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Formulation and Evaluation of Floating Tablets of Ranitidine HCl

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ABSTRACT

Floating tablets are retained in the stomach and are useful for drugs that are poorly soluble and unstable in intestinal fluids. Ranitidine HCl is absorbed only in the initial part of the small intestine and has 50 % absolute bioavailability. This present research describes an investigation of the formulation and evaluation of various parameters on the floating tablet of Ranitidine and to study the effect of HPMC (K15M) and HPMC (K100M) as a swelling agent and release retardant. The tablets were prepared by the direct compression technique, using matrix polymer, HPMC K15M, HPMC K100M, and stearic acid, sodium bicarbonate, magnesium stearate, talc, citric acid, lactose, PVP K30 as excipients. Different formulations were designed by using different concentrations of HPMC K15M and K100M. The lowest concentration used was 7 % of both HPMC and the highest concentration used was 14 % of both. Tablets were physically characterized for various parameters like general appearance, weight variation, hardness, friability, floating lag time, and total floating time and evaluated for in vitro release characteristics for 8 hrs in 0.1 N HCl medium at 37 ˚C. The result showed that all the pre-compression and post-compression parameters of floating tablets were within the limits of Pharmacopoeia, however, the dissolution profile of all the formulations was not within the limits of the theoretical drug release profile of the floating matrix controlled drug delivery system.

1. INTRODUCTION

A floating drug delivery system (FDDS) is one of the most important approaches for prolonging the retention time of drugs in the stomach [1]. Floating tablets are retained in the stomach and are useful for the drugs that are poorly soluble and unstable in intestinal fluids and drugs that have poor bioavailability are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption [2].

Ranitidine HCl is a histamine H2- receptor antagonist widely used in duodenal ulcers, gastric ulcers, Zollinger- Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis [3]. It is absorbed only in the initial part of the small intestine and has 50 % absolute bioavailability [4]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydro-dynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieving increased gastric residence time for the dosage form and sustained drug release [5]. Thus, this study is an investigation to formulate a floating tablet of Ranitidine.

2. MATERIALS AND METHODOLOGY

Table No. 1: Lists of materials used

Sr. No.	Uses	Materials
1.	API	Ranitidine HCl
2.	Swelling agent/release retardant	HPMC($K_{15}M$), HPMC($K_{100}M$) and Stearic acid
3.	Filler/diluents	Lactose
4.	Binder	PVPK30
5.	Glidant	Talc
6.	Effervescent agents	Sodium bicarbonate and citric acid
7.	Lubricant	Magnesium stearate

Nine batches of formulation was developed, the formulations were numbered from F1 to F9. For formulating the batches, the following steps were followed.

Weighing all excipients and API

Sieving all excipients through 30 mesh size

Mixing all ingredients in polythene bag for 5 minutes

Evaluation of pre-compression parameter was done

Powder blend was compressed using 8 mm die punch

Evaluation of post compression parameters was done.

Pre-compression parameters like angle of repose, bulk density, tapped density, Hausner ratio, Carr's index, void volume, and % porosity were determined. The above-prepared mixture was directly compressed. Evaluation of all batches of tablets was done [5-7].

Table No. 2: Composition of Ranitidine HCl floating tablet of different formulated batches

FC	Ranitidine HCl (mg)	HPMC K15M (mg)	HPMC K100M (mg)	Sodium Bicarbonate (mg)	Citric acid (mg)	Stearic acid (mg)	PVPK 30 (mg)	Talc (mg)	Magnesium stearate (mg)	Lactose (mg)
F1	167.39	24.5	24.5	17.5	13.5	17.5	17.5	3.5	3.5	60.61
F2	167.39	54.07	36.75	17.5	13.5	17.5	17.5	3.5	3.5	18.79
F3	167.39	36.75	36.75	17.5	13.5	17.5	17.5	3.5	3.5	36.11
F4	167.39	36.75	19.43	17.5	13.5	17.5	17.5	3.5	3.5	53.43
F5	167.39	49	24.5	17.5	13.5	17.5	17.5	3.5	3.5	36.11
F6	167.39	19.43	36.75	17.5	10.5	17.5	17.5	3.5	3.5	56.43
F7	167.39	24.5	49	17.5	10.5	17.5	17.5	3.5	3.5	39.11
F8	167.39	36.75	54.07	17.5	10.5	17.5	17.5	3.5	3.5	21.79
F9	167.39	49	49	17.5	10.5	17.5	17.5	3.5	3.5	14.61

Determination of λmax for Ranitidine HCl in 0.1 N HCl: Accurately 0.1g of reference Ranitidine HCl was weighed, and it was taken in the 100 mL volumetric flask containing a small amount of 0.1N HCl. Then the solution was shaken for 5 minutes for the complete dissolution of Ranitidine HCl in it and the volume to100 mL was made up of 0.1N HCl. The resultant solution was 1000 ppm. 2 mL was pipette and added to 100mL volumetric flask containing 0.1N HCl and volume was made up. The resultant solution was a 20 ppm solution. Then spectral scanning was done from 310 - 320 nm to find out the value of λmax [8].

Post-compression study: The tablets were evaluated by the following post-compression parameters [9, 10];

Weight Variation: Twenty tablets of each formulation were randomly selected and weighed individually by using an electronic balance. The average weight was calculated and the individual weight of the tablet was compared with the average weight. The weight variation of the tablet was calculated by using the formula below:

Weight variation = individual weight - average weight/average weight ×100

Tablet thickness: The thickness of the tablet was calculated by using a digital Vernier caliper. Ten tablets from the prepared formulation were randomly taken and thickness was measured.

Tablet Hardness: Tablet hardness testing was done to determine the breaking point of tablets. The hardness tester used for the study was the Monsanto hardness tester, which was performed by pressing a specifically dimensioned and loaded object into the surface of the tablet.

Friability test: Friability testing was done to test the durability of tablets during transit. Friability testing was done by using Roche friabilator. The individual weight of ten tablets of each formulation was weighed (Wo) and then carefully de-dusted at 100 revolutions and accurately weighed (W) again. Percentage friability was calculated by using the given equation below;

Friability = Initial weight (Wo) - Final weight (W)/Initial weight ×100%

***In vitro* dissolution test**: It was performed as described elsewhere [11]. The dissolution rate was studied by using a USP type I apparatus, at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. The temperature of the dissolution medium was maintained at 37 ± 0.2°C; the Aliquot of dissolution was withdrawn at every 1hour interval and filtered. The same quantity of the medium was added at the same temperature immediately after each sampling to keep the volume of the dissolution medium constant. The absorbance of the filtered solution was measured by UV spectrophotometric method at 313 nm and the concentration of the drug was prepared.

Floating lag time/Buoyancy test: The time between the introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remains buoyant were measured. The time taken for the dosage form to emerge on the surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and the total duration of time by which the dosage form remains buoyant is called Total Floating Time (TFT)[12]. Each tablet is put in an individual flask containing 100 mL of 0.1N HCl solutions. Then the time in minutes for each tablet to go from the bottom to the top of the flask (Floating Lag Time) and the time for which tablets constantly float on the water surface

(Total Floating Time) were measured.

3. RESULTS AND DISCUSSION

Determination of λmax: λmax of Ranitidine HCl was found to be 313 nm. A standard calibration curve of Ranitidine HCl was obtained by measuring absorbance at 313 nm and by plotting a graph of absorbance versus concentration.

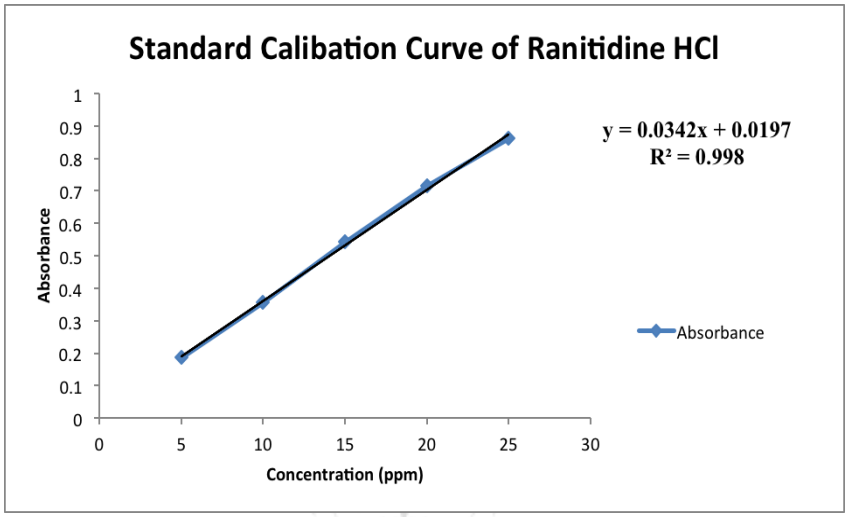

Figure No. 1: Standard calibration curve of Ranitidine HCl

PRE-COMPRESSION PARAMETERS

The angle of repose: The data obtained from the angle of repose for all the formulations were found to be within the range of 20 - 30. All the formulations prepared showed the angle of repose between 21.03 - 24.14 which reveals a good flow of powder thus prepared.

Bulk density: The bulk density of a powder depends on the particle size distribution, particle shape, and the tendency of particles to adhere together. The value of bulk density of all formulations prepared falls within the range of 0.3764 to 0.5920 g/cm^3.

Tapped density: It is found that the value of tapped density of all the formulations prepared falls within the range of 0.459 to 0.740 g/cm^3.

Carr's Index/compressibility: The compressibility index of the powder was found to be within the range of 16.59 to 20. This shows well to excellent flowability and compressibility of the powder mixture.

Hausner ratio of all formulations lies within the range of 1.21 To 1.25 showing good flow property of powder. A lower Haunser's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Table No. 3: Post-compression evaluation of formulated batches

Sr. No.	Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index	Hausner's ratio	Angle of repose (θ)	Void volume	% Porosity
1	F1	0.3764	0.459	17.99 .2	1.21	21.80	4.5	18
2	F2	0.4387	0.540	18.75	1.23	23.49	3	18.75
3	F3	0.5897	0.707	16.59	1.20	21.03	2	16.66
4	F4	0.460	0.564	18.43	1.22	22.75	5.5	29.72
5	F5	0.528	0.650	18.76	1.23	23.19	3	18.75
6	F6	0.560	0.700	20	1.25	23.74	3	18.75
7	F7	0.592	0.740	20	1.25	23.42	3	20
8	F8	0.5125	0.630	18.65	1.23	24.14	3	18.75
9	F9	0.574	0.717	19.94	1.25	22.61	3	20

Table No. 4: Post-compression parameters

Sr. No.	Formulation code	Friability %	Thickness (mm)	Weight Variation (mg)	Hardness (Kg/cm^2)
1.	F1	0.19	6.072 ± 0.014	360.8 ± 4.018	5
2.	F2	0.11	6.059 ± 0.020	350.5 ± 4.019	5.2
3.	F3	0.23	6.067 ± 0.014	350.95 ± 4.135	5.8
4.	F4	0.17	6.068 ± 0.017	349.25 ± 3.024	5.5
5.	F5	0.22	6.062 ± 0.021	350.2 ± 5.763	5.2
6.	F6	0.22	6.056 ± 0.026	349 ± 4.553	5.9
7.	F7	0.11	6.068 ± 0.022	350.2 ± 3.664	5.3
8.	F8	0.12	6.07 ± 0.018	349.8 ± 3.721	5
9.	F9	0.17	6.065 ± 0.024	349.75 ± 3.668	6

POST-COMPRESSION PARAMETERS

General appearance: Tablets were slightly pale yellow colored, round with a smooth flat surface.

Size and Shape: The size and shape of the tablets were as per the diameter of the die and punch used i.e. 8 mm.

Tablet Thickness: The thickness of all the formulated tablets falls within the range of 6.05 to 6.13 mm.

Friability: Friability indicates the ability of a tablet to withstand mechanical shocks while handling. The friability range was found to be 0.11 to 0.23 %, which indicates that all formulation batches, can withstand mechanical shock while handling before administration.

Hardness: The hardness of all formulated tablets was found to be 5 to 6 kg/cm^3.

Weight Variation: Since our formulation batch is 350 mg, so the weight variation permitted is ± 5% i.e. ± 17.5 mg is acceptable. All the formulated tablets were found within the range of 349 mg to 360.8 mg. Thus all formulation batches passed the weight variation test.

Table No. 5: Post-compression evaluation of formulated batches

Sr. No.	Formulation code	Floating Lag Time	Total Floating Time	Assay (%)
1.	F1	3 min 2 sec	< 1.5hr	100.05
2.	F2	3 min 16 sec	< 2 hr	99.80
3.	F3	3 min 20sec	< 2 hr	99.52
4.	F4	3 min 28 sec	< 2 hr	99.82
5.	F5	3 min 22 sec	< 2 hr	99.09
6.	F6	3 min 59 sec	< 2 hr	98.95
7.	F7	3 min 24 sec	< 2 hr	102.6
8.	F8	3 min 9 sec	< 2 hr	97.71
9.	F9	4 min 2 sec	< 2.5 hr	98.54

Floating Lag Time: The initial process to float involves gas generation from the system. This process occurs due to the reaction between sodium bicarbonate and HCl (acid-base reaction) with the release of CO_2. The floating lag time for all formulations was found between 2 minutes to 4 minutes.

Total Floating Time: The total duration of time by which dosage form remains float is the total floating time. The total floating time for all batches should be 12 hours and more. The total floating time of all formulated tablets was found within 1 hour 30 minutes to 2 hours 30 minutes, which doesn't comply with the intended result.

Assay: The result obtained shows that all formulation contains Ranitidine HCl not less than 97.71 % and not more than 102.6 %. This indicates the uniformity of dose in each batch and therapeutically equivalent.

Table No. 6: Drug release dissolution profile

Time (hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.58	11.14	11.68	11.85	12.51	11.39	11.98	6.19	7.46
2	13.11	12.42	11.81	11.88	11.14	12.12	8.96	8.63	9.22
3	14.46	15.4	15.17	14.62	14.3	14.62	25.86	11.95	11.47
4	19.96	19.1	18.08	18.8	18.31	20.2	12.58	11.79	12.18
5	17.68	17.45	15.72	16.27	11.63	12.18	12.49	11.63	11.24
6	25.38	24.76	21.07	23.81	23.74	24.05	11.95	12.18	13.13
7	25.83	24.68	24.52	24.84	25.78	24.84	57.85	57.74	54.94
8	24.76	24.41	23.97	23.9	23.26	23.97	14.85	12.1	12.34
9	-	-	-	-	-	-	13.2	13.28	14.15

In-vitro Dissolution Studies: All the formulated batches showed that not more than 12.58 % (21.06 mg) of the drug was released in the first 1 hour, formulated batches F1 to F6 showed not more than 25.83 % (43.29 mg), and formulated batch F7 to F9 showed not more than 57.85 % (96.85 mg) within 9 hours. This reveals that all the batches do not pass the dissolution test.

4. CONCLUSION

The effervescent-based floating drug delivery was a promising approach for the preparation of gastro-retentive floating tablets of Ranitidine HCl. The addition of gel-forming polymer (HPMC K15M and HPMC K100M) and gas-generating agent (sodium bicarbonate and citric acid) was essential to achieve *in vitro* buoyancy. These results indicate that a high amount of floating agent (sodium bicarbonate and citric acid) might have caused premature dissociation of tablet form. The combination of HPMC K15M and HPMC K100M in various percentages usually did not show an intended result, i.e. all the formulated batches were unable to release the desired concentration of the drug, concerning the time. As the dissolution studies of all formulations showed a decrease in the drug release after a certain time interval, which is unusual. The dissolution profile of F1 to F6 showed a decrease after 4 hours, whereas F7 to F9 showed a decrease after 3 hours.

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