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Original Article

DESIGN AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF NIZATIDINE: A TRIAL TO IMPROVE ITS EFFICACY

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ABSTRACT

Objective: This study was designed to prepare a gastro-retentive floating tablet of nizatidine in an attempt to prolong its gastric residence time and hence increase its efficacy.

Methods: The tablets were prepared by direct compression technique using hydroxypropylmethyl cellulose (HPMC k4M). The effect of different formulation variables including polymer concentration, incorporation of different concentrations of carbopol934 or sodium alginate as release retarding polymers and concentration of an effervescent mixture (sodium bicarbonate and citric acid) on drug release and floating properties was investigated. In addition, the optimized formulation (combined excellent floating behavior and sustained drug release) was compared to conventional nizatidine tablet for antiulcer activity in rabbits.

Results: The optimized formulation containing 175 mg HPMC k4M, 25 mg carbopol934 and 50 mg effervescent mixture showed 80% drug release within 10.6 h±0.3, floating lag time of about 5.00±0.2 min and total floating time of >24 hours. In vivo results proved that nizatidine floating tablet had more pronounced antiulcer effect than its conventional tablet.

Conclusion: The effervescent based floating tablet of nizatidine could be a promising approach to increase its gastric residence time up to 12 hours, thereby improving its antiulcer efficacy.

Keywords: Nizatidine, Hydroxypropyl methyl cellulose, Carbopol, Sodium alginate, Gastro-retentive.

INTRODUCTION

Gastro-retentive drug delivery systems are designed to prolong overall gastrointestinal transit time and improve the oral bioavailability of drugs that are having site-specific absorption in the stomach or in the upper part of the small intestine [1], drugs acting locally in the stomach [2] and for drugs that are poorly soluble or unstable in the intestinal fluid [3] . Different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems [4], swelling and expanding systems [5,6], floating systems [7] and delayed gastric emptying devices [8].

Floating drug delivery systems have bulk density less than gastric fluids and so remain buoyant in the stomach where the drug is released slowly. Floating drug delivery systems can be divided into effervescent and non-effervescent systems. The effervescent systems prepared with swellable polymers and effervescent components that upon arrival in the stomach; carbon dioxide is released and entrapped within the jellified polymer causing the formulation to float in the stomach. Non-effervescent systems prepared by mixing the drug with a gel, which swells in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these systems [9,10]. Nizatidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and commonly used in the treatment of peptic ulcer and gastroesophageal reflux. Its recommended dose is either 300 mg once daily at bedtime or 150 mg twice daily [11]. Nizatidine has short biological half life (1-2 hours) and susceptible to metabolism by colonic bacteria [12]. It has been reported that the local delivery of H_2- receptor antagonists increases the stomach wall receptor site bioavailability and increases efficacy of these drugs to reduce acid secretion [13]. Based on the mentioned criteria, nizatidine is a suitable candidate for gastroretentive drug delivery system. Little approaches have been carried out to improve the local delivery of nizatidine to stomach such as formulation of floating pulsatile tablets [14] and effervescent floating tablets with different viscosity grades of HPMC [15], Continuing that research, the aim of the present study was to develop a floating tablet of nizatidine with a view of prolonging gastric residence time and hence improving drug efficacy.

MATERIALS AND METHODS

Nizatidine was received as a gift sample from Jamjoom Pharmaceuticals, Jeddah, Saudi Arabia. Hydroxypropylmethyl cellulose K4M (HPMC K4M, 4000 cPs apparent viscosity as a 2% solution), carbopol934 and sodium alginate were purchased from Sigma Aldrich chemie GmbH, Germany. Magnesium stearate, hydrochloric acid, sodium bicarbonate, citric acid anhydrous and lactose were purchased from El-Nasr Pharmaceutical Chemicals, Egypt.

Preparation of nizatidine floating tablets

Floating tablets contained a mixture of nizatidine, HPMC K4M alone or in combination with carbopol934 or sod-alginate, effervescent mixture (sodium bicarbonate and citric acid, 1:1 w/w) and lactose as a diluent in weight proportions as mentioned in Table 1. The powder blend was then lubricated with magnesium stearate (1% w/w) and compressed into tablets using 10-mm flat-face round tooling on a single punch tablet machine (Korsch Frogerais, Type AO, Berlin, Western Germany). The compression force was adjusted to obtain tablets with hardness in range of 5 to 6 kg/cm^2.

Physical evaluation of floating tablets

Weight variation: Ten tablets were randomly selected from each batch and their average weight was calculated using a digital balance. Individual weight of each tablet was also determined and compared with the average weight.

Hardness, thickness and diameter: ERWEKA hardness tester (TBH 425 hardness tester, Heusenstamm, Germany) was used to determine the tablet hardness, thickness and diameter for all the formulated batches.

Friability: About 20 tablets were selected from each batch and evaluated for friability using ERWEKA Friabilator (TAR 120/220 Friabilator, Heusenstamm Germany).

Table 1: It shows composition (in milligrams) of nizatidine floating tablets.

Formulation Code	Nizatidine	HPMC- K4M	Carbopol934	Sodium alginate	Effervescent mixture (1:1) $NaHCO_3$: citric acid	Lactose
F1	150	50	-	-	50	250
F2	150	100	-	-	50	200
F3	150	200	-	-	50	100
F4	150	175	25	-	50	100
F5	150	150	50	-	50	100
F6	150	125	75	-	50	100
F7	150	175	-	25	50	100
F8	150	150	-	50	50	100
F9	150	125	-	75	50	100
F10	150	175	25	-	25	125
F11	150	175	25	-	100	50

Drug content uniformity

Drug content in each formulation was determined according to the method described by Salve and coworkers [16]. About 20 tablets were triturated and powder equivalent to average weight was transferred to 100ml volumetric flask. The volume was made to the mark with distilled water. This mixture was sonicated for 15 minutes, filtered through Whatmann filter paper No. 41, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically (Shimadzu UV-160A Spectro-photometer, Shimadzu, Japan) at 329nm [17]. Accordingly drug content was calculated.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa *et al.*[18]. Each tablet was placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the tablet constantly remained on the surface of medium was determined as the duration of floating.

Determination of swelling

Previous literature suggested that high swelling results in formation of a good polymer network which in turn may cause retention of tablet in stomach for longer period of time along with uniform drug release [19]. So, it is necessary to study the swelling behavior of the prepared tablets.

Tablets (n = 3) were initially weighed, then immersed into beakers containing 150 ml 0.1N HCl at 37 ± 0.5 ºC. After predetermined intervals the tablets were withdrawn blotted to remove excess water and reweighed [20]. Swelling characteristics of the tablets were expressed in terms of weight gain (equation 1).

$$\% \text{ swelling} = \frac{(\text{Weight of the swollen tablet} - \text{Initial weight of tablet})}{\text{Initial weight of the tablet}} \times 100 \text{ - (1)}$$

In vitro dissolution studies

The release of nizatidine from floating tablets (n = 3) was carried out by USP Dissolution Test Apparatus Type-II (paddle method; Pharma Test SP6-400, Hamburg, Germany). The temperature of the dissolution medium (0.1 N HCl, 900 mL) was maintained at 37 ± 1°C with a stirring rate of 50 rpm. This study was done for 8 h. The tablet was placed inside the dissolution vessel. A sample (5ml) of the solution was withdrawn hourly and the samples were replaced with fresh dissolution medium. The samples were filtered and analyzed spectrophotometerically at 329nm and percentage drug release was calculated using an equation obtained from a standard curve.

The mechanism of release was determined by fitting the dissolution data to the various kinetic equations such as zero-order [21], first-order [22], Higuchi [23], and Korsmeyer-Peppas [24] and finding the R^2 values of the dissolution profile corresponding to each model. The time required for 50% ($t_{50\%}$) and 80% ($t_{80\%}$) drug release was calculated according to the best fit model with the highest determination R^2.

Investigation of the anti-ulcer activity of nizatidine

The experiments were conducted according to the Guidelines for Animal Care and Treatment of the European Community. The protocol of this study was reviewed and approved by the Research Ethics Committee (REC) of the Pharmacology Department affiliated to the Faculty of Pharmacy, Zagazig University, Zagazig, Egypt.

Animals

Eighteen rabbits weighing 2–2.5 kg were used for the study. The animals were supplied from the Animal House of Faculty of Pharmacy, Zagazig University, Zagazig, Egypt. They were kept for one week with free access to food and water before the commencement of the experiment as pre-breeding period. The animals were maintained under standard 12-h light/dark cycle throughout the duration of the study.

Experimental procedure

Animals were divided into three groups (n=6). Group-I Control group of animals received saline (5 ml/kg, oral) twice a day for 5 consecutive days before ulcer induction. Group-II received conventional nizatidine tablet (100 mg tablet containing 35mg nizatidine [25], 64 mg lactose and 1mg magnesium stearate) followed by 5 ml/kg saline twice a day for 5 consecutive days before ulcer induction. The last dose was administered 1 hour prior ulcer induction. Group-III received intact floating tablet (100 mg tablet each containing 35mg nizatidine, 35mg HPMC, 5mg carbopol435, 10 mg effervescent mixture and 15 mg lactose) followed by 5 ml/kg saline, twice a day for 5 consecutive days before ulcer induction. The last dose was administered 1 hour prior ulcer induction. All the administrations were done by oral route. The rabbit mouth was opened, and wooden rod was inserted between the jaws. A gastric tube was centrally placed to the hole. Tablets were set on the tip of a gastric intubation tube, and administered in to the stomach of rabbit. After receiving the oral dose, 5 ml/kg saline was administered to facilitate the accession of the tablets [26]. After 24 hours of fasting, ulcer was induced with oral administration of 1ml/Kg of 0.15N HCl in 70% ethanol [27]. After 24 hours, the animals were sacrificed by an over dose of ether and the stomachs removed and opened along the greater curvature. The stomach was rinsed with saline and pinned flat on a corkboard. The stomachs were observed with a hand lens (x10). Erosions formed on the glandular portions of the stomach were counted and each given a severity rating on a 1 – 3 scale based on the diameter of the ulcer, < 1 mm (Pin point) = 1, 1 – 2mm = 2 and > 2 mm = 3

The mean ulcer index was determined by dividing the total ulcer indices in a group by the total number of animals in that group. The percentage ulcer protection was calculated as follows (equation 2) [28]:

$$\text{percentage ulcer protection} = \left[1 - \frac{(\text{ulcer index for test agent})}{(\text{ulcer index for control})}\right] \times 100 \quad -2$$

Statistical analysis

All results were expressed as mean ± SEM (n=6). The difference among means was analyzed by one-way ANOVA where (*) represents significant at p<0.05, (**) represents highly significant at p< 0.01,(***) represents very highly significant at p<0.001, when compared to control group.

RESULTS

Physical evaluation of floating tablets

The results of the physical evaluation are shown in Table 2. The weight of the tablet varied between 481 mg to 506.7mg for different formulations. The hardness for different formulations was found to be between 4.8 to 5.6 kg / cm^2, the thickness varied from 4.5-5.3 mm and the friability was below 1% for all the formulations.

Drug content uniformity

The drug content varied between 143.4 to 151.5 mg in different formulations (Table 2).

In vitro buoyancy studies

The floating lag time and duration of floating for all formulations are shown in Table 3. The formulations F4, F5, F6 and F10 remained buoyant for 24 h while the other formulae have variable duration of buoyancy . In order to investigate the effect of HPMC quantity on the floating properties of tablets, F1 – F3 were prepared. It was observed that as the polymer quantity increased, there was a decrease in the floating lag time and an increase in the floating duration. The formulation F1 exhibited a floating lag time and a floating duration of about 14.7 ± 1.3 min and 8 h, respectively, compared to 5.8 ± 0.3 min and 18 h exhibited by the formulation F3 . The formulations F4 - F9 demonstrates the effect of incorporating different amounts of carbopol934 and sod-alginate on the floating properties of tablets. It was clear that incorporation of small amount of carbopol934 (5% w/w) had no significant effect on floating lag time but prolonged the duration of floating. However, further increase in carbopol934 amount had a negative effect on floating lag time (Table 3). In addition, sod-alginate loading had a negative impact on floating properties i.e. the floating lag time was extended to 13.8 ± 0.3 min and the floating duration was shortened to 16h . The formulations F10 &F11 demonstrate the effect of effervescent mixture amount on floating behavior. Decrease in the amount of effervescent mixture (< 50 mg) increased the floating lag time, while its increase (> 50 mg) resulted in rapid floating (3.1 ± 0.2 min) with tablet disintegration after 4h. So, the optimum amount of effervescent mixture to be incorporated per tablet was found to be about 50 mg.

Table 2: It shows physical evaluation and drug content results of nizatidine floating tablets.

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight (mg)	Friability (%)	Drug content (mg)
F1	4.5 ± 0.1	10 ± 0.06	5.2 ± 0.3	486.3 ± 4.6	0.47 ± 0.03	145.2 ± 0.4
F2	4.9 ± 0.06	10.04 ± 0.01	5 ± 0.2	487.8 ± 1.3	0.51 ± 0.08	148.8 ± 1.2
F3	4.9 ± 0.04	10.04±0.003	4.9 ± 0.4	490.7 ± 2.8	0.57 ± 0.02	147.5 ± 1.6
F4	4.8 ± 0.11	10.04 ± 0.00	5.1 ± 0.08	493.3 ± 3.4	0.5 ± 0.06	144.9 ±1.1
F5	5.3 ± 0.06	10.03 ± 0.01	4.8 ± 0.2	504.6 ± 4.2	0.45 ± 0.03	150.1 ± 2.3
F6	5.0 ± 0.007	10.00 ± 0.00	5.3 ± 0.14	482.5 ± 2.3	0.42 ± 0.01	150.5 ± 2.9
F7	5.3 ± 0.07	10.09 ± 0.01	5.6 ± 0.52	494.3 ± 2.9	0.39 ± 0.05	151.5 ± 1.7
F8	4.9 ± 0.04	10.1 ± 0.005	5.2 ± 0.4	489.7 ± 3.2	0.61 ± 0.01	148.7 ± 3.1
F9	5.03 ± 0.03	10.07±0.007	5.2 ± 0.16	502.7 ± 5.5	0.45 ± 0.01	145.7 ± 2.1
F10	4.95 ± 0.01	10.07±0.003	5.3 ± 0.6	506.7 ± 4.5	0.45 ± 0.00	147.5 ± 1.9
F11	5.01 ± 0.008	10.06±0.006	5.5 ± 0.13	489.3 ± 1.7	0.4 ± 0.05	143.4 ± 2.2

Table 3: It shows dissolution and floating parameters of nizatidine floating tablets.

Formulation Code	Floating Lag Time (min) ± SD	Floating Time (h)	$t_{50\%}$ (h) ± SD	$t_{80\%}$ (h) ± SD	Release exponent (*n*)	rate of drug release (mg /h, mean ±SD)
F1	14.7 ± 1.3	8	2.4 ± 0.03	4.8 ± 0.1	0.5	11.8 ± 0.2
F2	10.00 ± 1.8	12	3.2 ± 0.1	6.2 ± 0.2	0.68	11.4 ± 0.3
F3	5.8 ± 0.3	18	4.4 ± 0.27	7.3 ± 0.5	0.88	10.0 ± 0.3
F4	5.00 ± 0.2	24	6.6 ± 0.3	10.6 ± 0.3	1.48	7.6 ± 0.16
F5	8.7 ± 0.8	24	7.8 ± 0.3	11.6 ± 0.38	1.78	7.1 ± 0.6
F6	17.3 ± 1.04	24	8.0 ± 0.2	12.0 ± 0.85	1.64	7.1± 0.6
F7	10.6 ± 0.8	16	5.2 ± 0.1	8.4 ± 0.38	0.93	9.4 ± 0.6
F8	13.7 ± 0.4	16	4.8 ± 0.8	7.7 ± 0.26	1.39	10.1± 0.32
F9	13.8 ± 0.3	16	4.6 ± 0.17	7.6 ± 0.66	1.2	10.1± 0.18
F10	12.2 ± 0.18	24	7.1 ± 0.1	11.0 ± 0.33	1.42	7.69 ± 0.08
F11	3.1 ± 0.2	4 then disintegrate	0.09 ± 0.32	3.4 ± 0.33	1.58	23.8 ± 0.9

Determination of swelling

Figure 1 demonstrates the effect of different variables on % swelling of nizatidine floating tablets. As per the result obtained after swelling, it was found that the formulations F3 & F4 possessed the highest % swelling among all the formulations. They swelled approximately 190-195% on the stipulated 8 hours study with maintenance of tablet integrity. On the other hand, F11 had about 213% swelling, but it ruptured after 4 hours.

A. Effect of HPMC k4M concentration;
B. Effect of different concentrations of carbopol934 and sodium alginate;
C. Effect of effervescent mixture amount

In vitro dissolution studies

Dissolution profiles of nizatidine from different floating tablets in 0.1N HCl are shown in Figure 2. The results of *in- vitro* dissolution studies are listed in Table 3.

Figure 2A represents the effect of various concentrations of HPMC (50, 100 and 200 mg per tablet) on drug release. Increasing the concentration of HPMC, resulted in a marked decrease in % drug release. The formulation containing HPMC polymer at concentration of 200 mg per tablet exhibited $t_{50\%}$ and $t_{80\%}$ of about 4.4 ± 0.27 h and 7.3 ± 0.5 h, respectively, compared to 2.4 ± 0.03 h and 4.8 ± 0.1h, respectively, exhibited by the formulation containing 50 mg HPMC per tablet.

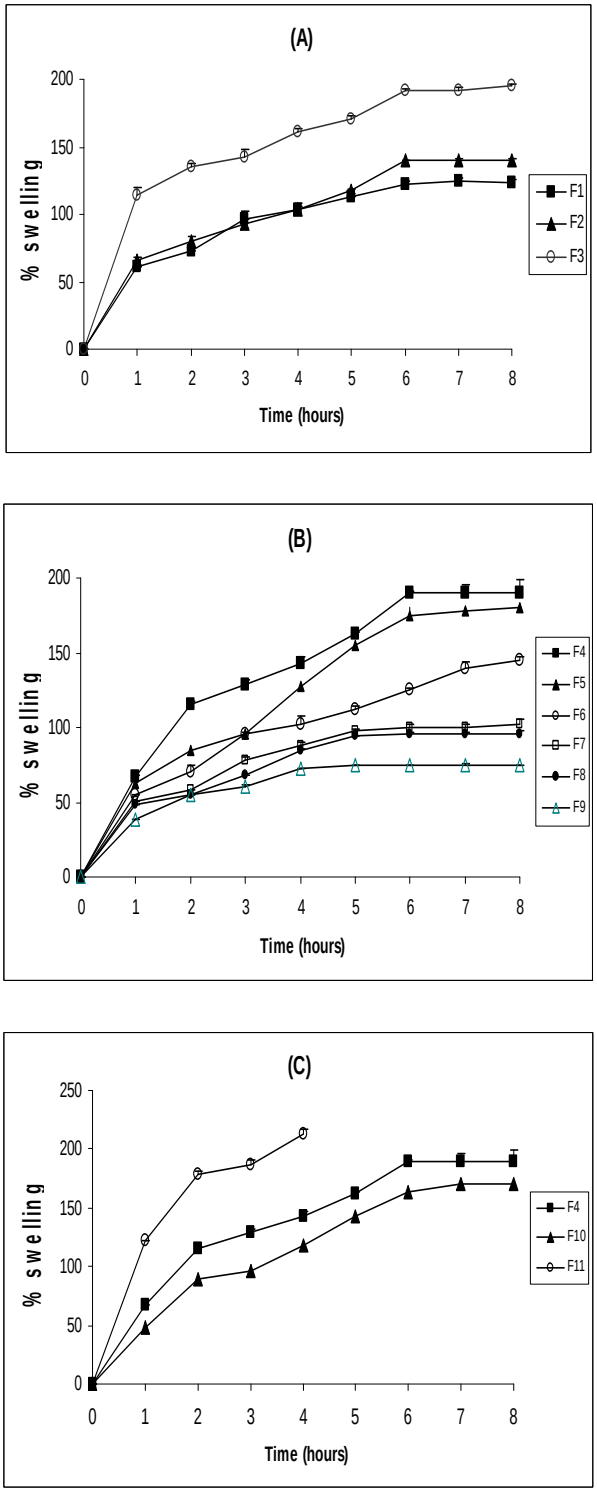

Fig. 1: It shows effect of different variables on % swelling of nizatidine floating tablets.

In order to further sustain the release of nizatidine from the floating tablets, formulations containing release retarding polymers such as carbopol934 and sodium alginate were prepared (figure 2B). The drug release rate was dependent on the type and concentration of the investigated copolymers. Drug release was better sustained in tablets contained carbopol934 (F4 – F6) rather than those contained sodium alginate (F7 – F9) and this effect increased by increasing the proportion of carbopol934 in the tablets. The floating tablets containing 75 mg carbopol934 (F6) showed drug release of 51.1 ± 0.47 % at the end of 8 h; while those containing 75 mg sodium alginate (F9) showed drug release of 83.03 ± 0.33 % up to 8 h. However, as mentioned before, the floating lag time was negatively affected by increasing the amount of carbopol934. The floating lag time from F4 & F6 was 5.00 ± 0.2 min and 17.3 ± 1.04 min, respectively, comprising 3.5-fold increase. So, the formulation, F4, was further selected to study the effect of effervescent mixture concentration (25, 50 and 100 mg per tablet) on % drug release (Figure 2C). The % drug release from formulations F11(contained 100 mg effervescent mixture) and F4 (contained 50 mg effervescent mixture) was 96 ± 0.74 % and 58.2 ± 0.12%, respectively, however, the F11 tablets disintegrated after 4 h.

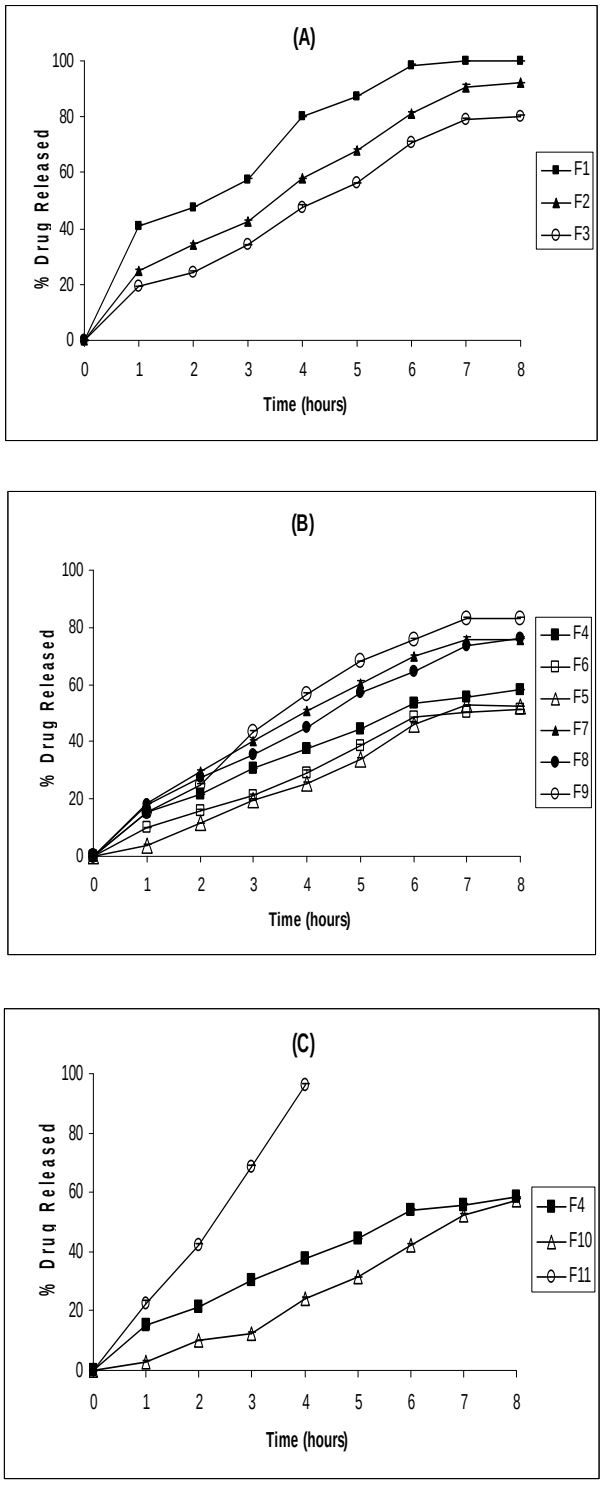

Fig. 2: It shows in *vitro* dissolution profiles of different floating tablet formulations in 0.1 N HCl.

A. Effect of HPMC k4M concentration;
B. Effect of different concentrations of carbopol934 and sodium alginate;
C. Effect of effervescent mixture amount

The best fit with the highest determination R^2 coefficients was shown by the zero order (R^2> 0.9). So, predominant drug release mechanism is controlled release. The time required for 50% ($t_{50\%}$) and 80% ($t_{80\%}$) drug release was calculated based on the zero order (Table 3). To confirm the exact mechanism of drug release from these tablets, the data were fitted to Korsmeyer and Peppas equation ($M_t/M_\infty = k\ t^n$, where M_t/M_∞ is the fraction of drug released after time t in respect to amount of drug released at infinite time, k is the rate constant and n is the diffusion exponent which characterizes the transport mechanism). For formulations F1, F2, F3 and F7, 0.5 < n < 1.0, while the other formulations possessed n value of more than 1.

Investigation of the anti-ulcer activity of nizatidine

Based on the results of *In vitro* buoyancy and dissolution studies, F4 had combined excellent floating behavior (floating lag time was 5.00 ± 0.2 min and the floating duration was 24h) and sustained drug release characteristics ($t_{50\%}$ = 6.6 ± 0.3 h & $t_{80\%}$ = 10.6 ± 0.3 h) was selected for comparison with conventional nizatidine tablet. Each tablet had a weight of 100 mg and contained 35 mg nizatidine.

In the control group, administration of 1ml/Kg of 0.15N HCl in 70% ethanol resulted in the production of gastric lesions. It was clear that pretreatment with nizatidine floating tablet (F4) for 5 days significantly decreased ulcer index (P<0.001) relative to conventional formula (P<0.05) (Figure 3). Moreover, the pretreatment of rabbits with nizatidine floating tablet (F4) for 5 days resulted in72.3% protection against ulcer compared to only 37.2% by conventional nizatidine formula, comprising 1.94-fold increase in nizatidine antiulcer activity.

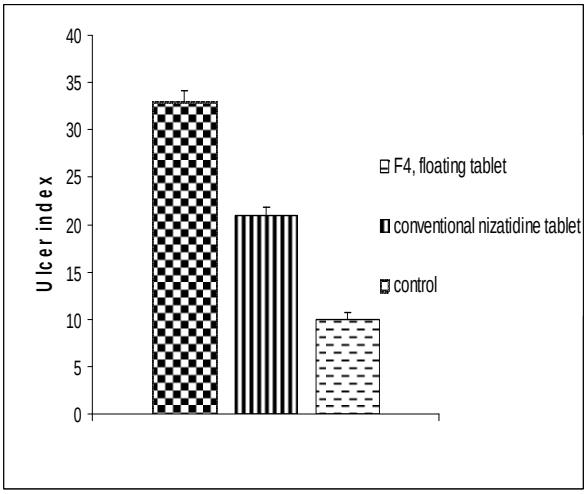

Fig. 3: It shows comparison of antiulcer activity of nizatidine floating tablet and conventional nizatidine tablet against ulcer induced by 0.15N Hcl in 70% ethanol in rabbits.

DISCUSSION

Physical evaluation of floating tablets

The results of physical evaluation indicated satisfactory physical characteristics of the prepared tablets.

Drug content uniformity

The assay for drug content indicated acceptable content uniformity (i.e., a variation of ±5%) in the prepared tablets.

In vitro buoyancy studies

Nizatidine tablets were prepared using HPMC k4M with or without carbopol934 or sod-alginate along with sod-bicarbonate and citric acid as effervescent mixture. The pH of the stomach is elevated under fed condition (~3.5); therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate [2]. The effervescent mixture induces CO_2 in presence of water. The gas generated is trapped within the gel formed by hydration of the polymer and thus decreasing the density of the tablet < 1and the tablet becomes buoyant [29].

The results demonstrated that, as the content of the polymer was increased, the floating lag time was found to decrease and the floating duration increased and this may be ascribed to the presence of HPMC in larger amount > 20% w/w and hence the particles are close enough to permit faster formation of gel layer which is viscous enough to retain the generated CO_2 for a longer period [29]. Carbopol loading (> 5% w/w) resulted in prolongation of floating lag time. This could be explained by the less hydrophilic nature of carbopol polymer than HPMC that takes longer time for swelling than HPMC. In addition, the very high viscosity of carbopol934 (30500 – 39400 m Pa .s) compared to HPMC (2308 – 3755 m Pa .s) resulted in delayed floating behavior [19]. Previous literature reported that viscosity of the gel-forming polymer influenced the *in vitro* buoyancy [2, 30]. In addition, Li et al. reported that a better floating behavior was achieved at higher HPMC/Carbopol ratio [31].

On the other hand, sodium alginate does not appear to swell at pH 1.2 and hence the floating is controlled only by HPMC. Similar results were reported by Prajapati *et al*.[32]. Sruthy and Anoop reported that floating tablets containing sodium alginate showed higher floating lag time [33].

It is important to optimize the amount of effervescent mixture incorporated, as it may not be able to aid & assist the polymers in swelling &floating. It was reported that the gas generating base decreases the lag time by accelerating the hydration of the swelling polymer, thus allowing a higher floating duration because of constant generation and subsequent trapping of CO_2 [34]. The results revealed that, when the concentration of the effervescent mixture was increased, the tablets were found to exhibit short floating lag time, however, tablet integrity was decreased. Moreover, the formulation (F10) containing lower effervescent mixture exhibited longer floating lag time because of the lower efficiency of the gas forming agent. Thus, effervescent mixture, 50 mg per tablet was essential to achieve optimum in vitro buoyancy (ie, floating lag time < 10 min and floating duration of 24 hours). It was reported that the increased amount of effervescent mixture caused a large amount of effervescence, which in turn resulted in pore formation and rapid hydration of the polymer matrix and thereby tablet disintegration before 12 h [35, 36]. Similar results were reported by Hasçiçek and coworkers [37].

Determination of swelling

The results revealed that as the amount of HPMC K4M increased, the % swelling increased. This result may be explained by the hydrophilic nature of HPMC K4M which when present at high concentration, rapidly hydrates leading to expansion and consequently an ordering of the polymer chains [38]. Tablets containing carbopol934 as copolymer (especially F4) showed higher % swelling than those containing sodium alginate. It was reported that carbopol swells in simulated gastric fluid, pH 1.2 [39], while sodium alginate does not appear to swell [40].

The amount of effervescent mixture incorporated had a significant effect on swelling properties of tablet. As the amount of effervescent mixture increased, the % swelling increased but the tablet integrity decreased. This may be due to the increased reaction of sodium bicarbonate and citric acid with the dissolution medium that increased the release of CO_2 and consequently the number of pores and swelling index were increased [41].

In vitro dissolution studies

The results suggested that the drug release can be reduced by increasing the concentration of HPMC polymer. This result could be ascribed to the formation of a thick gel structure which increased diffusion path length of the drug and hence delayed drug release

from the floating tablet. The strength of gel layer increased as the polymer proportion was increased [42]. The results are in agreement with that reported by Dhawan *et al.*, who mentioned that at higher polymer loading, the viscosity of the gel matrix is increased resulting in a decrease in the effective diffusion coefficient of the drug and hence decreases drug release into the dissolution medium [43].

The incorporation of different amounts of carbopol934 successfully retarded the drug release which may be attributed to increased imbibitions of water into polymer. Similarly, increases the swelling of carbopol which holds the water inside the matrix and thus decreases the release of drug from the dosage form [44]. It was reported that carbopol 934 is a high molecular weight polymer that hydrates and swells at pH 1.2 [45]. Previous literature suggested that, the degree of entanglement of the polymer chains increases with the increase in the molecular weight of polymer. So, the mobility of the drug within the polymer decreases and hence drug diffusion coefficient and release rate are decreased [46]. Incorporation of carbopol was found to compromise the floating capacity of the floating drug delivery system and drug release rate. These results are consistent with that reported by Li and coworkers [47].

On the other hand, the results of incorporation of different amounts of sodium alginate were not promising. This result could be ascribed to less swelling of alginate matrix in acidic medium [48]. Saeio and coworkers stated that there is a correlation between the swelling of polymer and drug release [49]. Higher swelling of the polymer led to increased dimension of the tablet and hence increased diffusion pathway that inhibits the passage of the drug molecules and retardation of drug release. Similar results were obtained by Pare and coworkers [30].

The results revealed that, when the effervescent mixture amount increased up to 50 mg per tablet, there was a marked increase in the release rate, however, the tablet integrity was negatively affected and the tablet disintegrated after 4h. This can be explained by the large amount of carbon dioxide gas produced upon contact with the dissolution medium. These carbon dioxide bubbles enlarge the matrix volume, result in pore formation and allowing an increase in the drug release rate and finally tablet disintegration [36, 50] .

In sustained release formulations diffusion, swelling and erosion are the three most important rate controlling mechanisms followed. The drug release from the polymeric system is mostly by diffusion and best described by fickian diffusion. But in case of formulations containing swelling polymers such as HPMC, other mechanisms include relaxation of polymers chain and imbibitions of water causing polymers to swell changing them from initial glassy to rubbery state [51]. So, it is necessary to apply the in vitro dissolution data to Korsmeyer and Peppas equation and calculate the n value which characterizes the release mechanism. When n = 1, indicates swelling-controlled drug release (case II transport), n = 0.5 indicates fickian diffusion and when n between 0.5 and 1.0 indicates anomalous transport, i.e. both swelling and diffusion controlled drug release. Lastly when n is more than 1.0, supercase II transport is apparent, which shows that the release is following zero order [52]. For formulations F1, F2, F3 and F7, n value was between 0.5 – 1 indicating the drug release by both swelling and diffusion while the other formulations possessed n value > 1 indicating the drug release followed zero order and the release rate was independent of time. Here the relaxation process of the polymer occurring upon water imbibitions into the system is the rate controlling step.

Investigation of the anti-ulcer activity of nizatidine

The results showed that oral administration of 0.15N HCL in 70% ethanol in rabbits induced severe gastric mucosal damage . Peskar et al., reported that intragastric instillation of concentrated ethanol induces macroscopic and histological mucosal injury within seconds, associated with vascular stasis, increased vascular permeability, subepithelial hemorrhages, and cellular exfoliation [53]. The pretreatment with different nizatidine formulations for 5 days significantly reduced gastric mucosal damage. Studies had shown that nizatidine is a potent inhibitor of basal, nocturnal and stimulated acid secretion [54]. Moreover, nizatidine exhibits a potent anti-acetylcholinesterase (AChE) activity and stimulates duodenal HCO3- secretion [55].

The in-vivo results can be correlated with the *in vitro* dissolution studies of nizatidine floating tablet (F4). Maintenance of a local concentration of nizatidine for a longer time in the stomach could protect nizatidine from metabolism by colonic bacteria and provide sustained therapeutic levels of nizatidine to protect the rabbits from occurrence of ulcer more effectively than its conventional formula.

CONCLUSION

The effervescent based floating drug delivery system by employing gel forming polymers (combination of HPMC k4M and carbopol934) and an effervescent mixture (mixture of sodium bicarbonate and citric acid) is a promising approach to increase the gastric residence time of nizatidine up to 12 hours, thereby improving its antiulcer efficacy.

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