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[Research article]

Design and characterization of nizatidine effervescent floating matrix tablets employing semisynthetic rate-retarding polymers

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ABSTRACT

Nizatidine effervescent controlled release floating tablets employing three grades of HPMC K4M, HPMC K15M and HPMC K100M in four ratios (1:0.5; 1:1; 1:5 and 1:2) were prepared and evaluated. FTIR, DSC and XRD studies on the formulations showed no interaction of nizatidine with the polymers employed in the study. Most of the tablet formulations showed values within the official limit upon pre and post- compression evaluation. The type of polymer affected the drug release rate and the mechanism. Polymer swelling was crucial in determining the drug release rate flotation. A lesser FLT could be achieved by increasing the concentration and increasing the viscosity grade of the polymer. The optimized formulation (NS6) offered best controlled release along with floating lag time of 1.2 min and total floating time of >14 h. Good stability was observed for 3 months during accelerated stability studies. The optimized formulation NS6 employing nizatidine: HPMC K15M in the ratio of 1:1 showed sufficient release for prolonged period, the dose could be reduced and the possible incomplete absorption of the drug could be avoided.

Key Words: HPMC K4M, K15M, K100M, Gastroretentive, nizatidine, Matrix tablets, *In vitro* studies.

INTRODUCTION

Controlling the release of drugs and prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract [1] and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolonged gastric retention. [2,3] In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size [4,5].

The robust approach is floating matrix tablets for continuously releasing nizatidine while reaching the absorption window ensuring maximum bioavailability and therapeutic effectiveness.

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It has been suggested that prolong local availability of H2 receptor antagonists may augment their effectiveness in treating H. Pylori related peptic ulcers using controlled release drug delivery locally. One of the most possible approaches for prolonged and predictable drug profile in G.I Tract is to control the gastric residence time (GRT) that is floating drug delivery systems will provide us with a new and important therapeutic options.
The aim of the present work is to develop and evaluate controlled release effervescent floating tablets of and nizatidine using semi synthetic polymers.

MATERIALS AND METHODS

Nizatidine (NIZ) was gift sample from Sai Sreenivasa Pharmaceuticals Pvt. Ltd. Hyderabad, India. HPMC with grades of K4M, K15M and K100M were obtained from ColorCon Asia Pvt. Ltd, Goa, India. HCl, Citric acid, Sodium bicarbonate, talc and magnesium stearate were purchased from S.D.Fine Chemicals, Mumbai, India. All other ingredients used were of analytical grade.

DRUG EXCIPIENT IN COMPATIBILITY STUDY [6]

The FTIR spectra (400 to 4000 cm^{-1} and resolution of 4 cm^{-1}) of the pure nizatidine and polymers were measured by preparing dispersion in dry KBr using Shimadzu FTIR 8400S (Bruker, Germany). The transmission minima (absorption maxima) in the spectra obtained with these polymers were compared. The presence of additional peaks corresponding to the functional groups was noted.

DSC thermographic analysis was done using a Shimadzu DSC-60 (Shimadzu, Japan). The behavior under heat was studied by heating the samples (2 mg) in an aluminium pan from 25 to 300°C at a heating rate of 10°C/min under a flow of nitrogen at 10 cm^3/min using an empty pan as a point of reference.

Powder XRD study was conducted using an automatic diffractometry (XRD 7000, Schimadzu, Japan) with a voltage of 40 kV and a current of 30 mA. The sweep measurements of 2θ angle were carried out at a scanning rate of 4^o min^{-1} over a range of 10 to 80^o. The results were interpreted using the computer program (XRD 7000, Schimadzu, Japan). The highest peak of diffraction was measured for crystallinity of the sample.

PREFORMULATION STUDIES OF POWDER BLENDS

The drug and polymer powders blends of different combinations as per Table-1, were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose using standard procedures [7]. The obtained values after testing are compared with the standard values and inferences were drawn.

PREPARATION OF FLOATING MATRIX TABLETS USING HPMC POLYMERS [8]

In the present investigation, wet granulation technique was employed to prepare tablets of HPMC of different viscosity grades (K4M, 4,000 cps; K15M, 15,000 cps; and 1,00,000 cps) at different drug to polymer ratios as per the composition given in Tables-1. Sodium bicarbonate and citric acid were employed as gas generating agents. PVP K30 dissolved in sufficient isoprpyl alcohol was used as granulating agent (binder). Magnesium stearate was used as lubricant and talc as a glidant. Punch of 12 mm size with corresponding dies were used for tablet compression the tablets employing Cadmach Press.
The granules were prepared by wet granulation method using warm purified water (50-55 ^oC). The wet mass was prepared by taking the calculated amount of mentioned ingredients as per composition in Tables- 01. The ingredients along with water were mixed to make dough and passed through #20 standard sieve meshes and dried at 60 ^oC in hot air oven for 1 h. The dried granules were sifted through #22 sieve meshes and lubricated with mixture of magnesium stearate and talc (pre-sifted through sieve #80). The mixed granules were compressed in tablet press using suitable punches as stated above.

Table 1: Formulation of nizatidine floating matrix tablets prepared using different grades of HPMC

Ingredients (mg)	NS1	NS2	NS3	NS4	NS5	NS6	NS7	NS8	NS9	NS10	NS11	NS12
Nizatidine	150	150	150	150	150	150	150	150	150	150	150	150
HPMC K4M	75	150	225	300	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	75	150	225	300	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	75	150	225	300
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30	30	30	30
Citric acid	15	15	15	15	15	15	15	15	15	15	15	15
PVP K30	12	12	12	12	12	12	12	12	12	12	12	12
Magnesium stearate	8	8	8	8	8	8	8	8	8	8	8	8
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	299	374	449	524	299	374	449	524	299	374	449	524

IN VITRO BUOYANCY STUDIES

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT). The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.*[9]**.** The tablets were placed in a 250 mL beaker containing 100 mL of 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

SWELLING STUDIES [10]

Formulated tablets were weighed individually (W_o) and placed separately in a petri dish containing 50 mL of 0.1N HCl. The Petri dishes were placed in an incubator maintained at 37±0.5ºC. The tablets were removed from the petri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula

$$\% W_U = (Wt\text{-}Wo/Wo) \times 100$$

Where: W_U – Water uptake, Wt – Weight of tablet at time t, Wo – Weight of tablet before immersion.

IN VITRO DISSOLUTION STUDIES

The release of nizatidine from the prepared floating tablets was studied using USP-Type II paddle apparatus (Electrolab TDT 08L, dissolution tester, U.S.P.). Drug release profile was carried out in 900 mL of 0.1N HCl maintained at 37±0.5°C temperature at 100 rpm. 5 mL of samples were withdrawn at regular time intervals up to 12 h. The samples were replaced by equivalent volume of dissolution medium and were filtered through 0.45 µm Whatman filter paper. The samples were suitably diluted and analyzed at 314 nm, using (Shimadzu UV 1700) UV spectrophotometer.

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi and Koresmeyer-Peppas equations. Based on the obtained R^2 values, the best-fit model was selected [11-12].

Anomalous diffusion or non-fickian diffusion refers to a combination of both diffusion and erosion controlled rate release. The *Korsmeyer Peppa's equation* is used to deteremine whether the drug release mechanism is Fickian or non-Fickian[13].

STABILITY STUDIES OF OPTIMIZED FLOATING MATRIX TABLETS [14]

The optimized floating matrix tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 40±5ºC/75% RH for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated. The drug content, floating lag-time and drug dissolution profile of the exposed samples were determined.

Student t-test is used to compare the means of two related (paired) samples analyzed by reference and test methods. It gives answer to the correctness of

the null hypothesis with certain confidence such as 95% or 99%. If the number of pairs (n) are small than 30, the condition of normality of x is required or atleast the normality of the difference (d_i). This test, also known as Welch's t-test, is used only when the two population variances are not assumed to be equal (the two sample sizes may or may not be equal) and hence must be estimated separately. The t statistic to test whether the population means are different is calculated as:

$$t = \frac{\bar{x_1} - \bar{x_2}}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}}$$

Where, $\bar{x}_1$ = mean of first set of values, $\bar{x}_2$ = mean of second set of values, S_1= standard deviation of first set of values, S_2= standard deviation of second set of values, n_1= total number of values in first set and n_2= total number of values in second set.

Significance of difference for floating lag time and assay values of the optimized formulation before and after accelerated stability testing was calculated based on Student's t-test.

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100 [15]. The dissolution profiles of products were compared using f_2 which is calculated from the following formula,

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{j=1}^{n} | R_j - T_j |^2]^{-0.5} \times 100\}$$

Where, n is the dissolution time and Rj and Tj are the reference and test dissolution values at time t. The similarity factor (f_2) was calculated for comparison of the dissolution profile before and after stability studies in the present study [16].

RESULTS AND DISCUSSION

DRUG-POLYMER COMPATIBILITY STUDIES

FTIR spectra of pure NIZ showed characteristic sharp peaks were observed at 1585.119, 1521.85 and 1436.71 cm^{-1}. These bands confirm the presence of characteristic groups like N–H stretching, N=O stretching and C–H deformation. Bands were observed at 753.92, 1017.27 and 1221.8 cm^{-1} due to stretching (bending =C–H and $=CH_2$),–CH deformation and–CH bending. Principle peaks were also found in the range corresponding to functional groups. Appearance of the principle peaks in spectrum confirms the drug sample is NIZ and is pure. The same bands were also found in the spectra of the formulations of NIZ using various polymers, which indicated that there was no drug-polymer interaction.

The DSC thermograms showed well defined peaks for NIZ in individual and combination with polymers. NIZ showed one sharp endothermic peak occurred at 137.5°C. Formulations of NIZ using HPMC K4M, HPMC K15M and HPMC K100M showed similar endothermic peaks at 145.2, 142.6 and 139.3°C respectively which indicated that there was no significant interaction between the drug and polymers employed in the study.

The diffractogram of NIZ exhibited a series of intense peaks at 13.25, 16.33, 20.74, 22.39, 24.21, 26.82, 28.49 and 30.51 which were indicative of crystalline nature of NIZ. As compared to NIZ and different formulations using polymers employed in the study showed insignificant diffraction pattern of peaks and their intensity which indicated that there was no variation in the crystanality of formulations as compared to the NIZ alone.

PRE-COMPRESSION FLOW PROPERTIES OF POWDER BLEND

The data obtained from pre compressional testing of powder blends are summarized in Table - 2.

Bulk density and tapped density

Bulk density and tapped densities showed good packing ability of the powdered blend for compression process. Bulk and tapped densities of different formulations were calculated. The results of bulk density ranged from 0.34±0.06–0.55±0.12 gm/cm^3 and tapped density from 0.40±0.04–0.60±0.05 gm/cm^3.

Carr's index (Compressibility index)

Carr's index of the powder of all formulations ranged from 3.51% to 20.69%. Formulation NS8 showed lowest Carr's index indicating good compressibility.

Haunsner's ratio

Hausner's ratio ranged from 1.036 to 1.260 which indicated that the powder blends of all formulations have the required flow property for direct compression.

Angle of repose

All the powder blends showed excellent flow ability as expressed in terms of angle of repose whose values were found in the range 18.76±1.16° to 26.35±0.13°. The powder blend of NS1 had the lowest value among all formulations composition showing excellent flow. As per pharmacopoeial standards (IP 1996) other formulations were within the range of excellent flow properties (25–30°) [17]. The obtained values of all the derived properties of powder combinations were within the limits, indicating that the powder blends possessed the required flow property for tablet compression.

Table 2: Pre-compression flow properties of powder blends

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)±SD
NS1	0.45±0.03	0.52±0.07	13.46	1.130	18.76±1.16
NS2	0.47±0.08	0.56±0.09	16.07	1.191	22.95±1.01
NS3	0.55±0.10	0.57±0.11	3.51	1.036	24.67±0.26
NS4	0.55±0.12	0.60±0.04	8.33	1.090	26.24±2.16
NS5	0.54±0.09	0.60±0.05	10.01	1.111	20.21±1.96
NS6	0.44±0.07	0.51±0.07	13.72	1.201	26.35±0.13
NS7	0.34±0.06	0.40±0.04	15.00	1.176	25.25±1.14
NS8	0.43±0.09	0.52±0.09	17.31	1.209	25.11±0.14
NS9	0.52±0.07	0.59±0.08	11.86	1.134	24.23±1.59
NS10	0.42±0.05	0.51±0.05	17.65	1.214	23.12±1.19
NS11	0.41±0.09	0.47±0.10	12.77	1.146	24.16±1.18
NS12	0.46±0.11	0.58±0.09	20.69	1.260	25.23±1.76

Table 3: Post-compression physicochemical evaluation of nizatidine floating tablets

Formulation code	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	FLT (min)	TFT (h)
NS1	4.1±0.055	295±0.84	0.4±0.045	100.11±0.62	1.4	>12
NS2	4.2±0.052	368±0.72	0.6±0.034	98.86±0.52	1.3	>12
NS3	4.5±0.063	445±0.33	0.5±0.042	99.65±0.42	1.3	>12
NS4	4.8±0.045	519±040	0.6±0.065	98.55±0.01	1.2	>12
NS5	4.3±0.033	293±0.55	0.4±0.066	96.86±0.94	1.2	>12
NS6	5.4±0.06	368±0.56	0.3±0.066	99.99±0.85	1.2	>12
NS7	5.0±0.034	445±0.46	0.4±0.026	98.88±0.96	1.2	>12
NS8	5.2±0.047	520±0.44	0.5±0.032	98.97±0.67	1.1	>12
NS9	4.7±0.026	295±0.37	0.6±0.074	98.95±0.91	1.3	>12
NS10	4.9±0.055	370±0.38	0.5±0.046	99.94±0.34	1.2	>12
NS11	5.3±0.062	443±0.52	0.40±054	97.95±0.83	1.3	>12
NS12	5.5±0.053	520±0.42	0.8±0.084	100.76±0.45	1.2	>12

FLT, floating lag time; TFT, total floating time

FORMULATION OF NIZATIDINE FLOATING TABLETS

All the tablets were prepared by effervescent approach. The concentration of all the three selected semi-synthetic polymers (HPMC) was decided on trial and error basis. Sodium bicarbonate and citric acid in the ratio of 1.0:0.5, were incorporated as a gas-generating agents based on earlier studies**.** PVP-K30 (5%) was used as binder. Talc (1%) was used as lubricant and magnesium stearate (2%) was employed as glidant to improve the flow of the powder. FTIR study showed that all the polymers used were compatible with nizatidine.

From the earlier literature it was evident that HPMC (Methocel K15M) is a good polymer for floating drug delivery system as it is a matrix forming and low density polymer henceforth suitably used for fabrication of floating matrix tablets.

POST-COMPRESSION EVALUATION OF NIZATIDINE FLOATING MATRIX TABLETS

The formulated floating tablets were subjected for post compressional evaluation such as visual inspection, hardness, weight variation, friability, uniformity of drug content, *in vitro* buoyancy, swelling, *in vitro* dissolution, stability and similarity studies. The results are summarized in Table 3.

Visual inspection

The prepared tablets were inspected visually for general tablet deformities. The tablets were smooth with uniform in size, shape and colour. There was no lamination or chipping was observed in all the tablets which indicated that the tablet-instrumentation was compatible with the powder blends and resulting in good tablet characteristics.

Hardness

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. Hardness in the prepared tablets was found to be in the range of 4.1±0.05–5.5±0.05 kg/cm^2. Hardness of the tablets was found to increase with an increasing of polymer concentration. The floating tablets prepared using HPMC K4M was found to be less harder than those prepared using HPMC K15M and K100M. Similar pattern of results was observed in the study done by Chauhan *et al*, [18].

Weight variation

The weight variation of prepared formulations was found in the range of 295±0.37–520±0.42 mg. All the batches of tablets were found to pass the weight variation test. The percentage deviation of the individual tablet weights from the average tablet weight was found to be within the I.P. limits of ±5%.

Friability test

The friability loss of prepared tablets was found to be between 0.30% and 0.80 % when tested using Roche friabilator. All batches of tablets passed the test and were within the limits which indicated that the tablets were mechanically stable.

Drug content uniformity

The drug content uniformity of the prepared tablets was examined as per I.P. specification and was found compliant. The drug content of the formulations was in the range 96.86±0.94% to 100.76±0.45% showing the uniformity of drug distribution in the prepared tablets [19]. None of the individual drug content values were outside the average content values of 90% to 110% as per IP.

***IN VITRO* BUOYANCY STUDIES**

The investigated gastric floating tablets employed $NaHCO_3$ and citric acid in 1:0.5 ratio, as gas-generating agents dispersed in a hydrogel matrix (HPMC K4M, HPMC K15M and HPMC K100M). These matrices are fabricated so that upon arrival in the stomach in the acidic environment reacts with the acid media and produces carbon dioxide. The evolved gas will get entrapped in the matrix leading to floating of the tablet.

The concentration of $NaHCO_3$ (30 mg) was kept constant as there is a chance for rapid erosion of tablet if more than polymer concentration. The floating lag time for all the formulation (Table -3) was found to be from 1.1–1.4 min and total floating time was more than 12 h which indicates the success of floating systems.

SWELLING STUDIES

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the floating tablets. 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 of the tablet. The swelling index of floating tablets of NS1–NS12 is shown in Figs.1-3. All the formulations formulated by HPMC polymers have exhibited good swelling and tablet integrity.

The formulation NS12 containing HPMC K100M (1:2) 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 was achieved in initial h and then diffusion and erosion started taking place. As reported by [20] 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 of HPMC which form quick gel on contact with water.

IN VITRO DISSOLUTION STUDIES

In vitro dissolution studies of NIZ floating tablet were evaluated in 0.1 N HCl (pH 1.2) for 12 h. The cumulative percentage of drug released from the tablets containing three viscosity grades of HPMC (K4M, K15M and K100M) in specified ratios was compared.

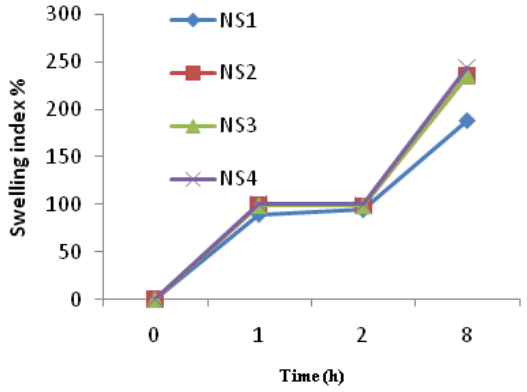

Fig. 1: Swelling studies of nizatidine floating tablets formulated with HPMC K4M

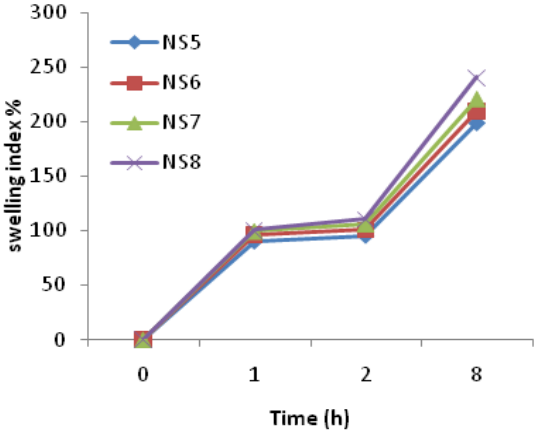

Fig. 2: Swelling studies of nizatidine floating tablets formulated with HPMC K15M

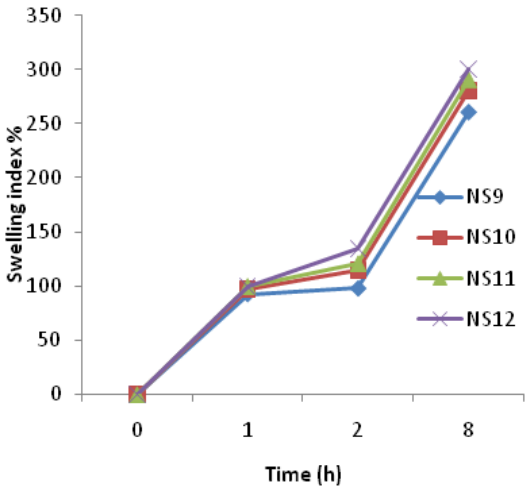

Fig.3: Swelling studies of nizatidine floating tablets formulated with HPMC K100M

The plots of cumulative percentage drug release vs. time (h) for formulations NS1–NS4, NS5–NS8 and NS9–NS12 were plotted and depicted in Figs. 4-6. The drug release rate was dependent on the type and concentration of the investigated polymers. The floating tablets containing HPMC K4M (NS1) showed drug release of 98% at the end of 12 h and those of HPMC K15M showed constant drug release up to 12 h (85%). The floating tablets containing HPMC K100M (NS9) remained stable for 12 h with a drug release of 93%. All the above discussed formulations exhibited highest Nizatidine release in each category of polymers.

The results revealed that the formulation NS1 and NS5 containing equal ratio of HPMC K4M and K100M were found best as the extent of drug release was found to be 98.32 and 96.12% respectively after 12 h.

The controlled release of drug from NS1 and NS5 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. 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 as discussed by [21] The faster drug release in case of

formulation containing low amount of HPMC K4M may be due to less tortuous diffusion path.

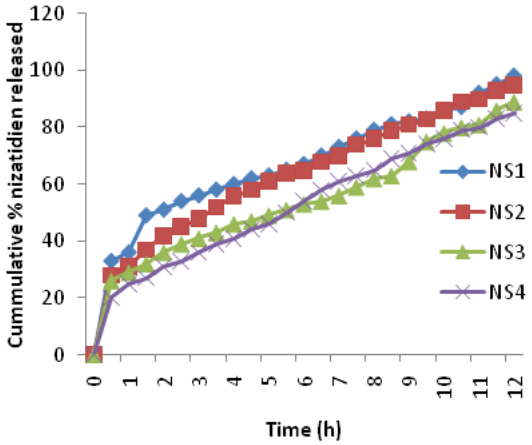

Fig. 4: *In vitro* drug release profiles of nizatidine floating tablets of HPMC K4M

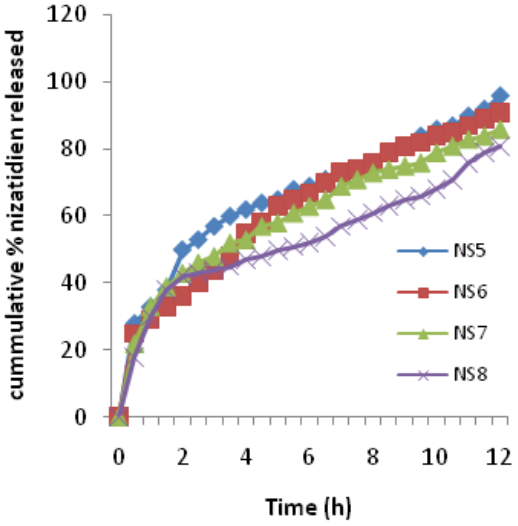

Fig. 5: *In vitro* drug release profile of nizatidine floating tablets of HPMC K15M

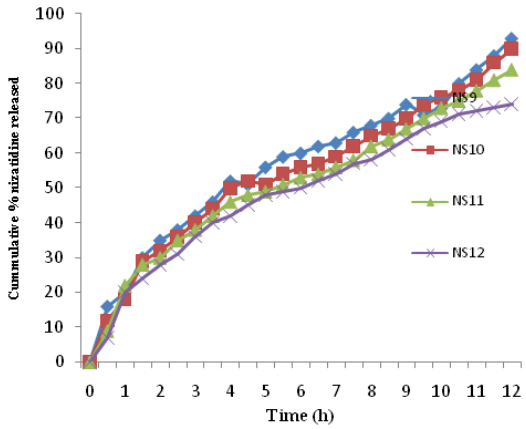

Fig. 6: *In vitro* drug release profile of nizatidine floating tablets of HPMC K100M

DRUG RELEASE KINETIC STUDIES

The mechanism of drug release for the above formulations was determined by calculating the correlation coefficient (R^2 value) for the kinetic models, viz., zero-order, first-order, Higuchi, and Korsmeyer–Peppas corresponding to the release data of each formulation. The results of the kinetic models are summarized in Table 4. For most of the formulations the R^2 value of Korsmeyer–Peppas and zero-order model was nearer to one than those of other kinetic models. Thus, it could be drawn from the results that the drug release follows zero-order and Korsmeyer–Peppas model mechanisms.

The 'n' values of Korsmeyer–Peppas model for the best formulations were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was found to be non-Fickian diffusion or anomalous diffusion for the formulations tested. The time required for dissolution of 50% (T_{50}) and 90% (T_{90}) were determined. The results of drug release kinetics are shown in Figs.7.

Formulation NS6 (drug-polymer in 1:1 ratio) showed a minimum lag time (1.2 min) and maximum floating time (> 12h) with maximum drug release (100.02%±0.12% in 11 h). It also showed good linearity (R^2 of 0.991) which indicates Higuchi order matrix release with non-Fickian diffusion mechanism. Therefore, formulation NS6 could be considered as optimized formulation from this set of twelve formulations prepared by three different grades of HPMC polymers. Similar conclusions were also drawn by earlier researchers who worked in the development of floating delivery systems [22,23].

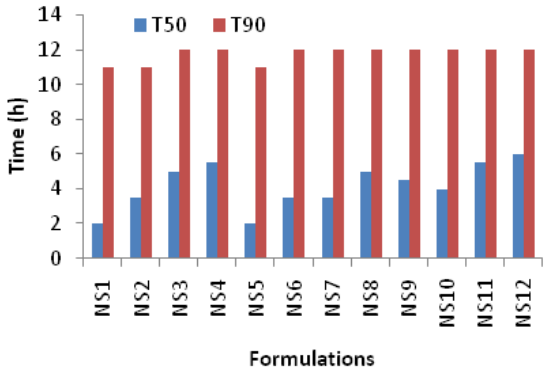

Fig. 07: T_{50} and T_{90} values of nizatidine floating tablets

STABILITY STUDIES

Based on floating lag time, floating time and *in vitro* drug release kinetics data, the formulation

NS6 was optimized. The tablets of batch NS6 were packed in an aluminum pouch and subjected to accelerated stability studies at 40°C and 75% RH for 3 months in a humidity chamber. The drug content, floating lag-time and drug dissolution profile of the exposed samples were determined. The similarity factor (f_2) was calculated for comparison of the dissolution profile before and after stability studies.

Table 5 shows the results of drug content and floating lag time of the formulation NS6 before and after the accelerated stability studies. Student t-test was conducted on drug content and floating lag time and the values obtained were 0.26 and 1.32 respectively which were lesser than the table value of 2.57 at 95% confidence limits. There was no significant difference observed in the drug content uniformity and floating lag-time before and after the stability studies.

SIMILARITY STUDIES

Similarity factor (f_2) for NS6 optimized formulations compared before and after stability testing was found to be 77.49, which was between 50 and 100. This indicates existing of a close similarity between the dissolution profiles of the tested formulation before and after stability studies. Hence, these results confirm that the developed formulation was stable under tested conditions.

Table 4: *In vitro* drug release kinetics of nizatidine floating tablets formulated with HPMC

Formulation	T_{50} (h)	T_{90} (h)	Zero order		First order		Higuchi	KorsmeyerPeppas	
			R^2	K_0 ($mg.h^{-1}$)	R^2	K_1 (h^{-1})	R^2	R^2	N
NS1	2.0	11	0.985	05.27	0.821	0.212	0.990	0.991	0.413
NS2	3.5	11	0.987	5.61	0.932	0.200	0.994	0.994	0.457
NS3	5.5	12	0.983	5.17	0.887	0.140	0.938	0.944	0.481
NS4	5.5	12	0.996	5.69	0.970	0.140	0.976	0.986	0.583
NS5	2.0	11	0.944	5.04	0.908	0.189	0.984	0.973	0.373
NS6	3.5	12	0.962	5.72	0.989	0.175	0.991	0.990	0.511
NS7	3.5	12	0.959	4.80	0.989	0.134	0.995	0.992	0.389
NS8	5.0	12	0.950	4.23	0.930	0.099	0.954	0.918	0.352
NS9	4.5	12	0.960	5.60	0.885	0.159	0.982	0.985	0.504
NS10	4.0	12	0.966	5.70	0.924	0.147	0.984	0.984	0.524
NS11	5.5	12	0.969	5.40	0.958	0.127	0.985	0.986	0.523
NS12	6.0	12	0.958	5.09	0.990	0.104	0.993	0.995	0.541

Table 5: Stability studies of optimized formulation NS6

Storage conditions	Drug content (%±sd)	FLT (min±sd)
Reference (NS6)	100±0.83	1.1±0.11
Test (40 ± 2^0 C/75±5% RH, 3 months)	99.88±0.99	1.2±0.18
t-test value	0.26	1.32

FLT, floating lag time; n=3

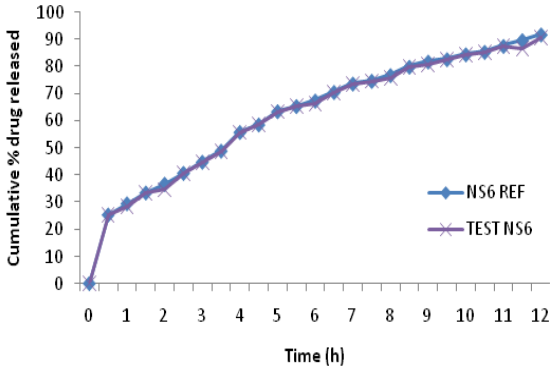

Fig.08 : Cumulative % of drug released vs time plots of formulation NS6 before and after stability studies

CONCLUSIONS

From the results of the study, it is evident that the gastroretentive floating tablets prepared from HPMCK15M in 1:1 ratio with the gas generating agents in 2:1 was crucial to achieve in vitro buoyancy and controlled drug release. The NIZ floating tablets were formulated by using gelling polymer HPMCK4M, which showed pleasing results in vitro dissolution but with high buoyancy lag time, total buoyancy time more than 12 h controlled drug released upto 12 h comparing with HPMCK15M that shows promising drug release and less floating lag time. On the other hand the formulation prepared by HPMCK100M has relatively less drug release with a high swelling index this may be attributed due to high viscosity of this polymer. Therefore this can be concluded that viscosity of polymer is a key factor affecting the release and floating properties of drug and this would be a feasible alternative to conventional oral dosage form of NIZ in order to retain the drug at the site of absorption and to increases the bioavailability of the drug there by reducing the dose or dosing interval. Thus, it was brought into being that the NIZ floating tablets of (NS6) was stable at 40°C/75% RH for a period of 3 months results were found satisfactory based on the similarity factor before and after stability testing.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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