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Research Article

Design and Development of Floating Tablet of Ranitidine Hydrochloride and Study the Effect of Formulation Variables

NATASHA SHARMA*[1], NEELAM BALEKAR[2], D.K. JAIN[2]

[1] Department of Pharmaceutics, Kota College of Pharmacy, Kota (RAJ.)-325003, INDIA

[2] College of pharmacy, IPS Academy, Rajendra Nagar, Indore (M.P.)-452012, INDIA

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ABSTRACT

The present investigation concerned with the development of Hydrodynamically Balanced Tablets of Ranitidine, which after oral administration are designed to prolong the gastric residence time and there by increase drug bioavailability. Preliminary trial batches were prepared and the best combination was selected on the basis of the floating behavior (floating time, total floating lag time). Than Ten batches of tablets were fabricated containing drug, and various grades of polymers HPMC K4M, HPMC K15M, HPMC K100M, HPMC 15cps, HPMC 3cps, and carbopol, along with gas generating agent sodium bicarbonate and calcium carbonate with acidulent adipic acid by using wet granulation technique to study the effect on these polymers on floating behaviors. The physicochemical properties of different formulations, their buoyancy lag time and total floatation time and swelling index were evaluated. It is found that the high viscosity grade polymers given better controlled release drug profile. The *in vitro* release studies (USP XXIII) indicated that the floating dosage forms containing (F9) HPMC K100M high viscosity grade polymer with calcium carbonate (effervescing compound) instead of sodium bicarbonate showed good drug release rate up to 12 h in comparison to other batches. The results indicate that gas powered hydrodynamically balanced tablets of ranitidine containing HPMC K100M provides a better option for controlled release action and improved bioavailability.

INTRODUCTION

Floating drug delivery systems (FDDS) or hydro dynamically balanced systems (HBS) one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract is to control the gastric residence time (GRT). FDDS will provide us with new and important therapeutic options by Singh B. M. (2000). FDDS or hydrodynamically balanced systems were first described by Davis (1968) [1].

FDDS have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate and released the drug slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

Author for Correspondence:

Email: natasha83sharma@gmail.com

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine and drugs show poor alkaline solubility and drugs that degrade in the colon**.** (Desai S., Bolton S, 1993) [2, 3].

Ranitidine hydrochloride (RHCl) is histamine H_2-receptor antagonist used to treat in active duodenal ulcers, gastric ulcers generally produced by the Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)**,** Zollinger-Ellison syndrome, Gastroesophageal reflux disease, and erosive esophagitis. 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 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine

hydrochloride is desirable. The short biological half-life of drug (~2.5-3 hours) also favors development of these formulation. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon. These properties of ranitidine hydrochloride do not favor the traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of ranitidine hydrochloride prepared with conventional technology may not be successful [4]. The present investigation applied a systematic approach to formulate the floating tablet of ranitidine with various grades of polymer hydroxyl propyl methylcellulose (HPMC) in various combinations. The prepared tablets were evaluated for physical parameters such as shape, dimension, hardness, friability test, weight variation test, buoyancy / floating Test, swelling index and drug content. All the tablets were evaluated for *In vitro* drug release studies [5,6].

MATERIALS AND METHODS

Ranitidine was obtained as gift sample (Ranbaxy Lab Ltd, Dewas, India). Other chemical and polymers such as hydroxyl propyl methylcellulose (HPMC K4M, K15M, K100M, 15CPS and 3 CPS) was obtained as gift sample from Ranbaxy Lab Ltd, Dewas, India). All other reagents and chemicals used were of analytical grade.

Preparation of Floating Tablet of Ranitidine Hydrochloride

Floating tablets containing Ranitidine Hydrochloride were prepared by wet granulation process using 2% PVP K-30 in Isopropyl alcohol as a binding agent using varying concentrations of different grades of polymers with Carbopol 934, sodium bicarbonate, calcium bicarbonate and adipic acid. Polymers and effervescent mixtures were blended in pestle and motor, 2% PVP-K30 solution in isopropyl alcohol was used as binder to form a moist mass. Granules were obtained by passing through the sieve no 12 the granules were dried at 45 ºC for 1 hour in oven dried granules were again passed through the sieve no. 22 and granules obtained was compressed in a tablet by using single punch hand operating tablet compression machine. Compositions of various formulation batches are shown in Table 1.

In vitro evaluation of floating tablets:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Pre-compression parameters:

a) Angle of Repose (θ):

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose
h = height of the heap
r = radius of the heap

b) Compressibility Index:

The flow ability of powder can be evaluated by comparing the bulk density (ρ_o) and tapped density (ρ_t) of powder and the rate at which it packed down [7]. Compressibility index was calculated by –

$$\text{Compressibility index (\%)} = \frac{\rho_t - \rho_o}{\rho_t} \times 100$$

Where ρ_o = Bulk density g/ml
ρ_t = Tapped density g/ml.

Post compression parameters:

Physical Parameters

The tablets were evaluated for shape, hardness (Monsanto hardness tester), thickness using calibrated varniear caliper, friability using Roche friabilator and weight variation test.

Drug Content

Twenty tablet of each formulation were crushed to powdered in pestle and motor and power equivalent to 100 mg of drug was added in 100 ml of 0.1 N HCL (pH 1.2). The resulting solution called the stock solution and filters the resulting solution through 0.45 µm membrane, diluted suitably and analyzed for drug content spectrophotometrically at 315 nm using 0.1 N HCL as a blank[8].

Table 1: Variation in final formulation by using various polymers

Ingredients*	Formulation batches									
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
Ranitidine HCl	316	316	316	316	316	316	316	316	316	316
HPMC K 100	80	-	-	-	-	-	-	40	80	-
HPMC K 15 MCR	-	80	-	-	-	-	40	40	-	-
HPMC K 4 MCR	-	-	80	-		-	40	-	-	-
HPMC 15 CPS	-	-	-	80	-	-		-	-	40
HPMC 3 CPS	-	-	-	-	80	-	-	-	-	40
Sodium alginate	-	-	-	-	-	80	-	-	-	-
Carbopol 934	20	20	20	20	20	20	20	20	20	20
$NaHCO_3$	50	50	50	50	50	50	50	50	-	50
$Caco_3$	-	-	-	-	-	-	-	-	50	-
Adipic acid	10	10	10	10	10	10	10	10	10	10
PVP K-30 (w/v)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Magnesium Stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%

Table 2: Various Pre-compression Parameters:

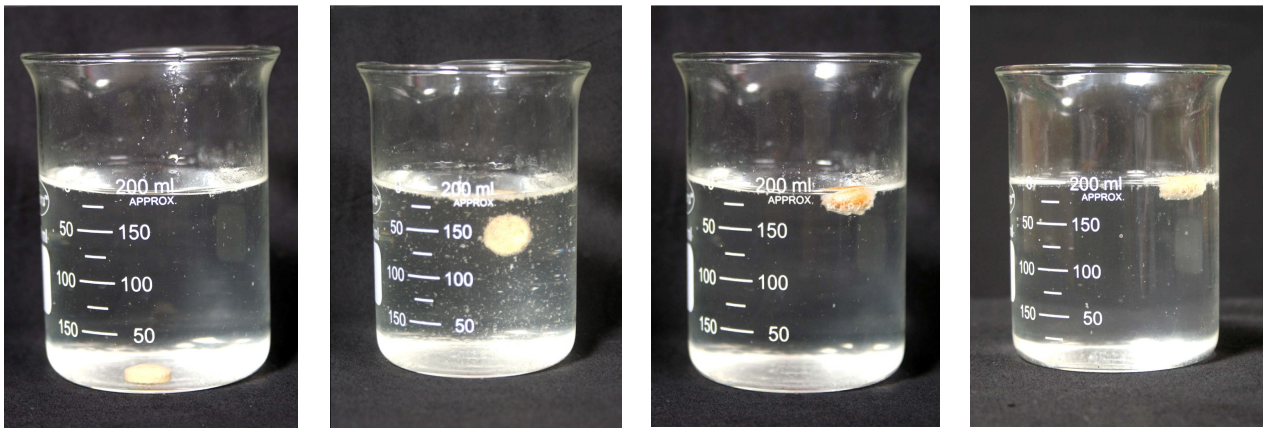
Batches	Bulk density	Tapped Density	Compressibility (%)	Remarks	Angle of Repose	Remarks
F_1	0.357	0.434	17.74	Good	34°.43′	Possible flow
F_2	0.343	0.396	13.38	Good	31°.70′	Good flow
F_3	0.350	0.433	8.3	Good	32°.15′	Possible flow
F_4	0.350	0.408	14.21	Excellent	34°.07′	Possible flow
F_5	0.386	0.468	17.52	Excellent	34°.77′	Possible flow
F_6	0.364	0.413	11.84	Good	30°.96′	Good Flow
F_7	0.360	0.428	16.02	Excellent	35°.36′	Possible flow
F_8	0.340	0.383	12.74	Good	39°.09′	Possible flow
F_9	0.335	0.376	10.90	Good	39°.28′	Possible flow
F_{10}	0.355	0.457	22.31	Faire to possable	39°.47′	Possible flow

Table 4: Swelling Index of various Formulations batches

Time	**Swelling Index (%)**									
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
1 hrs.	12	15	19	16	16	12	15	19	26	16
2 hrs.	29	35	30	20	25	29	35	30	34	25
3 hrs.	48	62	56	40	42	48	62	56	60	42
4 hrs.	68	85	72	61	63	51	75	72	71	63
5 hrs.	97	95	89	70	69	64	85	89	96	69

Table 3: Various post compression evaluation parameters

Batches	Uniformity of weight (mg)	Hardness (kg.cm^2)	Friability (%)	Drug Content (%)	Floating lag time (s)	Total floating Time (sec.)
F_1	480.65 ±1.29	5 ± 0.5	0.96	97.78	300S	>12 hrs
F_2	485.50 ±1.74	6 ± 0.7	0.77	97.15	145S	>12 hrs
F_3	481.55 ±1.18	6.5 ± 0.4	0.93	98.42	188S	>12 hrs
F_4	484.05 ±1.37	6 ± 0.5	0.84	94.63	68S	8hrs
F_5	485.65 ±1.49	5.5 ± 0.6	0.79	96.58	140S	7 hrs
F_6	483.49±1.49	6 ± 0.4	0.86	97.18	45S	7 hrs
F_7	485. 50 ±1.70	5 ± 0.5	0.85	98.13	180S	>12 hrs
F_8	484.30 ±1.39	6.5 ± 0.6	0.76	97.47	240S	>12 hrs
F_9	483.50 ±1.44	6 ± 0.7	0.89	97.83	420S	>12 hrs
F_{10}	485.61 ±1.24	5 ± 0.5	0.98	98.13	110S	7 hrs



At Initial Time | After 65 seconds | After 7 h | After 12 h

Figure 1: *In vitro* buoyancy studies

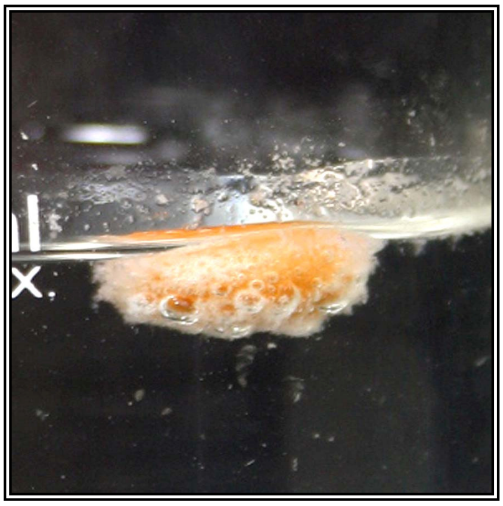


Figure 2: Tablet prepared by effervescent technique by using adipic acid and calcium carbonate

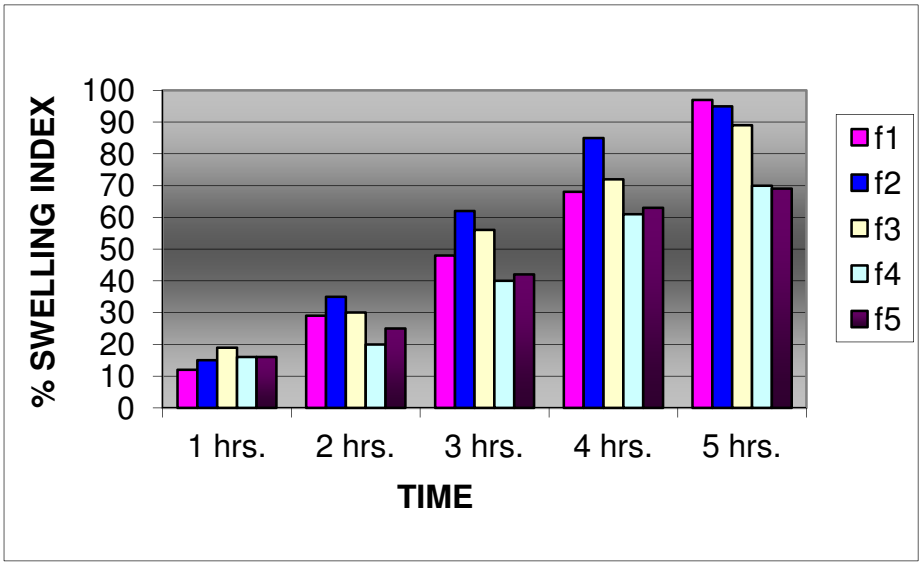


Figure 3: Swelling index graph of formulation F1, F2, F3, F4 and F5

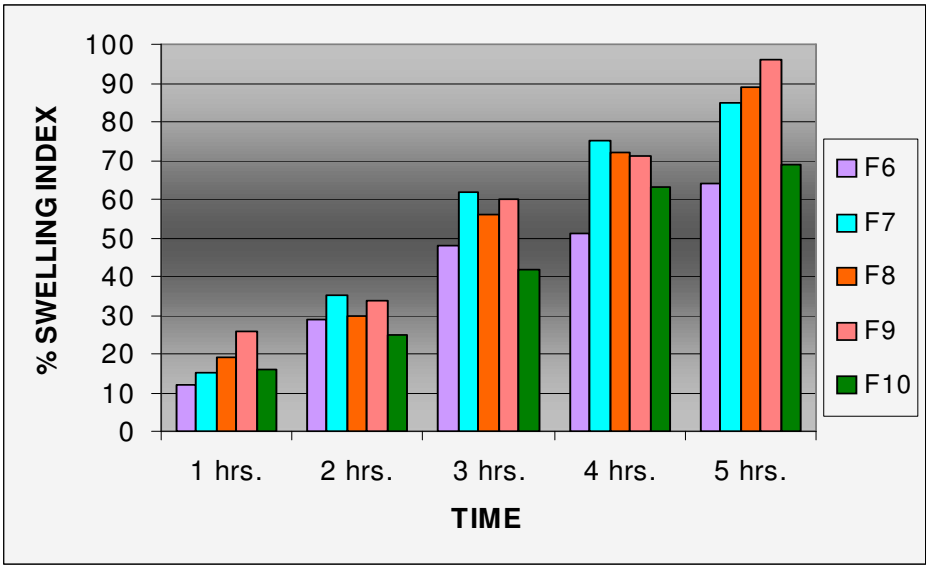


Figure 4: Swelling index graph of formulation F6, F7, F8, F9 and F10

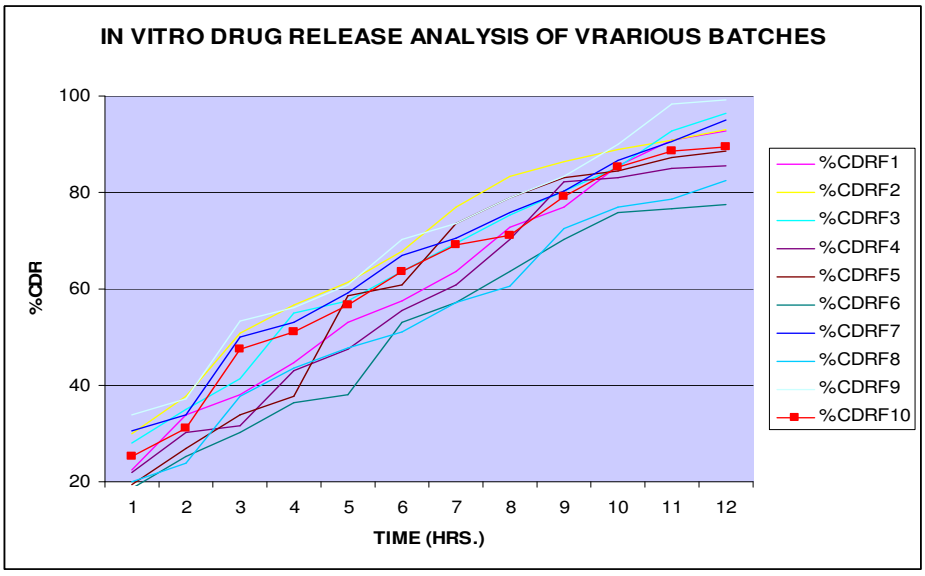


Figure 5: *In vitro* drug release study of various formulations

Buoyancy/Floating Test

Buoyancy capacity of tablets was determined using USP TYPE XXIII and the time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT) or total buoyancy time (TBT) [9,10,11].

Swelling Index (S.I.)

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and thickness over time. Percent Water uptake (%WU) was measured in terms of percent weight gain, as given by the equation.

$$\%WU = \frac{(W_t - W_0)}{W_0} \times 100$$

Where W_t = Weight of dosage form at time t and W_0 = Initial weight of dosage form.

***In vitro* drug release studies**

Drug release was studied using six station dissolution apparatus USP, XXII (paddle method) in 900 ml 0.1 N hydrochloric acid at 37±1 °C and 50 rpm, the difference being that although stirring was carried out using paddle shaft, the tablet were kept in to sinker (USP basket closed at both extremes) prior to their exposure into dissolution medium and the sinker was then placed horizontally at bottom. Moreover the paddle height was adjusted at 3.5 cm form the hemispherical bottom to avoid friction between the paddle shaft and sinker, which else may lead to erratic result. This ensured a complete exposure of tablet to the dissolution medium throughout the study [12, 13]. The study was performed in triplicate for a period of 24 hours. Five ml aliquots of sample were withdrawn at regular intervals and equal volume of pre-warmed (37±1°C) fresh dissolution medium was replaced. The samples withdrawn were filtered using 0.45 µm membranes, suitably diluted with 0.1 N hydrochloric acid and analyzed for drug content release using UV-VS spectrophotometer at 315 nm.

RESULT AND DISCUSSIONS

Pre-compression parameters: The result of various Precompression parameters was given Table 2. They were with in an acceptable limit.

Physical Parameters

Shape of Tablets: Microscopic examination of tablets from each formulation batch showed circular shape with no cracks.

Tablet Dimensions: Tablets mean thickness were almost uniform in all the formulations and were found to be in the range 0.5 – 0.6 mm. *Hardness:* The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in range of 5 – 6.5 kg/cm^2.

***Friability test*:** The test was found with in a limit. % friability of all tablets was found less than 1 %.

Weight variation: All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ± 5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values given in Table 3.

Assay of tablets: The percentage of drug content was found to be between 97.4% to 99.5%. This was with in acceptable limits.

Buoyancy/Floating Behavior of tablet: On immersion in 0.1N HCl solution pH (1.2) at 37^{0}C, the tablets floated, and remained buoyant without disintegration. Buoyancy behaviour of prepared tablet was given in Fig. 1, 2 and Table 3 shows the results of buoyancy studies and results of total floating time (TFT). Buoyancy lag time for formulation F1 to F10 in 0.1N HCl solution pH (1.2) at 37^{0}C are followed the order: F9>F1>F8>F2>F3>F7>F5>F4>F6. The total floating time (TFT) for formulation F1 to F10 in 0.1N HCl solution pH (1.2) at 37^{0}C are followed the order: F9, F8, F7, F3, F2, F1>F4>F5, F6, F10.

Swelling Index: Swelling study was performed on all the batches for 5 h. The results of swelling index are given in plot of swelling index against time (h) is depicted in Fig. 3 and Fig.4. The different formulations were arranged with respect to swelling index as: F1>F9>F2>F3, F8>F7>F4>F5, F10>F6. Maximum swelling index was observed with tablet containing HPMC K 100 M, HPMC K 15 M, and HPMC K 4 M with carbopol in ratio of (4:1) in Table 4.

***In vitro* Drug Release Studies:** The *in vitro* release of ranitidine from different formulations combination in Fig. 5 are shown that the release rates of the formulations were compares, it was found to follow the following order F9>F3>F7>F2>F1>F10>F5>F4>F8>F6. In the formulations F1, F2, F3, F4, F5, to F10 various grade HPMC were employed with carbopol 934

in single and two polymers with carbopol in combinations with ratio of 4:1. A decrease in the release rate was observed with an increase in the viscosity grades of the polymers. HPMC K-100 with carbopol (4:1) used in formulations F1 as a hydrophilic matrix polymers for controlling release of highly water soluble drug molecules Ranitidine. Drug release of 92.78 % at the end of 12 h. This slow release could be attributed to the formation of a thick gel structure that delays drug release from the tablets matrix.

CONCLUSION

Floating tablet of ranitidine showed acceptable weight variation, hardness and drug content. Buoyancy lag time, total floating time and swelling index studies showed satisfactory results. *In-vitro* dissolution of batch F1 to F10 containing HPMC K100M, HPMC K4M, HPMC K15M, HPMC 15CPS, HPMC 3CPS and Sodium alginate. Batch F9 containing HPMC K100M high viscosity grade polymer with calcium carbonate (effervescing compound) instead of sodium bicarbonate showed good drug release rate up to 12 h in comparison to other batches. The polymers HPMC K 100 and HPMC K 4 were used in combinations to measure the effect of their viscosity on drug release. Floating tablet of ranitidine containing HPMC K100M along with calcium carbonate and adipic acid exhibit better controlled release characteristics for 12 h. After the studies it was found that F9 formulation showed the better *in-vitro* drug release profiles.

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