

Development and *in vitro-in vivo* Behaviour of Nizatidine Floating Tablets

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ABSTRACT

The purpose of this research study was to develop and optimize a controlled- release floating tablet of highly water soluble drug Nizatidine in an effort to increase its gastric retention time in the stomach. The tablets were prepared by direct compression method and Hydroxypropylmethylcellulose (HPMC) of different viscosity grades, Carboxymethyl cellulose Sodium (NaCMC) were incorporated as retarding polymers. Sodium bicarbonate was incorporated as effervescent agent. Formulations were evaluated for weight variation, thickness, hardness, percentage swelling, friability, and in vitro drug release, and floating lag time, total duration of floating, dissolution efficacy and in vivo Mean Residence Time (MRT) in the stomach. The formulation F6 with HPMC K 4M exhibited floating lag time of less than 1min and floating time of more than 12 hrs. The drug release of the optimized formulation followed Higuchi kinetic model ($R^2=0.9832$) and the mechanism of drug release was found to be super case II according to Krosmeier-Peppas (n value is 0.60). In vivo nature of tablet was observed at different time intervals with help of radiographic pictures in healthy human volunteers and MRT in the stomach was found to be 320 minutes.

Key Words: Gastroretentive Controlled release. Nizatidine. X-ray imaging.

INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades mainly because of their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [1].

Most of the conventional oral drug delivery systems have shown some limitations related to fast gastric-emptying time. Therefore, control over the position of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem [2].

Gastroretentive Drug Delivery Systems (GRDDS) are particularly useful for the drugs that are characterized by Narrow Absorption Window (NAW) in the upper part of the gastrointestinal tract. It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical DF with gastroretentive properties would enable an extended absorption phase of these drugs. After oral administration, such a DF would be retained in the stomach and release the drug there in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs for these drugs [3, 4].

In recent years, several gastroretentive approaches like i) Floating drug delivery system [5] ii) expandable systems [6] iii) bioadhesive systems [7] and iv) High density systems [8], have been designed and evaluated with much success. Floating systems are of two types: A) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids.

In the study conducted by Abdul et al., 2002 [9], H₂-receptor antagonists, nizatidine and ranitidine were susceptible to metabolism by colonic bacteria, which in turn has ramifications for drug delivery and absorption. Thus, it is a logical way to improve the therapeutic efficacy of the drug if the gastric residence time of the dosage form is increased at the absorption site.

Hydrochloric acid secreted by gastric parietal cells is most damaging and most consistent component form of refluxate. For this reason, current GRDDS pharmacotherapy focuses mainly on minimizing gastric acidity, either by neutralizing acids once it has been secreted (antacids), or by blocking important stimulator of this pump histamine (H₂ receptor antagonist) [10].

Nizatidine is a histamine H₂-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastroesophageal reflux disease (GERD). Its oral bioavailability is about 70% and biological half life is about 2hrs.

The main objective of present investigation was to design and *in vitro/ in vivo* evaluation of more promising Nizatidine effervescent floating tablets for better delivery to stomach with an aim of increasing the mean residence time in the stomach. The optimum formula that combined excellent floating behaviour and sustained drug release characteristics was chosen for further *in vivo* investigation in human volunteer to determine the mean gastric retention period.

MATERIALS AND METHODS

Materials

Nizatidine was obtained as gift sample from Dr. Reddy's laboratories (Hyderabad, India). Hydroxypropyl methylcellulose (Methocel K4M, Methocel K15M) and sodium carboxymethyl cellulose (NaCMC 2400cps) were supplied by Aurabindo Pharmaceutical (Hyderabad, India) were supplied by Aurabindo Pharmaceuticals (Hyderabad, India). Sodium bicarbonate was supplied by S.D. Fine Chemicals Pvt (India). All other chemicals used were of analytical grade.

Methods

Preparation of floating matrix tablet.

Effervescent floating matrix tablet containing Nizatidine (150 mg) were prepared by according to the design depicted in table 1, by direct compression method. Various batches were prepared by varying the ratio of HPMC K4M, HPMC K15M and NaCMC to identify the most effective formulation.

The floating drug /polymer mixture was prepared by homogenously mixing the drug with HPMC K4M, HPMC K15M and NaCMC, gas forming agent and passing the mixture through sieve no.20.

The mixture (600mg) was then compressed using an 12-mm diameter die in a single stroke multi-station tablet machine (Cadmach Machinery Co, Ahmedabad, India). The hardness of the tablet was adjusted at 5 kg/cm² using Monsanto hardness tester (Cadmach Machinery Co, Ahmedabad, India).

Table. 1. The composition, in milligrams, of the investigated Nizatidine floating tablets

CODE	Nizatidine	SBC	HPMC K4M	HPMC K15M	NaCMC	MCC
F1	150	60	300	---	---	78
F2	150	60	240	---	---	138
F3	150	60	180	---	---	198
F4	150	60	120	---	---	258
F5	150	60	60	---	---	318
F6	150	60	90	---	---	288
F7	150	60	---	60	---	318
F8	150	60	---	90	---	288
F9	150	60	45	45	---	288
F10	150	60	30	30	---	318
F11	150	60	---	---	180	198
F12	150	60	---	---	300	78

All formulations containing 1% Talc, 1% of Magnesium stearate.

Evaluation of tablets

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values \pm SD.

Tablet thickness

A vernier caliper was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values

In Vitro Buoyancy Studies

The *in vitro* buoyancy was determined by floating lag time as per the method described by Rosa et al [11]. Briefly the tablets were placed in a 200-mL of 0.1 N HCl, maintained in a water bath at $37 \pm 0.5^\circ\text{C}$. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT). The *in vitro* buoyancy time for all the formulation were reported.

Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (600 mg) was extracted in 100 mL of 0.1N HCl. The solution was centrifuged at 3000 rpm for 15 min. The drug content was analysed at 242 nm using a UV/ visible spectroscopy (Systronics PC Based, 2202, Ahmedabad, India) after suitable dilution with 0.1 N HCl.

Tablet friability

According to the BP specifications [12], 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus (Campbell Electronics, Mumbai, India). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated for all formulation and was reported.

Water Uptake Studies

The swelling behaviour of dosage unit can be measured either by studying its dimensional changes, weight gain, or water uptake [13, 14]. Water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in 900 ml of distilled water which was maintained at $37 \pm 0.5^\circ\text{C}$, rotated at 50 rpm. Excess surface water was removed carefully using a filter paper. At selected regular intervals, the swollen tablet was withdrawn and reweighed. Percentage swelling of the tablet is expressed as percentage water uptake (%WU) [15, 16].

$$\% \text{WU} = \frac{(W_t - W_0)}{W_0} \times 100 \quad 1$$

Where W_t is the weight of the swollen tablet, and W_0 is the initial weight of the tablet.

Drug release studies

Drug release studies of the prepared floating tablets as well as the commercially available Nizatidine 150 mg tablets were performed, in triplicate, by using USP Dissolution Tester Apparatus, type- II (Paddle method) and the temperature is maintained at $37 \pm 0.5^\circ\text{C}$. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 mL of 0.1 N HCl solution (pH 1.2). Aliquots of 5mL were withdrawn from the dissolution apparatus at predetermined time intervals. The drug content was determined spectrophotometrically at a wavelength of 242 nm, as mentioned before. At each time of withdrawal, 5mL of fresh medium was replaced into the dissolution flask. The mean of at least three determinations was used to calculate the drug release. The dissolution profiles were evaluated for amount of drug released in initial 15 min ($Q_{15\text{min}}$), time taken to release 50% of the drug ($T_{50\%}$), Dissolution efficiency (DE)% [17] after 60 minutes and mean dissolution time (MDT) min [18].

Drug release kinetics

The kinetics of drug release was examined by plotting the data obtained from in vitro drug dissolution studies in various kinetic models such as Zero-order, First-order, Higuchi release model [19] and Korsmeyer and Peppas model [20]. The equation for these models is as follows
Zero-order release (Eq. 2) data is plotted as percent drug release *versus* time.

$$F = k \cdot t \quad (2)$$

Where F is the fraction of drug release,
k is the release constant and
t is the time.

First-order release (Eq.3) is obtained by plotting log percent drug released *versus* time.

$$\ln F = k \cdot t \quad (3)$$

Where F is the fraction of drug release,
k is the release constant and
t is the time

As per Higuchi release (Eq. 4) data is plotted as percent drug release *versus* square root of time.

$$F = k \sqrt{t} \quad (4)$$

In Krosmeier - Peppas model (Eq 4) the data obtained is plotted as log percent drug release *versus* log time.

$$F = kt^n \quad (5)$$

Where n is the diffusional Coefficient.

Abdominal X-ray imaging

X- Ray imaging studies were conducted to confirm the *in vivo* buoyancy of the tablet. Three healthy male human volunteers in the age group of 20-23 and weighing between 55-70 kg were selected for the study; they were made clear about the usage and adverse effects of the drug. The tablets loaded with Barium Sulphate were administered orally. During the study they were allowed to take light meal and water. The X-ray photographs were taken at different periods of time to find the total residence time of the tablet in the stomach [21, 22]. The institutional Human Ethical Committee approved the protocol for the study

RESULTS AND DISCUSSIONS

Physicochemical characteristics of tablets

Gastroretentive tablets of Nizatidine tablets were prepared by direct compression method using Micro Crystalline Cellulose (Avicel PH 101), as it imparts superior flow properties and enhances powder compaction in direct compression. Moreover it is reported that microcrystalline cellulose is capable of swelling in contact with aqueous fluids such as simulated gastric fluids leading to an increase in the water uptake capacity, porosity of the matrix and consequently would enhance the floating abilities of the dosage forms [23].

The data of physical parameters like thickness, content uniformity, weight variation, floating lag time and total duration of floating of all formulations are enclosed in the table 1.

Ray et al., [24] while working on Losoratan reported that an increase in hardness will lead to an increase in floating lag time due to difficulty in penetration of the dissolution medium into the dosage form. Based on these references the hardness of the tablet was adjusted to 5Kg/cm².

Floating behaviour

The investigated gastric floating systems employed NaHCO₃, as a gas-forming agent dispersed in a hydrogel matrix (HPMC K4M, HPMC K15M and/or NaCMC). These matrices are fabricated so that upon arrival in the stomach, sodium bicarbonate in the acidic environment reacts with the acid and produces carbon dioxide. The evolved gas will get entrapped in the matrix leading to floating of the tablet. The concentration of NaHCO₃ (10% w/w) is kept constant as there is a chance for rapid erosion of tablet if more than polymer concentration [25].

Fig.1 shows the *in vitro* buoyancy study of floating tablets of Nizatidine at different time intervals. The *in vitro* testing of prepared floating tablets of Nizatidine revealed the ability of most of the formulae to remain buoyant for more than 12 hours. The floating tablets F15 and F16 containing NaCMC showed floating time of less than 3 min but floated only for 4 hours suggesting that the concentration of the polymer was not sufficient to maintain viscous layer for the entrapment of CO₂. This might be due to less viscosity of the polymer. The floating lag time and floating time for all the formulations were shown in table 2.

Tab.2. Physicochemical properties of prepared Nizatidine floating tablets.

Formula Code	Tablet Thickness(mm)	Tablet Weight (mg)	Tablet Friability (Percent)	Drug Content (Percent)	Floating Lag Time (S)	Total Floating duration (h)
F1	4.5 ±0.2	600.27±2.79	0.45±0.06	96.6±0.98	75±0.65	>12
F2	4.53±0.04	598.43±2.56	0.59±0.19	96.6±0.45	62±1.42	>12
F3	4.43±0.10	599.56±2.78	0.34±0.10	86.6±0.56	54±0.96	>12
F4	4.65±0.34	601.02±1.07	0.21±0.05	93.3±1.43	49±1.72	>12
F5	4.53±0.23	597.87±3.56	0.48±0.15	99.9±0.97	35±1.43	>12
F6	4.63±0.67	602.45±1.98	0.54±0.20	101±1.03	30±1.94	>12
F7	4.53±0.72	601.5±1.56	0.61±0.12	100.6±0.74	76±0.32	>12
F8	4.12±0.43	602.45±1.82	0.59±0.08	99.3±0.43	70±0.53	>12
F9	4.63±0.94	597.65±1.23	0.52±0.09	99.3±1.32	52±0.53	>12
F10	4.73±0.53	601.25±1.25	0.56±0.18	99.6±1.94	30±0.45	>6
F11	4.32±0.49	599.05±1.05	0.65±0.05	97.5±2.31	25±0.98	1
F12	4.75±0.64	602.32±1.43	0.69±0.43	98.6±1.65	143±0.42	4

Swelling indices

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the matrix tablet. The floating tablets composed of polymeric matrices will build up a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet [26]. The formulations containing HPMC K4M and HPMC K15M have exhibited good swelling and tablet integrity. Complete swelling was achieved at the end of 4 h, followed by diffusion and erosion of the tablet as shown fig 2 and fig.3. The formulation F1 containing HPMC K4M (50% w/w of tablet) showed higher swelling compared to that of the formulations containing low amount of polymer. As, the amount of polymer concentration is increased the water uptake ratio is also found to be increasing.

As the polymer concentration is decreased, rapid swelling is achieved in initial hours and then diffusion and erosion started to take place. The formulations containing NaCMC has shown swelling initially but disintegrated in few hours of the study as it is a low viscous polymer compared to that of HPMC grade. As reported by Bertram and Bodmeier [27], the ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. The swelling index of the tablets increases with an increase in the polymer viscosity grades.



At initial time



After 10 seconds



After 20 seconds



After 30 seconds



After 6 hours



After 12 hours

Figure. 1. Photographs showing *in vitro* buoyancy study of optimized formula F6 in 0.1 N HCl at different time intervals.

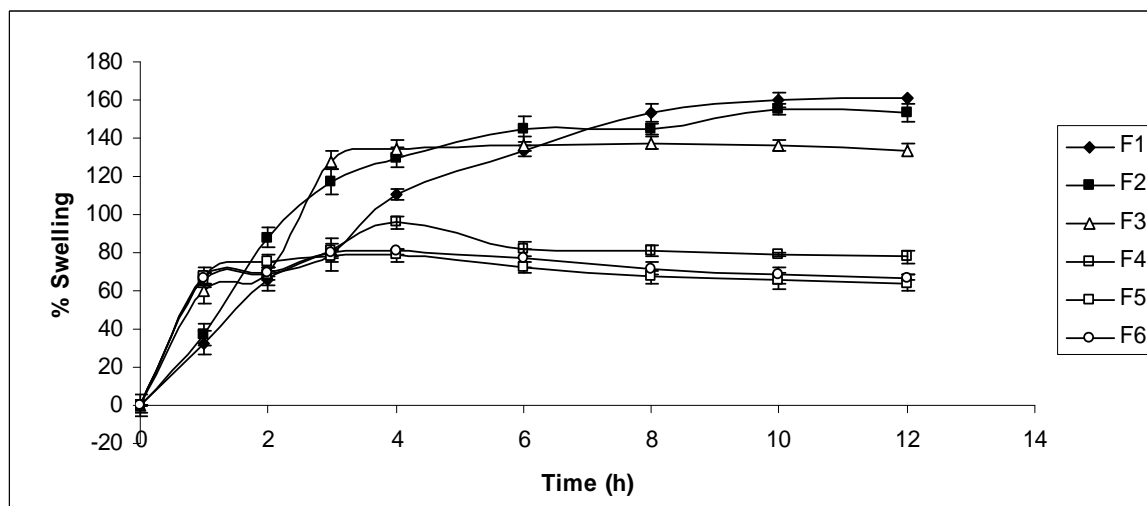


Figure.2. The influence of HPMC K4M on water uptake ratio of Nizatidine floating tablets (mean \pm SD, n=3).

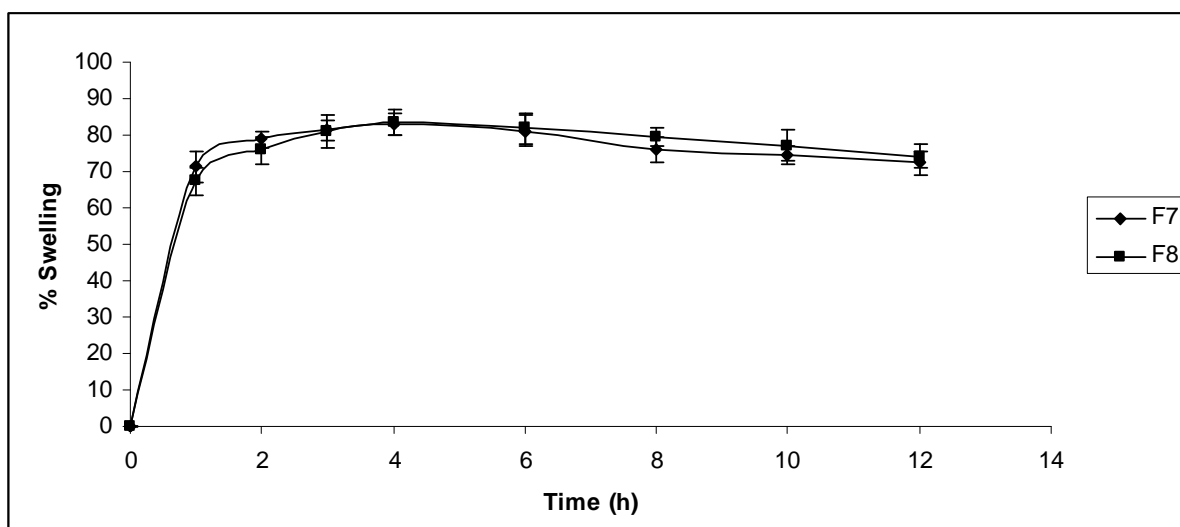


Figure.3. The influence of HPMC K15M on water uptake ratio of Nizatidine floating tablets (mean \pm SD, n=3).

The formulation with a combination of HPMC K4M and HPMC K15M has also been studied in order to study the effect of water uptake ratio. There has been no change in water uptake ratio was observed when we compared to individual polymers as shown in fig.4. Since, Hydroxypropyl methylcellulose forms quick gel on contact with water [28].

Drug release

In vitro dissolution studies of all the formulations were carried out in 0.1 N HCl. A rapid drug release rate was achieved following the dissolution of Axid 150mg tablets in 0.1 N HCl. Indeed, 99.56% of the drug was released within 15 min. The influence of HPMC K4M and HPMC K15M ratio on the release of Nizatidine from the floating tablets in 0.1 N HCl (pH 1.2) at $37 \pm 0.5^{\circ}\text{C}$ was shown in Fig. 5 and Fig 6 respectively. The drug release rate was dependent on the type and concentration of the investigated polymers. The floating tablets containing HPMC K4M (F6) showed drug release of 99.15% at the end of 12 h; floating tablets containing HPMC K15 (F7) showed constant drug release up to 12 h (98.33%). The floating tablets containing combination of HPMC K4M and HPMC K15M (F9 and F10) remained stable for 12 h with a drug release of 93.46%.

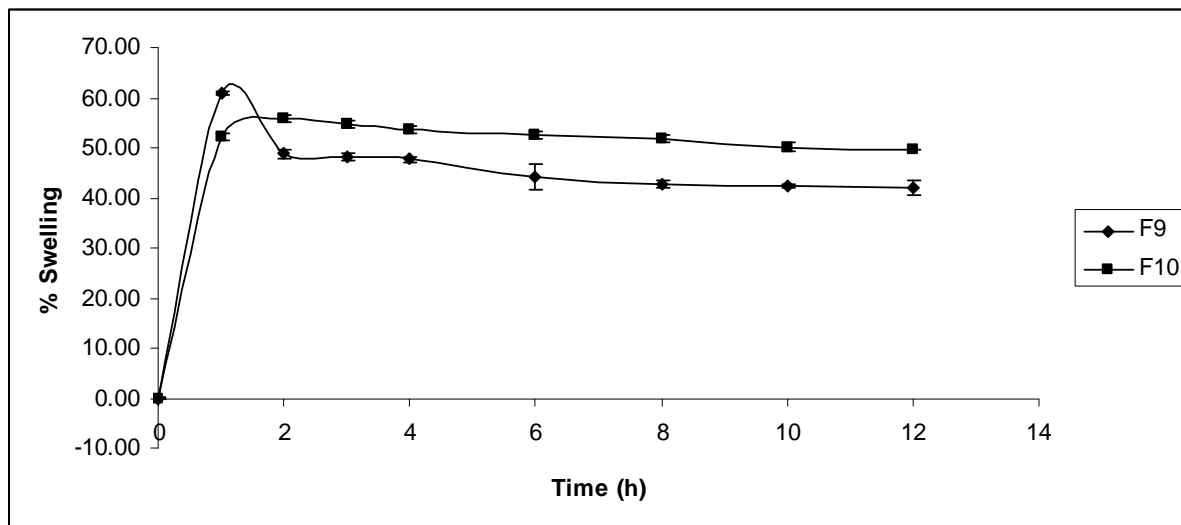


Figure.4. The influence of HPMC K4M/HPMC K15M ratio on the swelling indices of Nizatidine floating tablets (mean \pm SD, n=3).

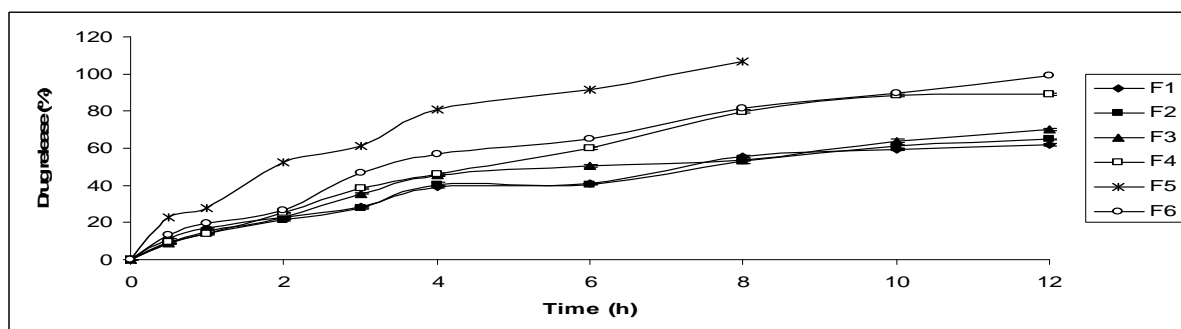


Figure.5. The influence of HPMC K4M ratio on the release of Nizatidine from the floating tablets in 0.1N HCl (pH 1.2) at $37\pm 0.5^{\circ}\text{C}$ (mean \pm SD, n=3)

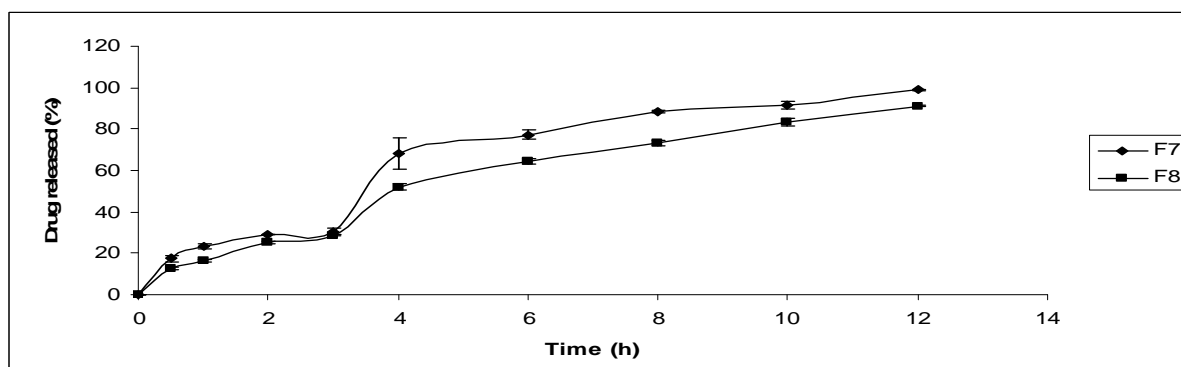


Figure.6. The influence of HPMC K15M ratio on the release of Nizatidine from the floating tablets in 0.1N HCl (pH 1.2) at $37\pm 0.5^{\circ}\text{C}$ (mean \pm SD, n=3)

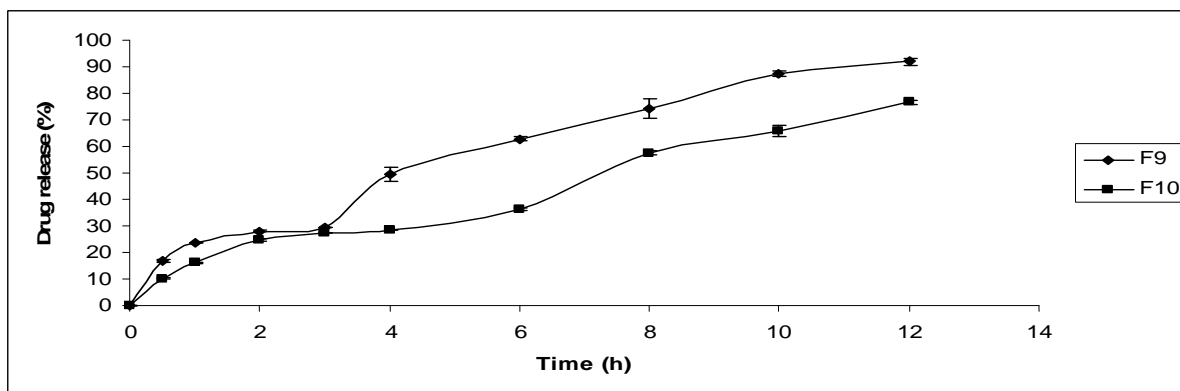


Figure.7. The influence of HPMC K15M/K4M ratio on the release of Nizatidine from the floating tablets in 0.1N HCl (pH 1.2) at $37 \pm 0.5^\circ\text{C}$ (mean \pm SD, n=3)

The *in vitro* drug dissolution was slightly more rapid, for the formulations (F11 and F12) due to rapid hydration of NaCMC. The controlled release of drug from F6 and F10 could be attributed to the formation of a thick gel structure and has delayed drug release from the floating tablet matrix. As the polymer proportion was increased, the polymer gel formed is more likely to be resistant to drug diffusion and erosion [29]. As the release rate-limiting polymer changes from a glassy state to rubbery state, a gel structure is formed around the tablet matrix, which considerably decreases the release of drug since it has to diffuse through this gel barrier into the bulk phase. The strength of gel depends on the chemical structure and molecular size of polymer [29-31]. The faster drug release in case of formulation containing low amount of Methocel K4M may be due to less tortuous diffusion path.

The mean dissolution time (MDT) and Dissolution Efficacy (DE) of all formulations were shown in table 3. As the MDT increases the dissolution efficacy is decreased.

Drug release kinetics

The regression coefficient (R^2) values of release data of all formulations obtained by curve fitting method for zero-order, first-order, and Higuchi and Krosmeier-Peppas model are reported in Table 4. Most of the formulations follow the zero order and Higuchi model. For the optimized formulation F6, the R^2 value of Higuchi 0.9832 (nearer to 1) is dominant than the other models which indicates that the drug release depended on the square root of the time (Eq. 4).

Table. 4. Mathematical modeling and release kinetics of Nizatidine from prepared floating tablets.

Formulation	Zero order	First order	Higuchi	Korsmeyer & Peppas	Peppas (n)
F6	0.9475	0.5597	0.9832	0.5888	0.60
F10	0.8986	0.5354	0.9428	0.5364	0.57

The mechanism of drug release is predicted by using Eq. 5 according to Krosmeier–Peppas. The n value of optimized formulation F6 is 0.60 and that of all formulations is between “0.45 to 0.85”. This indicates that the drug release depends on swelling, erosion, and diffusion. All formulations follow the non-Fickian/anomalous type of diffusion.

Based on the above, observations formulation F6 was chosen as optimized formula and it was evaluated for *in vivo* studies.

in vivo X- ray studies

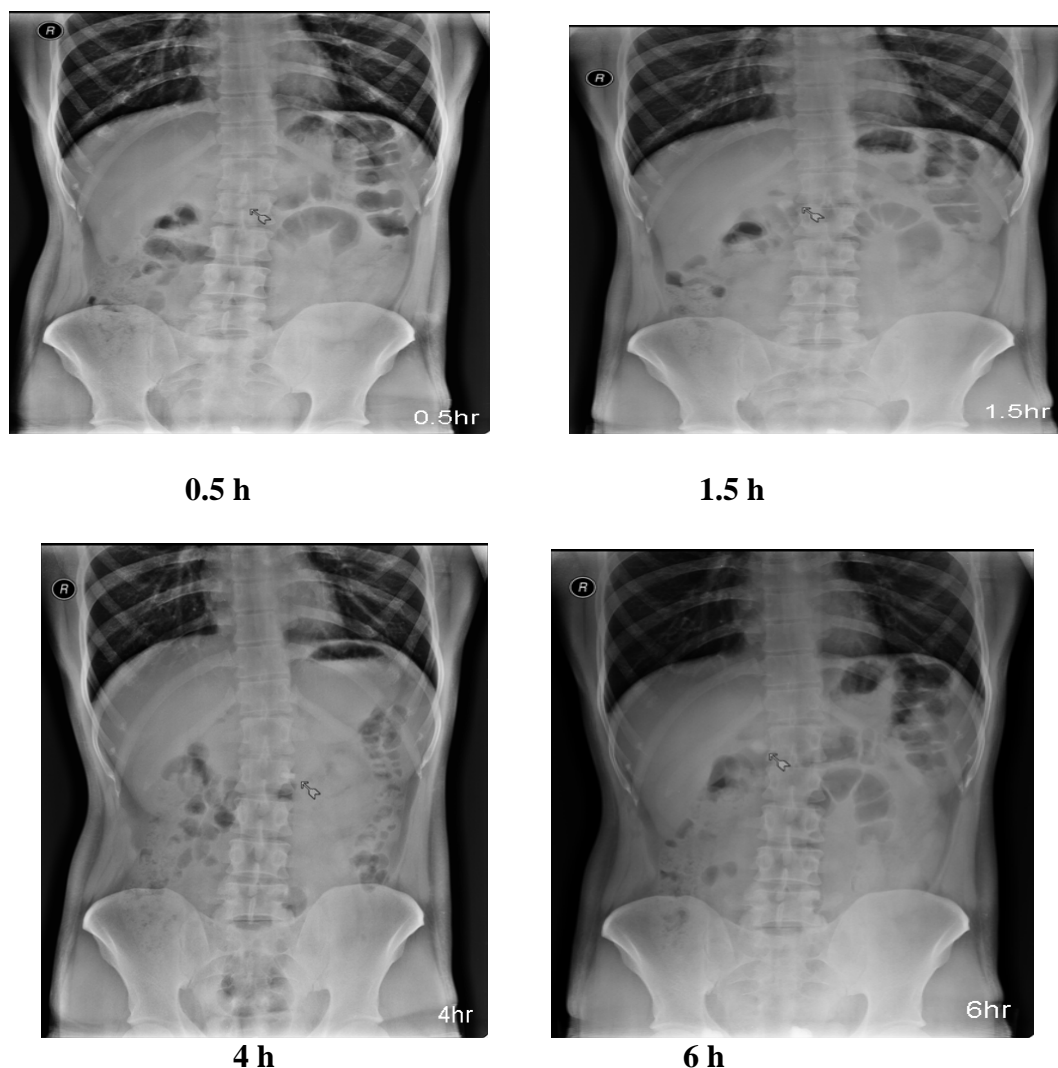


Figure.8. Radiographic images showing the presence of Baso₄-loaded floating tablets in the stomach at different time periods (the location of the tablet is indicated with an arrow).

The *in vivo* nature of the tablet was observed by taking radiographic pictures at different time intervals. Initially, the tablet appeared very clear, but later on, it appeared dull, due to swelling of the tablet. The gastric retention was due to floating in the first few hours, and later, it was due to obstruction of the tablet at duodenum as seen in Fig. 8. The radiographic pictures of healthy volunteers confirm the *in vivo* buoyancy in the stomach for 320 minutes. This gastric retention occurred due to swelling and floating characteristics of the dosage form.

CONCLUSION

The floating tablets of Nizatidine were successfully formulated by effervescent technique. The floating tablets containing HPMC K4M (F6) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability and sustained drug release properties. The optimized formulation F6 followed Higuchi kinetic model and the mechanism of drug release was found to be non-fickian according to krosmeier- peppas kinetic model. *In vivo* studies conducted on healthy volunteer supported prolonging of the gastric residence time. The mean gastric retention is found to be 320. This result indicates increase in MRT of the Nizatidine in the stomach.

Acknowledgements

The authors would like to thank Dr. Reddy's Hyderabad, India for gift sample of Nizatidine. Authors also thank St. Peter's Institute of pharmaceuticals sciences, India for providing facilities.

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