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Ranitidine Hydrochloride Floating Tablets of Intragastric Drug Delivery - Formulation and Characterization

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ABSTRACT

Floating drug delivery system has emerged as a potential candidate for gastroretentive drug delivery system. Despite colossal advancements in drug delivery, the oral route is the preferred route of administration of drugs due to ease of administration with high patient compliance. Gastroretentive drug delivery system can significantly extend the drug release for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability. The work was carried out with an objective of preparation and *in vitro* evaluation of floating tablets of Ranitidine hydrochloride as a model drug. Various formulations were prepared by wet granulation technique using the polymers such as HPMC K 100 M and HPMC K 15, HPMC E 5, Carbopol. The physiochemical properties of different formulations, total buoyancy lag time and floating time were evaluated. The formulation F5 was having the floating lag time of 90 sec and showed 98 % drug release at the end of 24 h. A combination of sodium bicarbonate and citric acid was found to achieve optimum *in vitro* buoyancy. The result of *in vitro* dissolution study showed that the drug release profile could be sustained by taking equal concentration of HPMC K 15and HPMC K 100M per tablet showed desired buoyancy with total floating time of >24 h. The optimized F5 formulation fitted in zero order drug release following Higuchi model. Hence it achieves the desired qualities for floating tablet and enhances patient compliance.

INTRODUCTION

Gastroretentive drug delivery system is one of salient pharmaceutical advancement technology. Gastric retention offers wide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. To enhance the longer drug action in upper part of the small intestine floating drug delivery system is an innovative drug delivery system [1]

Low-density systems also known as hydrodynamically controlled release system posses sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach. The gastric emptying rate will not get affected and significantly prolonged. To achieve the better control of fluctuations in plasma drug concentrations, the system floats on the gastric contents and the drug is released slowly at the desired rate. Floating drug delivery system minimizes mucosal irritation due to drugs since they have bulk density lower than gastric fluids.[2-3]

Floating dosage form is suitable drug delivery in the following contexts:

- Stomach is highly desirable for drug delivery
- Locally active in stomach
- Drug which posses' narrow absorption window in stomach or in upper small intestine.
- Drugs which disturb colonic bacteria
- Longer residence time in the stomach
- Drugs with low solubility at high pH value
- High variability in gastric emptying time [4-7].

Drugs with narrow absorption window and has highest solubility in gastric region are feasible for designing the floating drug delivery system[8].

Floating force (F) of minimal level is required to keep the dosage form buoyant in gastric fluids. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. The success behind formulating a floating drug delivery system involves many techniques such as hydrodynamically balanced systems (HBS), low density system, high density system, superporous hydrogel and magnetic systems [9-10].

Ranitidine is a competitive, reversible inhibitor of histamine at the H_2 receptors present in gastric cells. It leads to decreased gastric acid secretion, gastric volume and reduced hydrogen ion concentration. Ranitidine is used to decrease the amount of stomach acid produced, which can aid in the treatment of ulcers that are present and help prevent ulcer formation and also the heartburn from acid reflux[11].

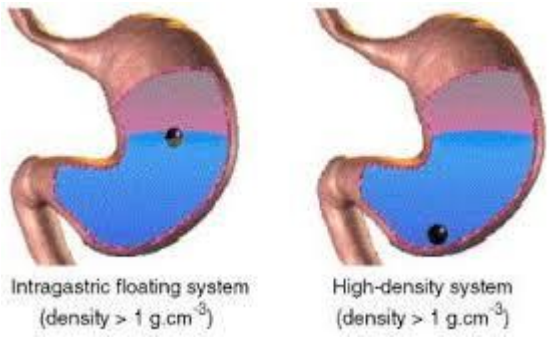

Fig 1: Intragastric floating system[12]

In high density system the drug action will be dipping to bottom of the stomach. Low density system involves the drug floats in the gastric juice. This is achieved by the liberation of carbon dioxide by chemical reaction between sodium bicarbonate and hydrochloric acid present in gastric juice and the gas ensures its floating nature[13-14]. the present work comprises of formulating Ranitidine hydrochloride as floating tablets for intragastic drug delivery to achieve a prolonged drug action.

MATERIALS AND METHODS

Ranitidine HCl, obtained as gift sample from Burgeon Pharmaceuticals, Chennai. HPMC E5, HPMC K 15, HPMC K 100 M, Carbopol 934, Guargum were obtained from Central Drugs Limited, Chennai. All the other chemicals used were of analytical grade.

Formulation of floating tablets[15 - 16]

The floating tablets of Ranitidine HCl containing 300 mg drug prepared by effervescent technology by wet granulation method. Ranitidine HCl was weighed accurately and passed through sieve # 30. The polymers HPMC E5, HPMC K 15, HPMC K 100 M, Carbopol 934 and all other excipients were passed through sieve # 40. Sifted materials were blended without addition of magnesium stearate and talc. Distilled water was added to dry-mixed blend of drug

and excipients slowly and the wet mass was mixed to get desired doughy consistency. The doughy mass passed through stainless steel sieve (#16) to form granules. Granules were dried in hot air oven at 50°C for 20 min and mixed with lubricant magnesium stearate and glidant talc. The final blend was compressed into tablets using single punch tablet rotary press (Cadmach)[16]. The details of the formulation were shown in Table 1.

FORMULATION OF RANITIDINE HCl FLOATING TABLETS

Table 1: Formulation of Ranitidine HCl floating tablet

Drug (mg)	F1	F2	F3	F4	F5
Ranitidine	300	300	300	300	300
HPMC E 5	90	60	-	-	90
HPMC K 15	-	-	-	-	-
HPMC K 100 M	-	-	75	90	60
Carbopol 934	-	-	75	60	-
Guar gum	60	90	-	-	-
Aerosil	45	45	45	45	45
PVP K 30	2	2	2	2	2
Sodium bicarbonate	50	50	50	50	50
Citric acid	40	40	40	40	40
Mg stearate	7	7	7	7	7
Talc	6	6	6	6	6
Total	600 mg	600 mg	600 mg	600 mg	600 mg

Evaluation studies

Preformulation parameters

Angle of repose

The angle of repose for prepared granules determined by Funnel method. The height of funnel is adjusted in such a way that tip of funnel just touches the apex of granules. Granules were

allowed to flow freely from the funnel. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

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

Where h and r are the height and radius of the heap of granules .[17]

Bulk Density

5 g of Ranitidine HCl granules were weighed separately and transferred into 100 ml measuring cylinder, initial volume was measured and calculated according to the formula[18]

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Volume}}$$

Tapped Density

Tapped density is found out by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus and it has been operated for a fixed number of taps until the powder bed volume has reached a minimum volume. From the weight of the granules in the cylinder, the minimum volume the tapped density may be calculated .[19]

Tapped density = Weight of granules/ Tapped volume of granules

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index [20]

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where,

TD = Tapped density

BD = Bulk density

The results of preformulation parameters were shown in Table 2.

Table 2: Preformulation studies of Floating Tablet Granules

Formulation	Angle of repose	Bulk density	Tapped density	Compressibility index	Hausner ratio
F1	29º 07′	0.45	0.55	18.18	1.22
F 2	26º 52′	0.49	0.58	15.51	1.18
F 3	28º 46′	0.46	0.56	17.85	1.21
F 4	26º 52′	0.42	0.52	19.23	1.23
F 5	25º 04′	0.45	0.51	11.76	1.13

Evaluation of tablets

Weight Variation

The formulated tablets were tested for weight uniformity. 20 tablets were collected and weighed individually. From the total weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is in permissible limits or not. The following formula was used to calculate weight variation.

$$\text{Percentage deviation} = \frac{\text{individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Test for Hardness

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. The hardness of five tablets was determined and the average value was calculated[22].

Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. 6 tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.[23]

Floating Time

Floating time was the time, during which the tablet floats in 0.1 N HCl dissolution medium (including floating lag time)

Floating Lag Time

In vitro buoyancy was determined by determining the floating lag time (i.e. the time period between placing the tablet in the medium and the tablet floating). It was carried out in beaker containing ml of 0.1 N HCl as a testing medium maintained at 37 °C. The time required for the tablet to emerge to the surface and float was determined as floating lag time.[24]

Estimation of drug content

Five tablets were weighed individually and the drug was extracted in 0.1 N HCL. The resulting solution was filtered through 0.45µ membrane. The absorbance was measured at 315 nm after suitable dilution using a Shimadzu UV-1601 double beam spectrophotometer[25]

***In vitro* release studies**

In vitro drug release studies were carried out by using USP paddle II dissolution test apparatus. 900ml of 0.1N HCl was taken as dissolution medium and maintained temperature at 37ºC±1ºC. The paddle was set for 50 rpm. Randomly selected six tablets from F5 were studied. 10 ml of sample was withdrawn at every 1 hour interval up to 24 h and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at 314nm using a Schimadzu UV- 1700 UV/VIS double beam spectrophotometer. Cumulative percentage drug release was calculated and shown in fig 2.

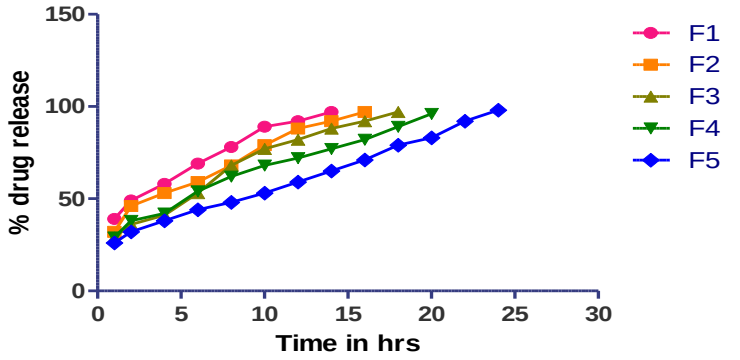

Fig 2: *In vitro* drug release of Ranitidine HCl

Kinetics of drug release

Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from sustained release gastroretentive matrix tablets. The kinetic models were zero order equation, first order equation, Higuchi model, Hixson-Crowell cube root law and Koresymer- Peppas model to further characterize the type of release.[26-29]

Table 3: Evaluation studies of Ranitidine hydrochloride Floating Tablet

Formulation	Hardness (kg/cm^2)	Friability (% w/w)	Average weight (mg)	Drug content (%)	Buyoancy lag time (secs)	Total Floating time (h)
F1	4.20	0.18	598	96.64	80 sec	21 hr
F 2	4.70	0.42	597	94.24	95 sec	22 hr
F 3	5.21	0.36	601	97.79	1min	20 hr
F 4	5.62	0.24	598	97.35	1 min	22 hr
F 5	4.91	0.17	599	98.45	90 sec	24 hr

Table 4: Stability study (*in vitro* drug release)

RESULTS AND DISCUSSION

An attempt was made to formulate Ranitidine hydrochloride tablet as floating drug delivery system by wet granulation method using various polymers like HPMC K 100, HPMC E 5, HPMC K 15, Guargum etc. Totally five batches were prepared.

The tablets were subjected to various preformulation parameters like angle of repose, bulk density, tapped density and Carr's index. All the preformulation parameters lie within prescribed IP limits. Among the formulation ranging from F1 - F5, F5 showed good flow property since the angle of repose was 25º 04′. From the result it can be seen that the bulk density values are less than $1.2gm/cm^3$ and Hausner,s ratio less than 1.35 indicate good flow characteristics of the floating tablets.

It was observed that there was change in buoyancy lag time and duration of buoyancy with the change in the proportions of polymer with sodium bicarbonate. This phenomenon might be due to the outermost hydrophilic colloid when contacts with an acidic medium (gastric fluid) hydrated to form an outside gel barrier around the tablets that acquired and maintained a bulk density of less than one thereby being buoyant in the medium.

Buoyancy lag time for 5 batches were 1 min 20 sec, 95 sec, 1 min, 1min and 90 sec respectively. The Ranitidine HCl floating tablets provide good floating behavior in the fluid medium same like stomach fluid. Gas generating agent concentration controls the floating properties of the tablet.

Changing the viscosity grade of HPMC from E5 to K100 had significant effect on drug release profile. *In vitro* drug release study reveals that F5 gave 98% drug release at the end of 24 h. This may be attributed to increased swelling and increased gel barrier between the dissolution medium outside and the drug inside the formulation as the concentration increases delayed drug release was obtained. Kinetic release data suggests that it follows zero order release fitted in to Higuchi model since r value was found to be 0.9721. The required release rate from the floating tablets can be readily obtained by changing the concentration of gas generating agent and the polymer. Hence F5 meets all the requirements for Ranitidine HCl floating tablet.

CONCLUSION

Ranitidine hydrochloride floating tablets were prepared by wet granulation method. The optimized formulation F5 floats in the stomach for > 24 h. A satisfactory drug release 98% was observed in F5 at the end of 24 hr. Stability studies shows that the formulation maintains its consistency and integrity during the period of storage. Hence the prepared tablet enhances the bioavailability making it as promising drug delivery system.

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