David Limited (Mfg.), Kolkata, India. Hydroxy propyl methyl cellulose (HPMC K-100M), ethyl cellulose were obtained as a gift sample from Emcee Pharmaceutical Pvt. Ltd., Kolkata. Dibasic calcium phosphate, citric acid, sodium bicarbonate was purchased from S.D. Fine Chemicals, Mumbai. Talc, magnesium stearate, lactose, PVPK- 90 (Loba Chemicals, Mumbai). All the other chemicals used were of high analytical grade.

Preparation of floating matrix tablet: Different tablet formulations were prepared by wet granulation technique (Formulation F-1 to F9, Table-1).All the ingredients were sifted through #22 mesh before processing. Required quantities of drug, polymer and effervescent agents were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcohol solution of ethyl cellulose, PVP) was added slowly. After enough cohesiveness was obtained, the mass was sieved through #20 mesh. The granules were dried at 45 °C for 1 h. Dried granules were lubricated with talc and magnesium stearate and the tablets were compressed on 10 station Lab Press compression machine (Cip machineries Pvt. Ltd., Ahmedabad using 11.9 mm diameter, circular concave punches. Each tablet contained 150 mg of RHCl and other pharmaceutical ingredients as listed in Table-1.

Characterization of granules and tablets: Prior to compression, granules of floating matrix SR layers were evaluated for angle of repose was determined by funnel method. The floating matrix tablets were evaluated for hardness, friability, weight variation and drug content were determined using pharmacopoeia procedure[11].

Hardness was determined using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation was also checked. Drug content was determined by weighing 10 tablets individually and extracting both the drugs using methanol. The solution was filtered through 0.45 µm filter paper and absorbance was measured at 224 nm after suitable dilution.

TABLE-1
COMPOSITION OF VARIOUS FORMULATIONS

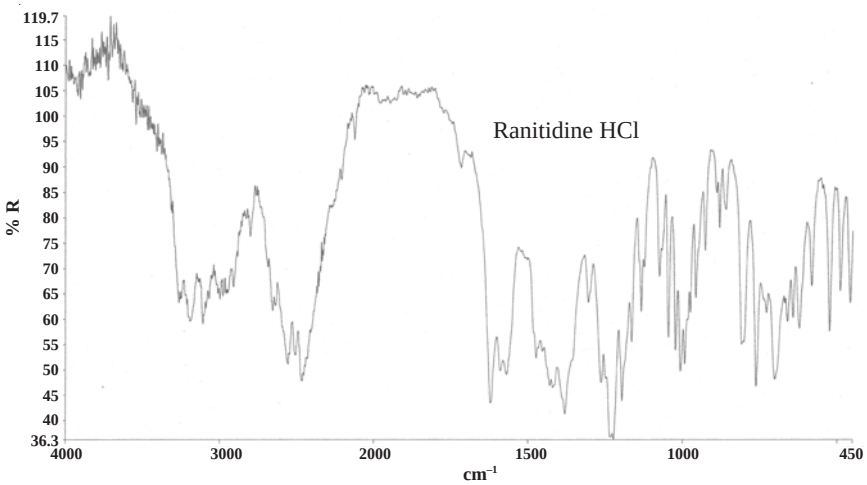
Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranitidine HCl	150	150	150	150	150	150	150	150	150
HPMC K100 M	110	220	330	110	220	330	110	220	330
Sodium bicarbonate	55	55	55	55	55	55	55	55	55
IPA	IPA qs	IPA qs	IPA qs	–	–	–	–	–	–
Ethyl Cellulose	–	–	–	20	20	20	–	–	–
PVP	–	–	–	–	–	–	20	20	20
Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Magnesium stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Citric acid	10	10	10	10	10	10	10	10	10
DCP	214	104	–	194	84	–	194	84	–
Total wt.	550	550	556	550	550	576	550	550	576

***In vitro* buoyancy and drug release studies:** The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using USP24 type II apparatus in 900 mL of 0.1 N HCl maintained at 37 ± 0.5 ºC and 75 rpm. The time required for tablet to rise to surface of dissolution medium and duration of time, the tablet constantly floats on dissolution medium were noted as lag time and total floating time, respectively.

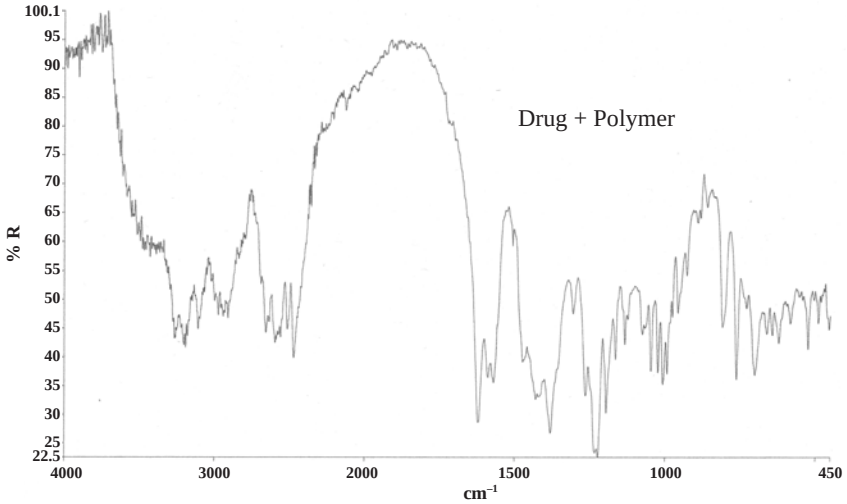
The *in vitro* buoyancy was also determined as per the method described by Rosa *et al.*[12]. The tablets were placed in a 100 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

The *in vitro* drug release was performed using USP XXIII type II apparatus in 900 mL of 0.1 N HCl maintained at 37 ± 0.5 ºC and 75 rpm. The samples were withdrawn at predetermined time intervals for period of 12 h and replaced with the fresh medium. The samples are filtered through 0.45 µm membrane filter, suitably diluted and analyzed by using double beam UV spectrophotometer at 224 nm. The content of drug is calculated using equation generated from standard calibration curve.

FTIR spectroscopy of ranitidine HCl and polymers: The drug polymer compatibility was ascertained by subjecting the drug, hydroxy propyl methyl cellulose to infrared spectrophotometer study. The spectra are given in Fig. 1.



a) Spectra of pure drug



b) Spectra of drug with polymer

Fig. 1

It has been observed that the absorption bands of both pure drug and drug with polymer remaining the same. It was concluded that no such interaction between the active medicament, polymer and other ingredient were occurred.

Mathematical modeling of release kinetics: The *in vitro* drug release data were fitted to various release kinetic models *viz.*, zero order, first order and Higuchi model. These models fail to explain the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data was also fitted to the well known exponential equation *i.e.* Korsemeyer-Peppas model.

Zero order kinetic model[13]: $Q_t = Q_0 + K_0 . t$

First order model: $\ln Q_t = \ln Q_0 + K_1 . t$

Higuchi model[14]: $Q_t = K . \sqrt{t}$

Korsemeyer-Peppas model[15]: $Q_t / Q_8 = K.t^n$

A value of n = 0.5 indicates case I (Fickian) diffusion or square root of time kinetics, 0.5 < n < 1 anamolous (non-Fickian) diffusion, n = 1 indicates case II transport and n > 1 super case II transport[16].

Polymer swelling studies: Swelling studies of the matrix tablets were carried out under the conditions of dissolution testing. The metallic baskets were weighed with a matrix tablet of the formulation and placed in the dissolution media. After 12 h of dissolution in phosphate buffer pH 6.8, the tablets were removed and wiped gently to remove the surface water. Water uptake and mass loss were determined gravimetrically as per the following equations[17,18].

$$\text{Degree of swelling (water uptake)} = \frac{\text{Swollen matrix weight} - \text{Original dry weight}}{\text{Original dry weight}} \times 100$$

RESULTS AND DISCUSSION

Characterization of granules and tablets: Granules of all the formulations were evaluated for angle of repose. Angle of repose obtained was in the range of 25.87° - 29.75° indicating satisfactory flow (data not given).

The total weight of floating matrix tablet ranged between 549 to570 mg. The hardness of the different formulations studied was in the range of 3.0-5.4 Kg/cm^2. The thickness of the tablets was found in the range of 4.64 to 5.43 mm.

The tablets also passed the friability test (F < 1 %), showing that all the formulations lie within the limits. The drug content of floating matrix tablet ranged from 99.50 ± 2.24 to 102.3 ± 3.25 as shown in Table-2.

TABLE-2
PHYSIO-CHEMICAL PROPERTIES

Formulation batch code	Drug content	Hardness	Thickness	Friability	Weight Variation
F1	99.56 ± 2.14	3.63 ± 0.15	5.432	0.64	549.65 ± 1.50
F2	101.25 ± 2.15	3.70 ± 0.12	5.262	0.67	550.25 ± 0.88
F3	100.00 ± 2.65	4.00 ± 3.20	4.64	0.54	555.2 ± 1.58
F4	98.89 ± 2.36	5.06 ± 0.15	5.39	0.46	550.25 ± 0.49
F5	102.30 ± 3.25	5.26 ± 0.32	5.114	0.48	549.85 ± 0.82
F6	99.50 ± 2.24	5.40 ± 30.20	4.998	0.45	569.75 ± 1.49
F7	100.00 ± 2.38	4.50 ± 0.05	5.214	0.5	549.5 ± 0.56
F8	102.24 ± 3.36	4.60 ± 0.11	5.252	0.56	550.12 ± 1.12
F9	99.56 ± 2.24	4.70 ± 30.11	5.006	0.58	572.5 ± 1.30

***In vitro* buoyancy and mechanism of drug release studies:** Hydroxypropyl methyl cellulose (HPMC) was selected for current study because it is a low density polymer and forms a viscous gel on contact with the aqueous media. Sodium bicarbonate

induced CO_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet becomes buoyant.

All the formulations except F4, F5 and F6 had floating lag time less than 5 min. These 3 formulations namely F4, F5 and F6 had lag floating time of 25 to 33 min (Table-3). This increased lag time may be due to presence of ethylcellulose (hydrophobic polymer). All the formulations floated constantly on dissolution medium for more than 12 h.

TABLE-3
in vitro RELEASE AND LAG FLOATING TIME

Time (h)	Cumulative % release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	29.19	24.19	19.86	22.47	19.73	15.99	26.52	20.18	16.70
2	43.37	38.53	32.48	30.27	25.94	22.01	35.73	28.95	24.43
4	60.13	55.27	48.60	44.83	37.60	32.50	49.15	40.54	33.80
6	79.50	73.51	67.71	56.75	48.98	41.71	60.87	52.03	45.69
8	90.85	87.39	80.37	72.34	64.54	55.60	74.56	66.51	59.41
10	104.03	95.48	90.02	85.40	77.92	69.97	88.37	80.45	74.13
12	-	-	-	93.90	86.40	81.31	97.45	92.35	84.56
Avg, Lag floating time (min) (n = 3)	2.50	4.70	9.00	18.50	25.50	30.50	5.30	6.30	10.50

HPMC forms a viscous gel on contact with the aqueous media, which may be useful in controlled delivery of highly water soluble drugs. The *in vitro* release profiles of formulations F1 to F9 are shown in following Fig. 2.

The dissolution results showed that all formulations except F1, F2 and F3 exhibited retarded drug release for over a period of 12 h. An ideal sustained release formulation should release the required amount of drug in the initial hour followed by slow and uniform release. Tablets of formulation F1, F2, F4, F7 and F8 released more than 20 % of drug in 1st hour. Formulations F1, F4 and F7 containing 110 mg of polymer showed more than 85.03 % of drug release within 10 h. Formulations F2, F5 and F8 containing 220 mg of polymer exhibited drug release about 95, 77 and 80 %, respectively within 10 h. Formulations F3, F6 and F9 containing 300 mg of polymer showed retarded drug release about 90, 69 and 74 %, respectively as shown in Table-3.

The concentration of the polymer and its high viscosity were found to have a marked effect on the drug release process. Release profile of the formulations prepared were fitted into zero order, first order, Higuchi's and Korsmeyer-Peppas models to describe the kinetic behaviour of the drug release mechanism from the matrix tablets, the most suitable being the one that best fits the experimental results. The choice of a specific model for a particular data set depends on the shape of the plot obtained

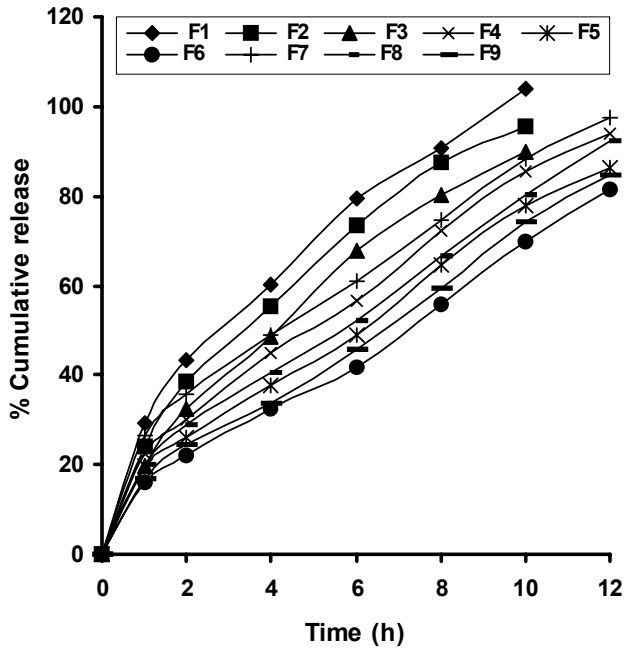


Fig. 2. Dissolution profile graph
F1 = (HPMC k100:20 %, IPA:qs), F2 = ((HPMC k100:40 %, IPA:qs),
F3 = ((HPMC k100:60 %, IPA:qs), F4 = (HPMC k100:20 %, EC:5 %),
F5 = (HPMC k100:40 %, EC:5 %), F6(HPMC k100:60 %,EC:5 %)
F7 = (HPMC k100:20 %, PVP k30:5 %), F8 = (HPMC k100:40 %, PVP k30:5 %),
F9 = (HPMC k100:60 %,PVP k30:5 %)

as well as on the underlying mechanism. Table-4 lists the values of regression coefficient of all models and release exponent (n), of Peppas model for formulations F1 to F9. Water soluble drugs are primarily released by diffusion of dissolved drug molecules across the HPMC gel layer. The formulations with lower levels of HPMC exhibited more burst release which can be attributed to the dissolution of the drug present initially at the surface of the matrix tablets as the tablet imbibes water and starts swelling. As the dissolution progresses, the gradual swelling of the outer layer creates proportionately new areas for drug diffusion. Since the matrix is hydrophilic, the permeation of dissolution medium takes place in the matrix and initiates dissolution of the drug from the inner layers. The dissolution rate is counter balanced by the gel formation of the matrix, which takes place simultaneously. The balance between the swelling and the gelling characteristics of the matrix system is critical in maintaining the desired drug release rate[19,20].

The *in vitro* release profile of the drug from all the formulations could be best expressed by Higuchi's equation as the plots showed high linearity (R^2: 0.9525-0.996) as shown in following Table-4. Tablets of batches F1, F2, F3, F4 and F7

TABLE-4
MECHANISM OF KINETICS

Formulation code	R^2 value of various release kinetics				n-value
	Zero order plot	First order plot	Higuchi's plot	Korsmeyer's & Peppes Plot	
F1	0.9419	0.9190	0.9960	0.9982	0.540
F2	0.9480	0.9009	0.9933	0.9970	0.590
F3	0.9660	0.9059	0.9852	0.9980	0.660
F4	0.9708	0.9460	0.9840	0.9900	0.580
F5	0.9795	0.9620	0.9709	0.9790	0.610
F6	0.9873	0.9690	0.9525	0.9770	0.650
F7	0.9555	0.9500	0.9909	0.9900	0.526
F8	0.9792	0.9560	0.9735	0.9800	0.600
F9	0.9863	0.9610	0.9525	0.9800	0.650

R^2 = Regression coefficient, n = slope.

followed Higuchi and Korsmeyer kinetics with high linearity, whereas formulations F5, F6, F8 and F9 followed zero order kinetics. To confirm the diffusion mechanism the data were fit into Korsmeyer'e equation.

The use of Korsmeyer-Peppas equation particularly, the interpretation of release exponent (n) values gives an insight into the release mechanisms. The n values ranged from 0.526 to 0.65. The lower n values indicated a Fickian diffusion type release mechanism, slightly higher n values of more than 0.62 indicated coupling of diffusion and macromolecular release mechanism. Formulations F1, F2, F4, F5, F7 and F8 exhibited diffusion-dominated drug release, whereas the mechanism of drug release from formulations F3, F6 and F9 was diffusion coupled with erosion.

Polymer swelling studies: At early times, significant water concentration gradients are formed at the matrix/water interface leading to water imbibition into the system, due to swelling of HPMC and resulting in dramatic changes of dimensions of the system. On contact with water the drug dissolves and diffuses out of the device[21]. The profile of the liquid penetration rate into the matrix tablets have been studied by Wan *et al.*[22-24] and their results indicated that the compacts containing HPMC of higher molecular weight show a greater liquid uptake and the polymer surface swells to form continuous gel layer and the matrix size increases. The studies showed that the maximum hydration degree was observed during the first hour of release. This was attributed to the presence of hydroxypropoyl groups which renders them more hydrophilic and thus more molecules are entrapped in HPMC matrices resulting in a gel type structure. These results are in accordance with studies reported by Cheong *et al.*[25].

Swelling study indicates that the swelling of the tablet increases with respective to time and directly proportional to the concentration as well as viscosity of the polymer.

Conclusion

Floating matrix tablets of ranitidine HCl were successfully prepared and evaluated for various *in vitro* parameters. Among the various formulations prepared using

different concentration of polymers and binders, F7 and F8 showed acceptable lag floating time and was able to sustain the drug release for a period of 12 h in a controlled manner. Mechanism of drug release was matrix diffusion controlled and followed zero order kinetics, respectively. All the formulations showed excellent buoyancy. Further the integrity of the formulations was confirmed by FTIR studies. The results suggest that the floating matrix tablets could perform better than the conventional SR dosage forms, leading to improved efficacy and better patient compliance.

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