

THE PHARMA INNOVATION

Preparation and evaluation of floating matrix tablets of Ranitidine Hydrochloride

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The objective of this research was to prepare a gastroretentive drug delivery system of Ranitidine hydrochloride. Quick GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to decreased efficacy of the administered dose and thus less patient compliance. Floating matrix tablets containing 150 mg Ranitidine were developed using different effervescent salts and polymer in combinations. The tablets were prepared by direct compression method, using polymers such as Hydroxy propyl methyl cellulose, Psyllium husk and Carbopol 934 in combination. Sodium bicarbonate and citric acid was incorporated as a gas-generating agent. Different tablet properties, floating lag time and floating time, swelling index and in-vitro drug release for 12h in 0.1mol/l HCl at 37°C were studied. The result of floating lag time indicates that increased content of Sodium bicarbonate and Citric acid in the formulations causes decreased floating lag time. All the batches showed floating time more than 12 hours. It is also observed that formulation A7 containing highest combination of polymer shows better controlled release behavior.

Keyword: Floating Matrix Tablet, Floating Time, Gastroretentive, Controlled Release, Ranitidine Hydrochloride.

INTRODUCTION: Ranitidine hydrochloride (RHCl) is a histamine H₂-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis¹.

The indicated oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. In the treatment of endoscopically-diagnosed erosive esophagitis, the dosage is 150 mg ranitidine 4 times a day²⁻⁴. A conventional dose of 150mg can inhibit gastric acid secretion up to 5 hrs but not up to 10 hours. An alternative dose of 300mg leads to plasma fluctuations; thus a sustained release dosage form of RHCl is desirable. The short biological half-life of drug (~2.5-3 hrs) also favors development of a sustained release formulation¹.

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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 bioavailability⁵⁻⁶. Colonic metabolism of ranitidine is also partly responsible for the poor bioavailability of ranitidine from the colon⁷.

These properties of RHCl do not favor the traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of RHCl prepared with conventional technology may not be successful.

A gastroretentive drug delivery system that can be retained in the stomach and also help increase the local delivery of ranitidine hydrochloride would also be very useful. There are a number of approaches that can be used to prolong gastric retention time, such as floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices⁸⁻¹⁰.

From the above requirements, it was decided to develop a dosage form to deliver ranitidine hydrochloride in the stomach as a floating drug delivery system using a low density approach.

A floating drug delivery system, which was less dense than gastric juice due to the incorporation of at least one porous structural element, has been described¹¹. Recently, research has been carried out using ranitidine hydrochloride as an effervescent-type drug delivery system¹².

The present investigation applied a systematic approach to the development of gastroretentive (Ranitidine hydrochloride) dosage forms.

Materials and Methods:

Materials

The chemicals were used Ranitidine Hydrochloride (Globe Pharmaceuticals Ltd, Bangladesh.), HPMC 2910, 15cps (Merck, Germany.), Microcrystalline Cellulose (Opsonin Pharma Ltd, Bangladesh), Psyllium husk (India), Carbopol 934 (Loba chemie pvt ltd, India), Sodium Bi-carbonate (Merck, India), Mg Stearate (Bangladesh), Citric acid Anhydrous (Merck, India), Colloidal Silicon Di-oxide (India).

Methods for Preparation of floating matrix tablet of Ranitidine Hydrochloride

Accurately weighed all the ingredients were passed through stainless steel mesh no. 100 separately. Ranitidine hydrochloride and all the excipients except lubricants were mixed. Finally Magnesium stearate and Colloidal silicon dioxide were added and mixed. Tablets were compressed on a single punch tablet compression machine using 13.2mm round, flat beveled punch and kept in a sealed air tight container.

Evaluation of floating matrix tablets

Thickness and diameter²⁰

The thickness and diameter of the tablets were determined by using slide calipers. Thickness and diameter of ten tablets was determined randomly. It was expressed in mm.

Crushing strength^{13,15,20}

The Veego hardness tester was used to determine the tablet crushing strength. Scale was adjusted to zero and load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the hardness of tablet. Hardness was expressed in Kg/cm².

Table 1: Composition of Ranitidine Hydrochloride floating matrix tablet

Ingredients (mg/ tablet)	Formulations						
	A1	A2	A3	A4	A5	A6	A7
API/ Excipients							
Ranitidine Hydrochloride	167.5	167.5	167.5	167.5	167.5	167.5	167.5
HPMC2910, 15cps	290	300	310	320	330	340	350
Psyllium Husk	40	50	60	70	80	90	100
Carbopol 934	5	10	15	20	25	30	35
Sodium Bicarbonate	10	20	30	40	50	60	70
Citric acid Anhydrous	2.5	5	7.5	10	12.5	15	17.5
Microcrystalline Cellulose	323.41	285.91	248.41	210.91	173.41	135.91	98.41
Colloidal Silicon Di-oxide	2	2	2	2	2	2	2
Magnesium Stearate	4	4	4	4	4	4	4

HPMC 2910, 15cps- Hydroxy propylmethylcellulose

Friability^{13,14, 20}

Friability was determined by using Veego Friabilator. Ten tablets were weighed and placed in the friabilator and then operated at 25 rpm for four minutes. The tablets were then de-dusted and weighed. It was expressed in percentage. The difference in the two weights was used to calculate friability.

$$\text{Friability} = 100 \times \left(1 - \frac{W}{W_0} \right) \quad \text{Where, } W_0 = \text{Initial weight,} \\ W = \text{Final weight}$$

Weight variation test^{20,13,14,15}

Ten tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and

none of tablet differs by more than double percentage limit.

Swelling index^{21,24}

The swelling index of the tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals and weighted till it come to constant weight and the swelling index was calculated by the following equation

$$\text{Swelling Index} = \frac{W_t - W_0}{W_0} \times 100$$

Where, W_0 is the initial weight of the tablet,
and W_t is the weight of the tablet at time t.

Tablets composed of polymeric matrices form a gel layer around the tablet core when it comes in contact with water. This gel layer governs the drug release. The kinetic of swelling is important because the gel barrier is formed by water penetration. Swelling is also vital to ensure floating.

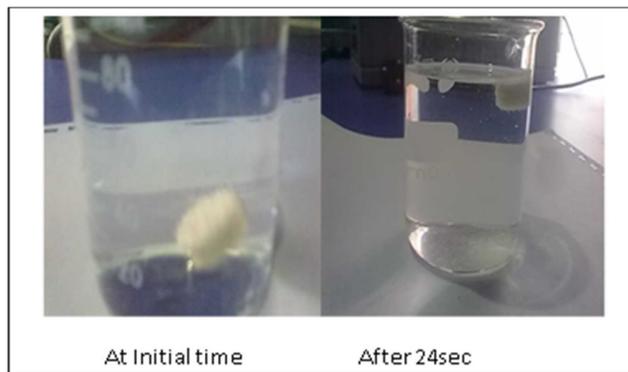


Fig.1: Floating lag time of Ranitidine Hydrochloride floating matrix tablet

Floating lag time^{22,23}

A tablet was placed in a 100ml beaker with 100 ml of 0.1N HCl fluid maintained at $37\pm 1^\circ\text{C}$. Then the time taken by tablet to move from bottom to top of the beaker was measured.

Floating time^{22,23}

Floating time was carried out in disintegration apparatus. About 100 ml of 0.1N HCl fluid was transferred in to 100ml Beaker in 1000 ml beaker at $37\pm 1^\circ\text{C}$. One tablet was placed in the apparatus and studies were carried out.

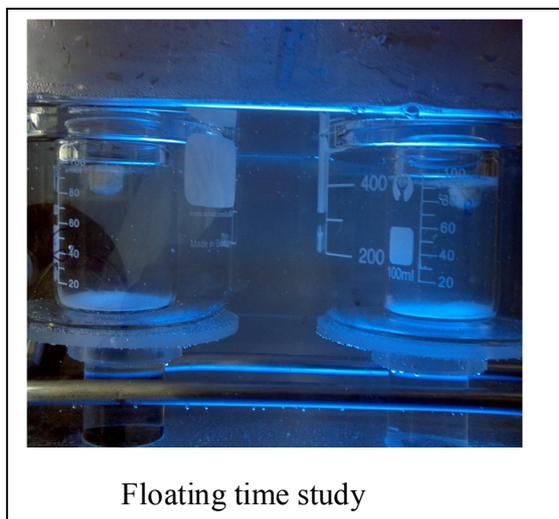


Fig.2: Study of Floating time of Ranitidine Hydrochloride tablet on disintegration test apparatus

Drug content^{1,18}

10 tablets were weighed and triturated. The tablet triturate equivalent to 20 mg of the drug was weighed accurately. Dissolved in 0.1N HCl and diluted to 100 ml with the same. It was filtered through Whatman filter paper no. 41. Absorbance was read at 313nm against the reagent blank.

The content of Ranitidine hydrochloride was determined by using the equation.

$$\text{content/ Tablet} = \frac{\text{Std wt.} \times \text{X Sample Abs.} \times \text{X Sample Dilution time} \times \text{X Std. potency} \times \text{X Avg. wt. of Tablet Drug}}{\text{Sample wt.} \times \text{X Std. dilution time} \times \text{X Std. Abs} \times \text{X Label claim}} \times 100$$

In vitro release studies for floating tablets^{18,19}

The In-vitro dissolution study was carried out in USP dissolution test apparatus, type 2 (paddle type) using 900ml of 0.1N HCl as dissolution medium. The temperature of dissolution media was maintained at $37\pm 0.5^\circ\text{C}$. The paddle rotation speed was kept at 50 rpm. One tablet at a time was weighed and taken for study. 5ml of the sample was withdrawn at every 1-hour interval for 12 hours and the same volume was replaced with pre-warmed fresh dissolution media. The sample withdrawn was diluted to suitable volume with 0.1N HCl and the absorbances were recorded at 313 nm using UV-VIS spectrophotometer.

Results

Pre-compression parameter

The prepared powder for the matrix tablet were characterized with respect to the angle of repose, Bulk density untapped, Bulk density tapped, Hausner ratio and Carr's index, which is shown in Table 2 for the above formulation. The Angle of repose was within 28° - 30.4° for all the formulations indicating satisfactory flow behavior.

Table 2: Pre-compressional and Physical properties evaluation

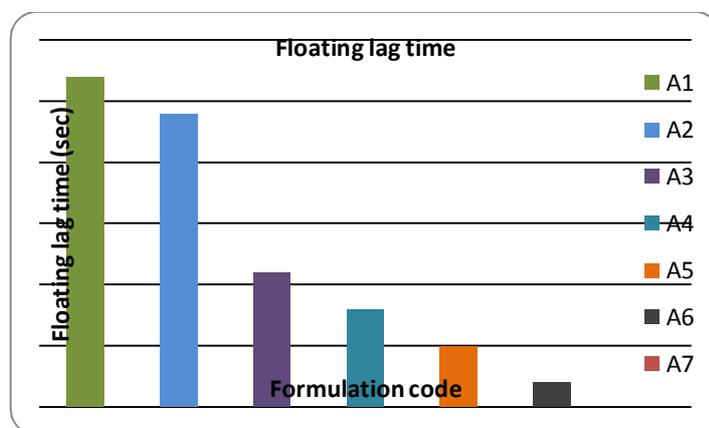
Formulation	Bulk density Untapped gm/cm ³	Bulk density Tapped gm/cm ³	Hausner's Ratio	Carr's Index (%)	Angle of repose (θ)	Thickness (mm) ±SD	Diameter (mm)	Friability (%)	Hardness (Kg/cm ²)±SD	Weight variation (gm) ±SD
A1	0.32	0.50	1.56	36	30.0°	5.65±0.013	13.2	0.48	9.4±0.053	0.842±0.00421
A2	0.33	0.52	1.58	36.5	29.8°	5.65±0.010	13.2	0.53	8.7±0.053	0.844±0.00426
A3	0.31	0.52	1.68	40.3	29.9°	5.7±0.013	13.2	0.44	7.4±0.070	0.845±0.00484
A4	0.31	0.51	1.65	39.2	30.4°	5.75±0.010	13.2	0.52	5.7±0.062	0.841±0.00424
A5	0.32	0.513	1.60	37.6	29.7°	5.7±0.013	13.2	0.56	8±0.066	0.842±0.00452
A6	0.339	0.53	1.56	36	28.0°	5.75±0.010	13.2	0.58	5.7±0.073	0.843±0.00455
A7	0.35	0.54	1.54	35	29.7°	5.75±0.013	13.2	0.47	5.8±0.066	0.844±0.00447

Physicochemical parameters

All prepared formulations were subjected for weight variation study and results given in table 2. 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 5.7 to 9.4 Kg given in the table 2. The friability of all tablets was found to be in range of 0.44-0.58 which is less than 1% that showed good mechanical strength.

Table 3: Floating lag time and floating time

Tests	Formulation						
	A1	A2	A3	A4	A5	A6	A7
Floating lag time (sec)	27	24	11	8	5	2	0
Floating time (hour)	>12	>12	>12	>12	>12	>12	>12

**Fig. 3: Floating lag time of Ranitidine Hydrochloride floating matrix tablet**

It is quite evident from the above table that floating lag time was decreased with increased content of Sodium bicarbonate and Citric acid in all the formulations which was due to generation of CO₂. Floating time for all the formulations was >12 hours which is optimum to provide controlled release of the drug.

In-vitro drug release study

Drug release study was done by using USP Dissolution test Apparatus II at $37\pm 0.5^\circ\text{C}$ temperature and at a speed of 50 rpm in 900 ml 0.1N HCl was used as a dissolution medium. Different combination of polymers was used to prepare floating matrix tablets of Ranitidine

Hydrochloride. It was observed that formulation A7 containing highest combination of polymer and gas generating agent shows better controlled release behavior, while formulation A1 containing least amount of polymer and gas generating agent shows less promising as controlled release floating matrix tablet

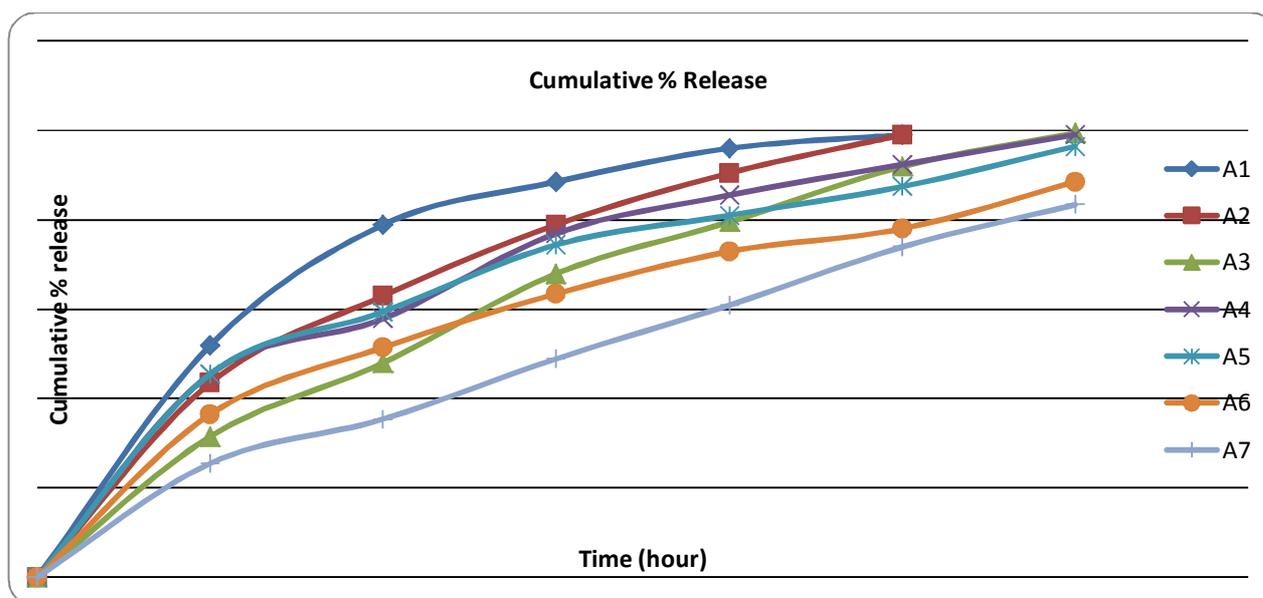


Fig.4: Dissolution profile of Ranitidine Hydrochloride floating matrix tablet.

Discussions

The floating matrix tablets of Ranitidine hydrochloride were prepared by direct compression technique using different polymer combination containing Hydroxy Propyl Methyl Cellulose (2910, 15cps), Carbopol 934 and Psyllium husk. Sodium bicarbonate, Citric acid were used as gas generating agent. Microcrystalline cellulose was used as diluents. Colloidal silicon di-oxide and magnesium stearate were used as glidant and lubricant respectively. The formulated floating matrix tablet's weight variation were within the range of pharmacopoeial specifications. The hardness of formulated tablet's were within $5.7\text{kg}/\text{cm}^2$ - $9.4\text{kg}/\text{cm}^2$ (A1 highest $9.4\text{kg}/\text{cm}^2$ and A6 lowest $5.7\text{kg}/\text{cm}^2$) indicates satisfactory mechanical

strength. The friability was less than 1% for all the formulations, which indicates good mechanical resistance of the tablet. The formulated tablets showed uniformity in drug content. The tablet swelled (A3 197.6% and A4 211%). It is quite evident from the findings that floating lag times decreases with increased content of Sodium bicarbonate and Citric acid in combination. The combination of Sodium bicarbonate and Citric acid provided desired floating ability. It was observed that the gas generated is trapped and protected within the gel, formed by the polymer HPMC (2910, 15cps), Carbopol 934 and Psyllium husk in combination and reinforces the floating ability of the tablet thus decreasing the density of the tablet below 1 and tablet becomes buoyant for a longer time. All the batches showed floating time more than 12

hours which is quite significant for a floating matrix tablet. It is also observed that formulation A7 containing highest combination of polymer and gas generating agent shows better controlled release behavior while formulation A1 containing least amount of polymer and gas generating agent shows less promising as controlled release floating matrix tablet.

Conclusion

In this study, the floating matrix tablets of Ranitidine hydrochloride were prepared by direct compression technique using different polymer combination containing Hydroxy Propyl Methyl Cellulose, Carbopol 934 and Psyllium husk. Sodium bicarbonate and Citric acid were used as gas generating agent. Microcrystalline cellulose was used as diluents. Colloidal silicon di-oxide and magnesium stearate were used as glidant and lubricant respectively. All the batches showed floating time more than 12 hours which is quite significant for a floating matrix tablet. It is also observed that formulation A7 containing highest combination of polymers and gas generating agent shows better controlled release behavior.

There is a further scope to conduct stability study, the in-vivo and laboratory studies by using various experimental animal models.

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synthetic dyestuffs produce hazardous by-products, some of which possess carcinogenic intermediates and hence a ban has been imposed by Germany and some other European countries on the use of benzidine dye in textile garments exported into their countries.^[3]

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