AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Nizatidine Floating Tablets

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ABSTRACT

The present study aims at the formulation of a floating drug delivery system of an antiulcer drug nizatidine using different grades of HPMC (K100, K4M, K15M & K100M) and an effervescent agent i.e. sodium bicarbonate. It was found that the release rate of nizatidine from tablet formulations prepared from HPMC K100LV was very high as compared to that from formulations containing higher viscosity grades namely K4M, K15M and K100M. In the current study, it was also found that overall rate of drug release tends to decrease with increase in concentration of HPMC. These observations are in agreement with the results reported in literature i.e. with the increase in polymer concentration and viscosity grade, the viscosity of gel layer around the tablet also increases leading to enhanced diffusional path length for the drug to follow and thus limits the release of active ingredient.

Keywords: Nizatidine, gastroretentive, floating drug delivery, sustained release

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Received 10 August 2012, Accepted 18 August 2012

Please cite this article in press as: Garg A *et al.*, Formulation and Evaluation of Nizatidine Floating Tablets. American Journal of PharmTech Research 2012.

INTRODUCTION

Gastroretentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug there in a controlled and sustained manner so that the drug can be supplied continuously to its absorption sites in the upper GIT[1,2]. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment due to their availability in gastric pH for longer duration of time. The system is also suitable for local delivery to the stomach and upper part of the small intestine[3,4].

Over the last three decades, a variety of approaches have been used to enhance the retention of an oral dosage form in the stomach, including floating systems[5,6], swelling and expanding systems, bioadhesive systems[7,8,9,10], modified shape systems[11,12,13], high density systems[14], concomitant administration of pharmacological agents that delay gastric emptying[15,16], raft forming systems[17,18] and other delayed gastric emptying devices[16,17,19]. From the formulation point of view, FDDS appears to be the most suitable and logical approach to prolong gastric residence time of drugs[20].

Nizatidine is an H_2-receptor antagonist mainly used for treatment of conditions where a controlled reduction of gastric acid is required such as acute duodenal ulcer, acute benign gastric ulcer, and gastroesophageal reflux (GERD) and prophylactic use in duodenal ulcer. The drug has very short elimination half-life of 1-2 h and low absolute oral bioavailability. The drug is prescribed as 150 mg twice daily for acute duodenal ulcer, acute benign gastric ulcer and GERD duration of 8-12 weeks. These attributes like stomach as site of action, short half life and low oral bioavailability make it a suitable candidate for FDDS. Therefore, an attempt has been made to develop stomach-specific FDDS of nizatidine to achieve local action of drug in the stomach by increasing its gastric residence time and also releasing it at a controlled rate to ensure ‘once a day’ administration and optimum bioavailability, thereby, minimizing its side effects and hence enhanced patient compliance.

MATERIALS AND METHODS

Nizatidine was received as a gift sample by Shasun chemicals and Drugs Ltd, Cuddalore, India. Different viscosity grades of HPMC i.e. K100 LV, K4M, K15M & K100M were obtained as gift samples from Colorcon Asia Pvt. Ltd., Goa. PVP-K 30 and Talc were purchased from Central Drug House (P) Ltd, New Delhi. Magnesium Stearate was purchased from Sd fine-chem limited,

Mumbai. All other ingredients were of analytical grade.

Preparation of Nizatidine floating tablets (Preliminary Trials)

Nizatidine (150 mg) was mixed with different polymers like HPMC K100LV, K4M, K15M and K100M by geometric mixing. Drug, polymer and other excipients (except talc and magnesium stearate) were mixed thoroughly, passed through sieve number 40 and compressed using multipunch tablet compression machine after adding talc and magnesium stearate. 16 different formulations were prepared (Table 1) in which amount of all the ingredients (except polymers) were kept constant including drug.

Table 1: Tablet Formulations for Preliminary Trails

Formulation	Nizatidine (mg)	HPMC K100 (mg)	HPMC 4M (mg)	HPMC 15M (mg)	HPMC K100 M	Sodium Bicarbonate (mg)	PVP K30 (mg)	Talc (w/w%)	Magnesium stearate (w/w%)
F_1	150	100	-	-	-	100	100	2	1
F_2	150	75	-	-	-	100	100	2	1
F_3	150	150	-	-	-	100	100	2	1
F_4	150	300	-	-	-	100	100	2	1
F_5	150	-	100	-	-	100	100	2	1
F_6	150	-	75	-	-	100	100	2	1
F_7	150	-	150	-	-	100	100	2	1
F_8	150	-	300	-	-	100	100	2	1
F_9	150	-	-	100	-	100	100	2	1
F_{10}	150	-	-	75	-	100	100	2	1
F_{11}	150	-	-	150	-	100	100	2	1
F_{12}	150	-	-	300	-	100	100	2	1
F_{13}	150	-	-	-	100	100	100	2	1
F_{14}	150	-	-	-	75	100	100	2	1
F_{15}	150	-	-	-	150	100	100	2	1
F_{16}	150	-	-	-	300	100	100	2	1

*HPMC- hydroxypropyl methylcellulose

Physical Evaluation of floating matrix tablets

Weight Variation

20 tablets of each formulation were weighed individually using digital weighing balance and their average weight was calculated. Then individual tablet weight was compared with average weight.

Hardness

The tablet hardness was measured using Monsanto tablet hardness tester. The force required to crush the tablet was recorded as hardness in Kg/cm^2.

Friability

10 tablets were weighed accurately and then placed in Roche-type friabilator which was rotated

at 25 rpm for 4 min (i.e. 100 revolutions). Then tablets were taken out of the friabilator and again weighed after dusting. The percent friability was calculated as follow:

$$\% \text{ Friability} = (W_i - W_f / W_i) \text{ X } 100$$

Where, W_i – initial weight of tablets, W_f – final weight of tablets

Drug Content

From each formulation, ten tablets were weighed and powdered. A quantity of powder equivalent to 150 mg of nizatidine was accurately weighed and dissolved in 100 ml of 0.1 N HCl and stirred for 30 minutes. The solution was filtered, diluted appropriately and analyzed spectrophotometrically at 314 nm using 0.1 N HCl as blank. The drug content was determined from absorbance values using calibration curve[21].

Floating Lag Time (FLT) and Total Floating Time (TFT)

The floating behavior of the tablets was evaluated by placing them in beaker containing 200 ml of 0.1N HCl (pH 1.2). The beaker was kept over a magnetic stirrer. The time taken by the tablets to emerge on the surface of medium was noted as floating lag time and the total time duration for which tablets remained buoyant was noted as total floating time[22].

Dissolution study

In vitro drug release study of the tablets as well as nizatidine 150 mg marketed capsules (obtained as gift sample from Dr. Reddy's) was performed in USP XXIII dissolution apparatus type II (paddle type) containing 900 ml of 0.1 N HCl (pH 1.2) kept at 37^0C with paddle speed of 75 rpm. Samples of 5 ml were withdrawn at predetermined time intervals of 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 24 h and replaced with fresh medium each time[23]. The samples were filtered and analyzed spectrophotmetrically at 314nm. Release profiles of different formulations of floating tablets were compared with release profile of marketed formulation. Also, the effect of different viscosity grades of HPMC in different concentrations on the release profile of nizatidine from FDDS was determined.

Water Uptake Study

The swelling of the tablets takes place due to the ability of polymers to hydrate and swell. The swelling characteristics of the tablet was determined by immersing the tablet in a beaker containing 200 ml of 0.1 N HCl (pH 1.2) and stirred at 37 ^{0}C. After the predetermined time intervals, tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed. Swelling index (SI), expressed as percentage, was calculated using following equation[23,24].

$$SI = \frac{\text{weight of swollen tablet - initial weight of tablet}}{\text{initial weight of tablet}} \text{ X } 100$$

Kinetic Modeling of drug release

In order to examine the release of nizatidine from prepared floating tablets, the results of dissolution studies of all the formulations were examined using different kinetic models i.e. zero order, first order, Higuchi model and Korsmeyer-Peppas model. The regression coefficient R^2 value closer to 1 indicates the model fitting of release mechanism[25]. The major advantage of fitting the data to such expression is that dissolution properties can be treated and analyzed by statistical and mathematical methods[26].

RESULTS AND DISCUSSION

All the batches of prepared tablets were evaluated for various physical parameters like weight variation, hardness, friability and drug content uniformity. The results are shown in Table 2. The hardness of all the formulations was kept between 4-6 Kg/cm2. The tablets must have an optimum hardness in order to have less floating lag time and longer total floating time. The reason is that a high degree of hardness may reduce the porosity of tablets and the compacted polymer particles on the surface of tablets cannot hydrate rapidly on contact with gastric fluid. Consequently, the ability of tablet to float can be significantly reduced. On the other hand, very low hardness results in tablets which are friable and therefore not acceptable. Hence, there must be an optimum hardness for tablets to remain buoyant and to meet pharmacopoeial requirements of stability. The friability values for all the prepared batches were less than 1. Weight variation and drug content were within the USP limits (Table 2).

Floating Lag time and Total Floating Time

On placing the tablets in the beaker containing 0.1 N HCl, all the tablets first sank to the bottom and then they came up to the surface. The beakers were kept over magnetic stirrer to simulate the peristaltic movements of the GIT and FLT (Floating lag time) and TFT (Total floating time) were determined visually. All the tablets remained buoyant for more than 20 h (except F1, F2 & F3) on the medium without disintegration. All the formulations had FLT of less than two minutes. F1-F3 had total floating time of 15 h, 13 h and 18h respectively whereas F4 had 20 h. It was found that the formulation (F2) having low viscosity grade HPMC K100LV floated for small duration of time (13 h) as compared to formulations (F6, F10 & F14) containing same concentrations of higher viscosity grades i.e. K4M, K15M and K100M (Table 3). Also, formulations (F1, F3 & F4) containing higher concentration of same polymer K100 showed

Table 2: Values of various physical parameters of nizatidine floating tablets

Formulation	Weight Variation (n=20)	Hardness (n=3)	% age Friability (n=6)	Assay (n=10)
F1	453.25±6.5	5.17±0.24	0.69	99.67
F2	432.15±9.3	6.0±0.16	0.58	97.32
F3	511.7±11.7	4.67±0.15	0.38	98.51
F4	663±9.91	5.9±0.15	0.51	98.84
F5	460.2±6.7	5.9±0.12	0.78	99.02
F6	432.6±6.3	5.03±0.03	0.71	99.26
F7	516.9±11.2	5.87±0.12	0.58	98.68
F8	659.25±8.9	5.97±0.06	0.39	99.45
F9	456.9±7.9	5.6±0.06	0.69	97.2
F10	436.45±9.3	4.9±0.1	0.35	101.46
F11	519.6±13.8	5.97±0.15	0.45	98.49
F12	668.65±1.6	5.97±0.06	0.67	99.36
F13	459.75±6.5	5.8±0.06	0.58	98.64
F14	434.85±9.2	5.67±0.15	0.30	100.54
F15	516.05±6.2	5.53±0.06	0.53	98.66
F16	662.25±9.1	5.9±0.1	0.42	99.78

Hardness (Kg/cm2); All values are given as Mean±S.D

Table 3: Floating Lag time (FLT) and Total Floating Time (TFT) of different formulations

Formulation	FLT (sec)	TFT
F1	13	15 h
F2	15	13 h
F3	22	18 h
F4	24	20 h
F5	61	>20 h
F6	30	>20 h
F7	44	>20 h
F8	60	>20 h
F9	110	>20 h
F10	60	>20 h
F11	45	>20 h
F12	30	>20 h
F13	18	>20 h
F14	41	>20 h
F15	27	>20 h
F16	12	>20 h

floatation for longer duration of time than formulation F2 with lower concentration. This may be due to the ability of higher viscosity grade and concentration of HPMC to hold the generated carbon dioxide for longer period of time.

In Vitro Dissolution Studies

The in vitro dissolution profile of nizatidine marketed formulation is given in Figure.1. It can be

seen that marketed capsule releases 100 % of the drug within 2 h. But in case of floating tablets release of the drug was controlled. These studies were carried out for 24 h. In all the formulations, the amount of drug was kept constant i.e. 150 mg which is the dose of the drug (Table 1). In case of formulations F1-F4 (containing HPMC K100 LV in varying concentrations), a complete drug release was achieved within 12 h for F1 and F2 and 14h and 16 h for F3 and F4 (Figure 1). However, the release data shows that as level of polymer increases, release rate decreases. A higher viscosity grade polymer HPMC K4M was used for formulations F5-F8 in varying concentrations. In case of F6 (containing 75 mg of K4M), a complete drug release was achieved within 12 h whereas in F5 (containing 100mg of K4M) almost complete drug release i.e. 96% was achieved in 16 h. F7 & F8 (containing 150 and 300 mg of K4M) were found to sufficiently sustain the drug release with 101.4 % and 96.3% release after 24 h (Figure. 2). A similar pattern of drug release was obtained with formulations F9-F12 containing another higher grade of HPMC K15M in different concentrations (Figure 3). Formulations F11 and F12 were found to sufficiently sustain the drug release with 97% and 95% release after 24 h. Formulations F13-F15 were formulated with HPMC K100M (having a viscosity of 100,000 cps). All of these controlled the drug release to such an extent that the drug release was not complete even after 24 h. However, the release rate was found to decrease with increasing concentration of the polymer (Figure.4). The marketed capsule released 100% drug within 2 h where as formulations F7, F8, F11, F12, F13, F14 & F15 controlled the drug release for 24h as shown in Figure 5.

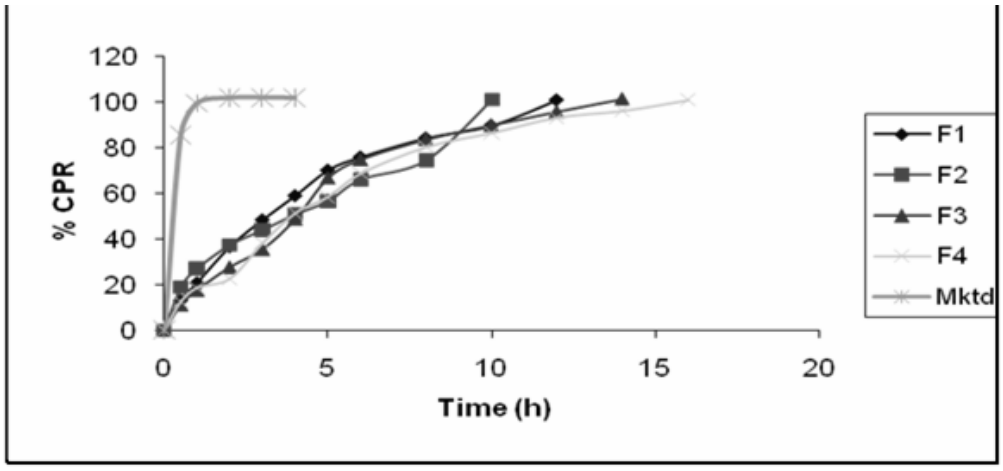

Figure 1: In vitro release profile of formulation F1-F4

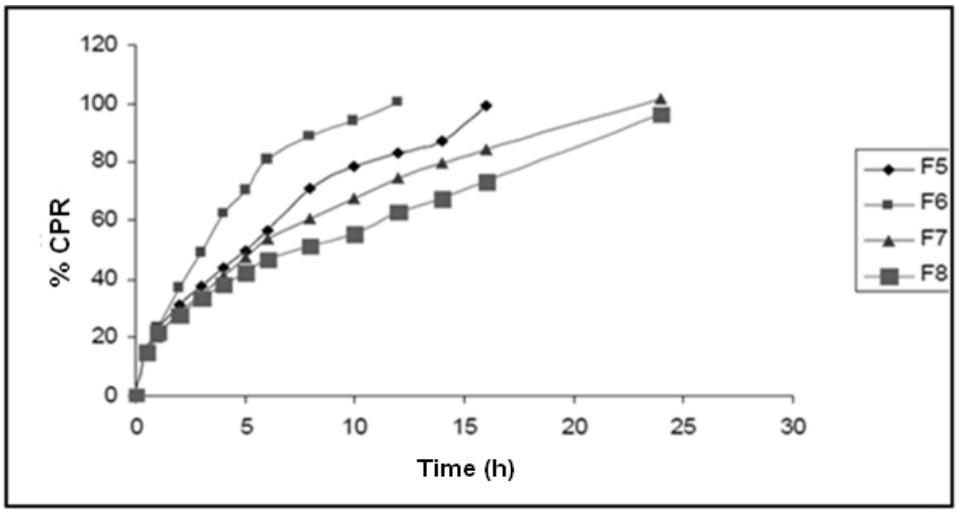

Figure 2: In vitro release profile of formulation F5-F8

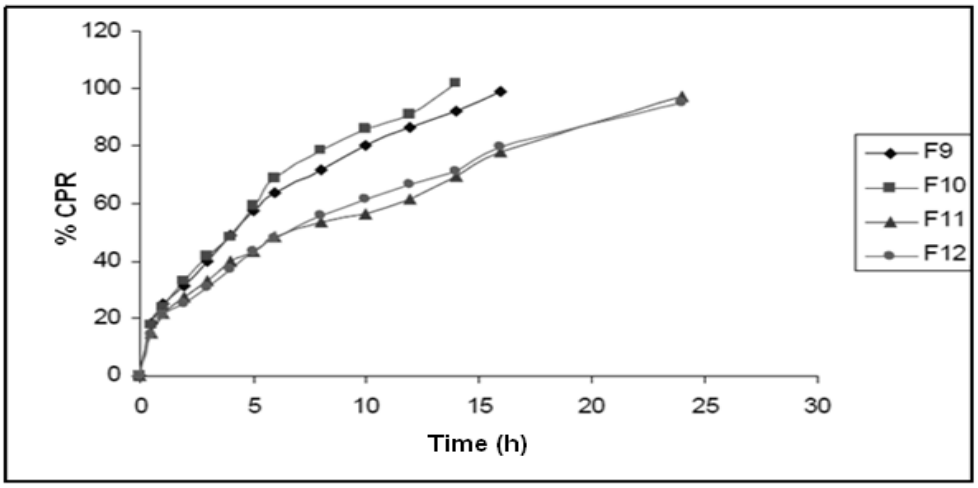

Figure 3: In vitro release profile of formulation F9-F12

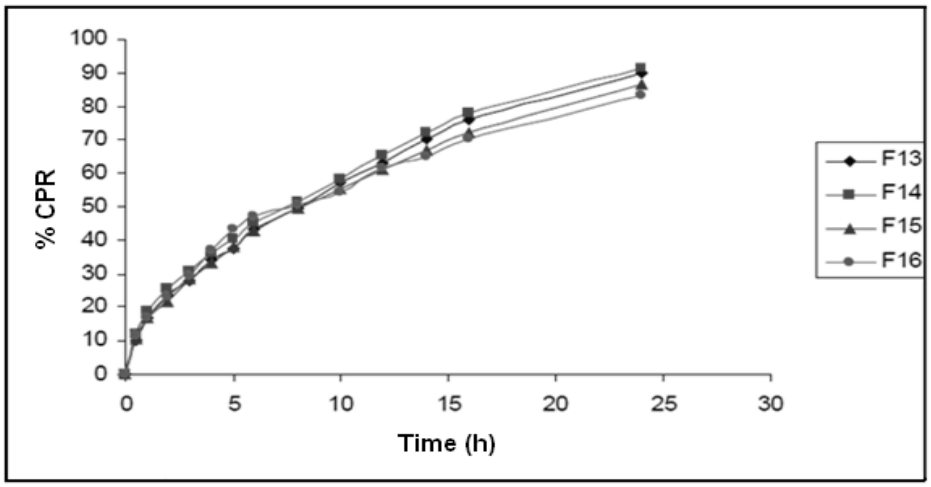

Figure 4: In vitro release profile of formulation F13-F16

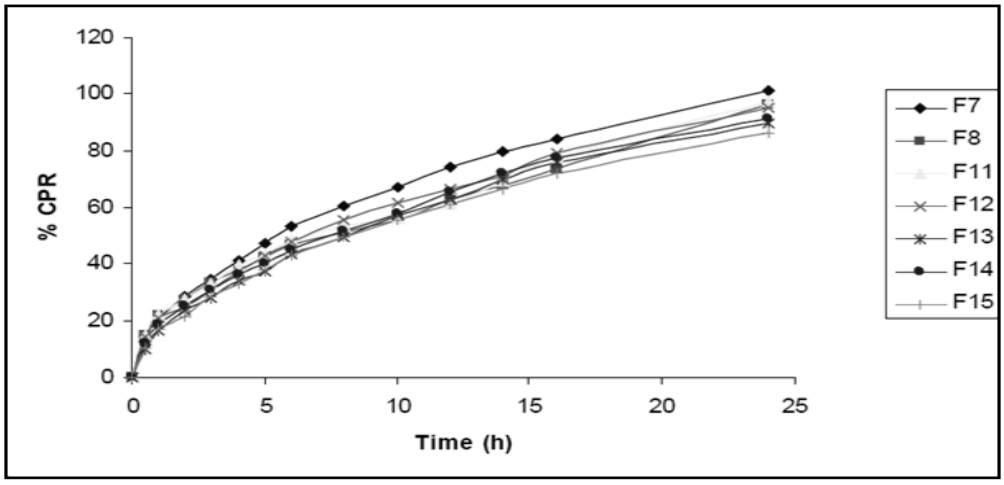

Figure 5: In vitro release profile of optimized formulations

Swelling Studies

Maximum swelling was achieved at the end of 8 h for formulation F13, 12 h for F7, F8, F11 and F14 and 16h for F12 as shown in Table 4.

Table 4: Comparison of swelling index of optimized formulations

Time	F7	F8	F11	F12	F13	F14
0	0	0	0	0	0	0
1	47.40±1.13	59.71±1.56	53.99±1.72	69.99±1.75	48.99±2.02	44.39±1.58
2	58.01±1.01	82.36±2.13	72.98±2.09	90.69±2.27	59.68±1.46	50.42±1.46
3	82.04±1.97	107.63±1.53	95.96±2.06	117.03±2.61	75.32±2.12	65.33±2.30
4	101.97±3.55	132.32±2.11	107.29±2.58	128.99±1.67	101.67±3.18	83.02±2.70
5	132.69±2.09	153.73±2.60	141.33±3.21	160.32±2.12	130.78±1.67	114.58±3.04
6	142.26±2.09	161.13±1.55	150.49±1.53	173.97±1.03	144.01±3.61	127.40±2.44
8	155.74±2.08	166.34±2.07	158.71±1.58	185.29±1.17	153.71±1.52	135.67±1.09
12	164.60±2.87	180.99±1.67	173.96±2.08	189.34±2.08	150.80±1.10	142.63±1.45
16	146.42±1.67	176.29±1.12	169.99±1.98	211.67±1.57	145.55±2.29	139.31±1.07
24	129.38±2.70	173.77±2.41	161.28±4.21	193.46±4.39	144.69±0.57	131.60±2.34

All values are expressed as mean ± S.D, n=3

The plot of swelling index versus time is given in Fig.6. Swelling is generally essential to ensure floating. It was observed that HPMC grade also affect the swelling. S.I values start decreasing when polymer erosion starts in the medium. A direct correlation between swelling and drug release was observed. It was found that with an increase in polymer concentration, swelling increases but the rate of drug release slows down. It may due to the reason that increase in polymer concentration results in formation of thicker gel network that retards the drug release. The swelling of the tablet in release media ensures that it will have high gastric residence time and will not pass through the pyloric sphincter.

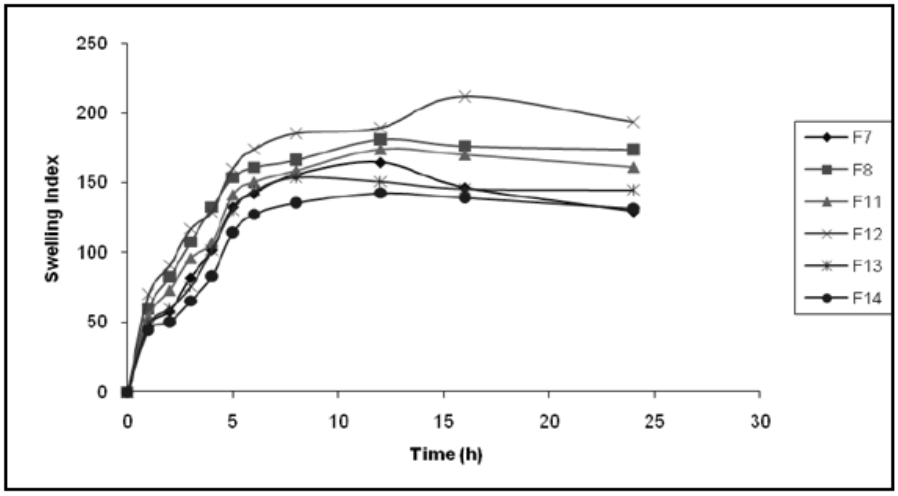

Figure 6: Plot of swelling index of optimized formulations versus time

Analysis of Release Mechanism

R^2 value in case of Higuchi release was found to be higher than zero order and first order in all the formulations suggesting that the drug released from the formulation by diffusion process. The n value in case of Korsmeyer-Peppas model suggested whether the diffusion was fickian or non-fickian. The results suggested that drug release from three formulations (i.e. F8, F11 and F12) followed fick's law (i.e. Fickian diffusion) and rest followed no-fickian anomalous transport as shown in Table 5. Thus both Fickian diffusion and polymer relaxation play an important role in controlling drug release.

Table 5: Kinetic Treatment of the Floating Matrix Tablet

Formulation	Zero-order plot	First-order plot	Korsmeyer-Peppas plot	Higuchi plot
	R^2	R^2	R^2	R^2
F7	0.906	0.449	0.998	0.998
F8	0.930	0.435	0.993	0.992
F11	0.925	0.437	0.993	0.991
F12	0.920	0.456	0.994	0.997
F13	0.930	0.495	0.997	0.996
F14	0.923	0.469	0.998	0.997
F15	0.924	0.485	0.998	0.998

CONCLUSION

Floating matrix tablets of nizatidine were prepared using different grades of HPMC like K100, K4M, K15M & K100 M. All the formulations were evaluated for different parameters like floating lag time, floating duration, physical tests, in vitro dissolution study, release mechanism and swelling characteristics. Weight variation, hardness, friability and drug content of all the formulations were within the pharmacopoeial limits. All the formulations had floating lag time below 2 minutes.Total floating time of formulations F_1-F_4 were $\leq$ 18 h whereas all other

formulations floated for more than 20 h. Formulations F_7, F_8, F_{11}, F_{12}, F_{13}, F_{14} and F_{15} sufficiently sustained the drug release for 24 h.The drug release mechanism from prepared formulations was confirmed to be mainly diffusion. Formulations F_8, F_{11} and F_{12} followed fickian diffusion (n = 0.456-0.498) whereas rest followed non-fickian anomalous transport (n = 0.503-0.702). The overall rate of drug release was found to decrease with increase in concentration and viscosity grade of the polymers. From the results of present study, it may be suggested that maintaining local concentration of nizatidine in the stomach for prolonged period of time by formulating stomach-specific FDDS may be a better therapeutic approach to treat gastric ulcers and GERD.

ACKNOWLEDGMENTS

Authors are very thankful for the Dept. of Pharm. Sciences, LPU, Phagwara (Punjab) for providing the facilities to carry out the work. Authors are also very grateful to Mr Gopal Krishan Duvedi and Mr Harish Kumar for their technical assistance and continuous support.

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