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Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF EFFERVESCENT FLOATING MATRIX TABLETS OF NIZATIDINE USING NATURAL AND SEMI SYNTHETIC POLYMERS

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ABSTRACT

The aim of this study was to develop a floating gastroretentive dosage form using effervescent technique so as to increase the patient compliance and to provide a prolonged therapeutic effect. Nizatidine was used as a model drug because of its short elimination half-life and localized action in the gastric region. Nine batches containing 75mg of Nizatidine per tablet were developed using release modifiers like xanthan gum and HPMC K100M both individually and in 1:1 combination at 30, 40 and 50% concentrations. Sodium bicarbonate and tartaric acid were used as gas generating agents. The drug-excipient compatibility, pre and post compression parameters, buoyancy properties and swelling index were evaluated. *In-vitro* dissolution studies were carried out in 0.1N HCl (pH 1.2) at 37±0.5°C. Increase in polymer concentration showed significant retardation of drug release and increase in swelling property. Release kinetics were studied by fitting the data into various models and release mechanism, predicted drug release were studied. Best formulation among the designed batches was selected based on cumulative percentage of drug released by the end of twelfth hour and by comparing the predicted and obtained drug releases at the end of 5th and 8th hours respectively.

KEYWORDS: Nizatidine, Floating tablets, Effervescent tablets, Release kinetics, Xanthan gum, HPMC-K100M.

INTRODUCTION

Patient compliance is gaining a significant importance as a factor to be considered while designing the dosage forms. Patients being treated with conventional oral formulations containing drugs with shorter half-lives require frequent dose administration, which effects the patient compliance. This can be overcome by sustaining the drug release. The bioavailability of these dosage forms is influenced by various factors, the gastric residence time (GRT) being one of the important ones as the dosage forms are removed from the gastrointestinal tract (GIT) before all of the drug in them is released into the body[1,2]. So the real challenge in the development of an oral controlled release drug delivery system is just not to sustain the drug release but also to prolong the presence of dosage form within the GIT until all the drug is completely released at the desired period of time[3].

The gastroretentive dosage forms (GRDF's) can overcome this problem by retaining themselves in the gastric region withstanding the peristaltic waves, constant contractions, grinding and churning movements of the stomach. Gastric retention however is not suitable for the drugs that cause gastric irritation/lesions and for those that are unstable in the strong acidic environment. Flotation is one of the techniques by which gastric retention can be achieved.

Floating drug delivery system (FDDS), as first described by Davis in 1968, have bulk density lower than that of the gastric fluid (1.004 g/cm^3) and thus remain buoyant in the stomach for a prolonged period of time releasing drug into the body at a predetermined rate[4]. After the release of drug, the residual system is eliminated from the stomach by natural gastric emptying process.

Floating systems are of two types:

1. Effervescent systems, which depend on carbon dioxide gas generated upon contact of the dosage form with the gastric fluid and
2. Non-effervescent systems, which can be further divided into four sub-types, which are hydrodynamically balanced systems; microporous compartment systems; alginate beads and hollow microspheres (microballoons) respectively[5].

Compressed hydrophilic matrices are commonly used as oral drug delivery systems because of their good compatibility. Drug release from hydrophilic matrix tablets is controlled by formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water into tablet and also movement of dissolved solutes out of the tablet matrix. The overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the gel barrier that forms around the tablet. The extent of matrix swelling, erosion and diffusion of the drug determine the kinetics as well as mechanism of drug release[6].

Floating drug delivery is of particular interest for drugs which: a) act locally in the stomach; b) are primarily absorbed in the stomach; c) are poorly soluble at an alkaline pH; d) have a narrow window of absorption and e) are unstable in the intestinal or colonic environment[7].

Nizatidine is a competitive, reversible inhibitor of the histamine H_2 receptors of the gastric acid secreting cells. It inhibits the nocturnal gastric acid secretion and gastric acid secretion stimulated by food, caffeine, betazole and pentagastrin[8]. This drug is used for the treatment of duodenal ulcers and gastro esophageal reflux disorder (GERD). Short half-life of 1.3 – 1.6h and its site of action in the gastric region make Nizatidine a suitable candidate for floating drug delivery system.

The objective of the present investigation was to design, formulate and *in-vitro* evaluate the effervescent floating matrix tablets of Nizatidine. The tablets were formulated using release modifying, gel forming polymers like HPMC K100M and/or xanthan gum and gas generating agents like sodium bicarbonate and tartaric acid.

MATERIALS AND METHODS

Nizatidine was obtained as a gift sample from Dr Reddy's Laboratories, Hyderabad. Hydroxypropyl methylcellulose K100M was obtained from Colorcon Asia Pvt Ltd, Goa. Xanthan gum was purchased from LobaChemie, Mumbai. Lactose, ethyl cellulose, sodium bicarbonate and tartaric acid

were purchased from SD Fine Chem Ltd, Mumbai. Magnesium stearate and talc were purchased from Molychem, Mumbai. All the ingredients were of analytical grade and were used as it is.

Drug - Excipient Compatibility Studies

The drug excipient compatibility was studied by observing for any possible chemical interactions between the API and excipients using Fourier Transform Infrared (FTIR) spectroscopy following KBr disk method. The API and polymer were mixed in 1:1 ratio and then mixed with IR grade KBr and disks were punched at high pressure using a hydraulic press. These pellets were scanned over a range of 500 to 4000cm^{-1} using Bruker alpha spectrophotometer with opus 65 software and the results obtained were shown in figures 1-4.

Preparation of Nizatidine Floating Tablets

Tablets containing 75mg of Nizatidine were prepared according to the design depicted in table 1 by direct compression method**.** The weighed quantities of respective powders, namely the active ingredient Nizatidine; release modifying polymers xanthan gum and/or HPMC K100M; gas generating agents sodium bicarbonate and tartaric acid; ethyl cellulose binder; lactose diluent were passed through sieve #16 separately. Mixing of powders was carried out using a pestle in a mortar for 10min. Magnesium stearate and talc were then added to the mixed powders. Mixing was continued for another 5min. Finally 400mg of the powdered mixture was weighed approximately and was fed manually into the die of a multistation rotary tablet press (Rimek Mini Press II compression machine) to produce the desired tablets. The hardness of the tablets was adjusted at 5kg/cm^2 using Monsanto hardness tester.

***In-Vitro* Evaluation of the Powdered Blend**

Angle of Repose

It is the maximum angle that can be obtained between the free standing surface of the powdered heap and the horizontal plane. It was determined by height cone method. A funnel was fixed at a desired height and powdered blend was filled in it and then allowed to flow down freely onto a graph paper fixed on a horizontal surface and the height and radius of the heap formed were noted. Angle of repose was calculated using the formula,

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

Where, h = height of the heap obtained,

r = radius of the heap obtained.

Bulk Density

The powder sample equivalent to 5gms was filled in a 25ml graduated cylinder and powder was leveled and the unsettled volume (V_b) was noted. The bulk density was calculated in gms/cm^3 by the formula,

$$\text{Bulk density } (\rho_b) = \frac{M}{Vb}$$

Where, M = Mass of powder taken, V_b = Bulk volume.

Tapped Density

The powder sample equivalent to 5gms was filled in a 25ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times. Volume was considered as tapped volume (V_t). The tapped density was calculated in gms/cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = \frac{M}{Vt}$$

Where, M = Mass of powder taken, V_t = Tapped volume.

Compressibility Index (Carr's Index)

Compressibility index of the powder can be computed based on the bulk and tapped densities, using the formula

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

It indicates the flow properties of the powder and was measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

The results obtained for the evaluation of powdered blend were shown in the table 2.

***In-Vitro* Evaluation of the Prepared Tablets**

Tablet Thickness

A vernier calipers was used to determine thickness of 5 randomly selected tablets. Results were expressed as mean values as shown in table 3.

Tablet Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and mean hardness of the tablets was determined which was given in the table 3.

Friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (W_o) and transferred into the friabilator's chamber. The friabilator was operated at 25rpm for 4 minutes (or run up to 100 revolutions). The tablets were dedusted and reweighed (W). The% friability was then calculated as

$$\text{Percentage of Friability} = 100 \left(1 - \frac{W}{W_o}\right)$$

Percentage friability of tablets less than 1% was considered acceptable. The results were shown in the table 3.

% Drug Content

Ten tablets were accurately weighed and crushed. A quantity of powder equivalent to 75mg of drug (400mg) was extracted in 100 ml of 0.1N HCl. The solution was centrifuged at 3000 rpm for 15 min. The drug content was analyzed at 208 nm using a UV-Visible spectrophotometer after suitable dilution with 0.1 N HCl. Mean drug content of all the batches was shown in table 3.

Weight Variation

Ten tablets were selected at random and average weight was determined. % maximum positive deviation and % minimum deviation were calculated as per the formulae

$$\text{\% Maximum positive deviation} = \left(\frac{W_H - A}{A}\right) \times 100$$

$$\text{\% Minimum negative deviation} = \left(\frac{A - W_L}{A}\right) \times 100$$

Where, W_H = Highest weight in mg, W_L = Lowest weight in mg, A = Average weight of tablet in mg.

They were shown in the table 4.

Buoyancy Studies

The time taken by the dosage form to emerge onto surface of the medium was the Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and duration of time the dosage form remained buoyant was 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 beaker containing 100 ml of 0.1N HCl as per USP maintained at 37±0.5°C and the FLT and TFT were visually determined and were shown in table 4.

Swelling Index

The swelling studies were carried out by determining % swelling index. The individual tablets were weighed accurately and kept in a beaker containing 0.1N HCl. Tablets were taken out carefully after designated time, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling was calculated by using formula;

$$\% \text{ Swelling index} = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100$$

Swelling index was carried for 3h and was shown in figure 5.

***In-Vitro* Dissolution Study**

In-vitro release studies were carried out using USP XXIII, type 2 dissolution test apparatus (Lab India, DS 8000), employing a paddle stirrer at 50rpm using 900ml of 0.1 N HCl maintained at 37± 0.5°C as the dissolution medium. 5 ml of the sample was withdrawn at every hour by means of a syringe fitted with a prefilter and same volume of the fresh medium was replaced. The samples were analyzed for drug content after suitable dilution by measuring absorbance at λ_{max} of 208 nm against 0.1N HCl as a blank using a UV-Visible Spectrophotometer (Lab India, UV 3000). All the studies were conducted in duplicate and the mean data at the end of 12th hour was shown in figure 6.

Kinetic Modeling of Drug Release Profiles

The dissolution profiles of all batches in 0.1N HCl were fitted to zero order, first order, Hixson-Crowell, Higuchi matrix model and Korsmeyer-Peppas model. The model with the highest correlation coefficient (R) was considered to be the best fitting one[10, 11]. The regression coefficient (R^2) values and the release rate constants were given in table 5 and 6 respectively.

Table 1: Composition of different batches of tablets (mg per tablet)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nizatidine	75	75	75	75	75	75	75	75	75
Xanthan Gum	200	160	120	-	-	-	100	80	60
HPMC K100M	-	-	-	200	160	120	100	80	60
Lactose	-	40	80	-	40	80	-	40	80
Ethyl Cellulose	20	20	20	20	20	20	20	20	20
Sodium Bicarbonate	50	50	50	50	50	50	50	50	50
Tartaric Acid	50	50	50	50	50	50	50	50	50
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total Weight	400	400	400	400	400	400	400	400	400

Table 2: Flow properties of the powdered blend of Nizatidine formulations

Formulation	Angle of Repose	Bulk Density (gms/cc)	Tapped Density (gms/cc)	Carr's Index (%)	Hausner's Ratio
F1	28°16'	0.533	0.621	14.17	1.16
F2	29°49'	0.537	0.632	15.03	1.18
F3	31°29'	0.541	0.658	17.78	1.22
F4	28°12'	0.532	0.619	14.05	1.16
F5	29°28'	0.539	0.645	16.43	1.20
F6	30°31'	0.554	0.671	17.44	1.21
F7	27°50'	0.538	0.622	13.50	1.16
F8	28°22'	0.547	0.643	14.93	1.17
F9	29°46'	0.585	0.691	15.34	1.18

Table 3: Mean thickness, Hardness, % Friability and % Drug content

Formulation	Mean Thickness (mm)	Mean Hardness (Kg/cm^2)	Friability (%)	Mean % Drug Content
F1	4.82	4.73	0.55	97.92
F2	4.86	4.93	0.61	96.38
F3	4.81	4.67	0.68	98.32
F4	4.92	5.06	0.53	97.44
F5	4.84	5.03	0.65	97.70
F6	4.86	4.42	0.69	97.36
F7	5.06	4.90	0.57	97.00
F8	5.02	5.10	0.62	96.30
F9	4.98	4.69	0.64	97.71

Table 4: Weight variation and floating properties

Formulation	Average Weight (mg)	% Maximum Positive Deviation	% Minimum negative deviation	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	395	3.79	3.79	177	8
F2	402	1.99	3.07	142	>12
F3	402.5	1.86	3.10	82	>12
F4	402	1.99	0.49	25	>12
F5	404	1.48	3.46	18	>12
F6	406	0.98	1.47	10	6
F7	396	1.01	1.51	364	8
F8	406	3.44	1.47	235	>12
F9	404	1.48	0.99	112	>12

Table 5: Regression coefficient (r^2) values of different batches

Formulation	Zero Order	First Order	Hixson Crowell	Higuchi Matrix	Korsmeyer Peppas
F1	0.928	0.980	0.978	0.991	0.983
F2	0.914	0.980	0.980	0.992	0.983
F3	0.909	0.903	0.967	0.994	0.985
F4	0.979	0.961	0.984	0.974	0.996
F5	0.963	0.976	0.993	0.988	0.990
F6	0.959	0.937	0.984	0.979	0.979
F7	0.969	0.989	0.989	0.979	0.991
F8	0.960	0.989	0.987	0.987	0.994
F9	0.954	0.990	0.986	0.989	0.995

Table 6: Release rate constant values of different batches

Formulation	Zero Order K_o	First Order K_1	Hixson Crowell K_{HC}	Higuchi Matrix K_H	Korsmeyer Peppas K_{KP}
F1	7.915	0.143	0.040	23.231	21.626
F2	8.685	0.174	0.047	25.567	25.252
F3	9.341	0.206	0.055	27.543	28.207
F4	7.668	0.129	0.037	22.174	14.568
F5	8.342	0.154	0.043	24.298	19.042
F6	13.820	0.281	0.076	33.125	26.133
F7	6.218	0.093	0.027	18.049	13.04
F8	6.488	0.100	0.029	18.886	14.538
F9	6.685	0.105	0.030	19.496	15.686

Table 7: Diffusion exponent, Release mechanism and Best fit model

Formulation	Diffusion Exponent 'n'	Drug release mechanism	Best fit model
F1	0.535	Non Fickian Anomalous transport	Higuchi-Matrix
F2	0.506	Non Fickian Anomalous transport	Higuchi-Matrix
F3	0.488	Non Fickian Anomalous transport	Higuchi-Matrix
F4	0.705	Non Fickian Anomalous transport	Korsmeyer-Peppas
F5	0.619	Non Fickian Anomalous transport	Korsmeyer-Peppas
F6	0.643	Non Fickian Anomalous transport	Hixson-Crowell
F7	0.659	Non Fickian Anomalous transport	Korsmeyer-Peppas
F8	0.628	Non Fickian Anomalous transport	Korsmeyer-Peppas
F9	0.607	Non Fickian Anomalous transport	Korsmeyer-Peppas

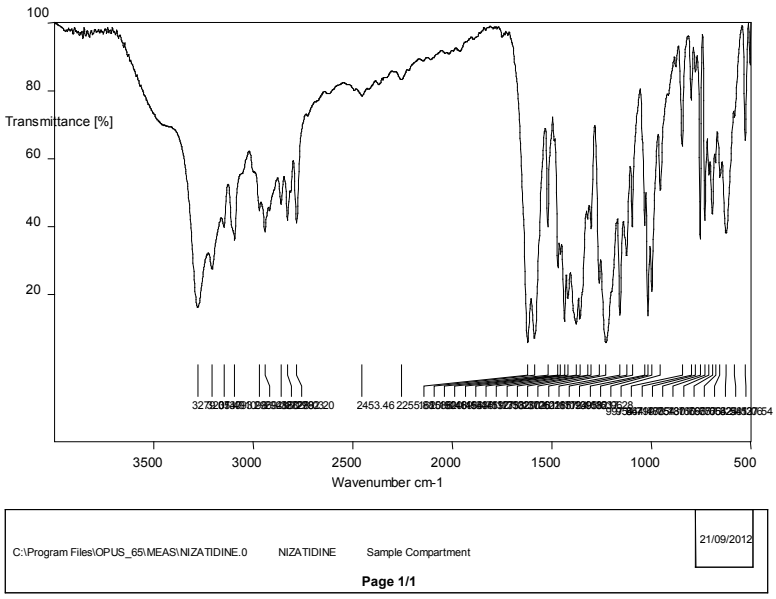

Figure 1: FTIR Spectrum of Nizatidine

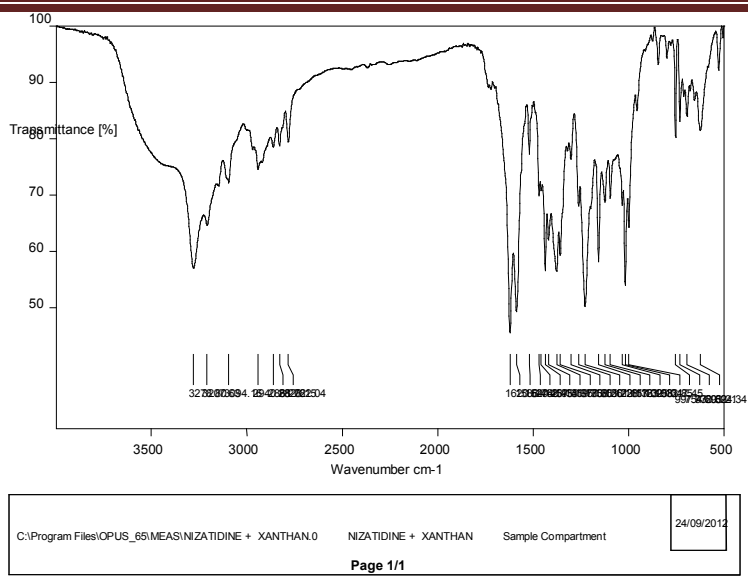

Figure 2: FTIR Spectrum of Mixture of Nizatidine and Xanthan gum

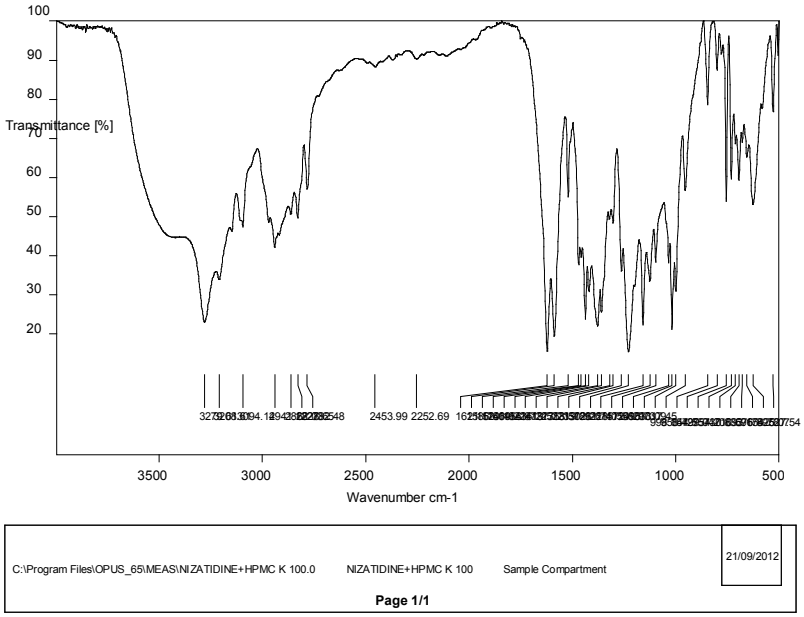

Figure 3: FTIR Spectrum of Mixture of Nizatidine and HPMC K100M

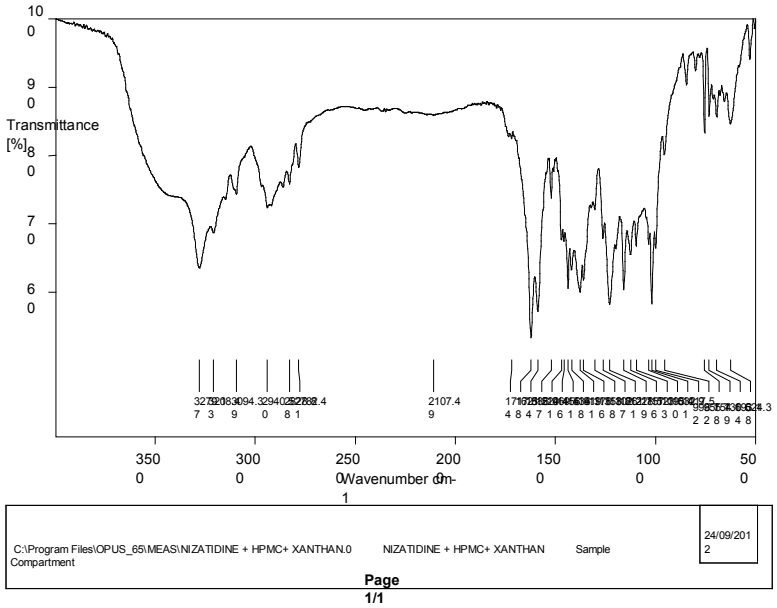

Figure 4: FTIR Spectrum of Mixture of Nizatidine, Xanthan Gum and HPMC K100M

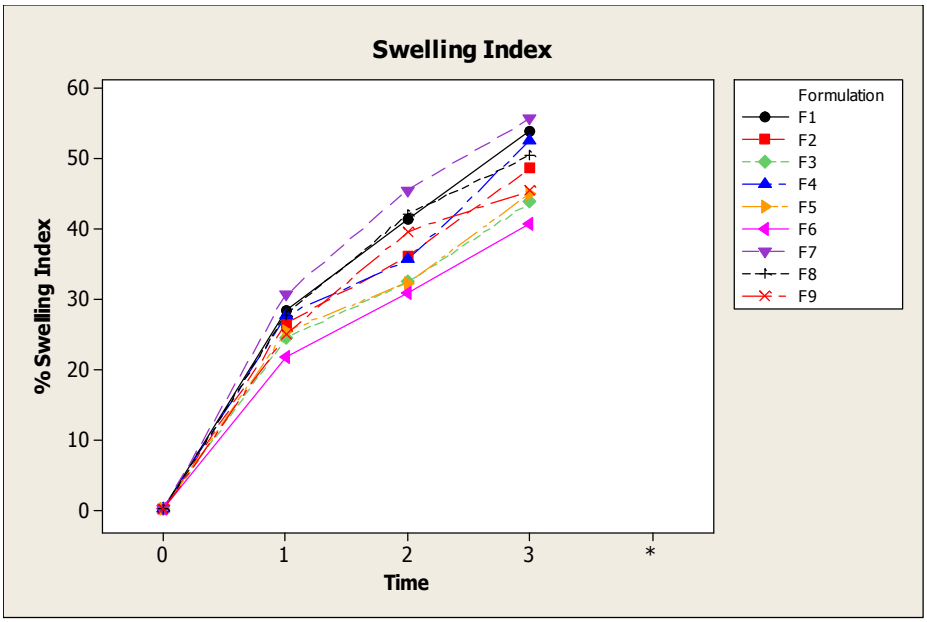

Figure 5: Swelling Studies of Nizatidine Floating Matrix Tablets

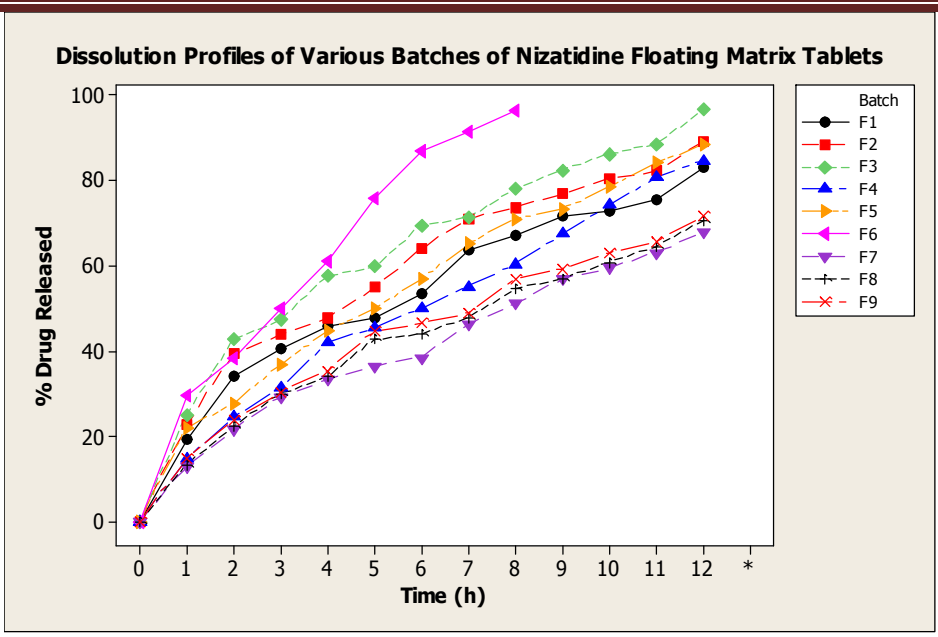

Figure 6: Dissolution Profile of Various Batches of Nizatidine Floating Matrix Tablets

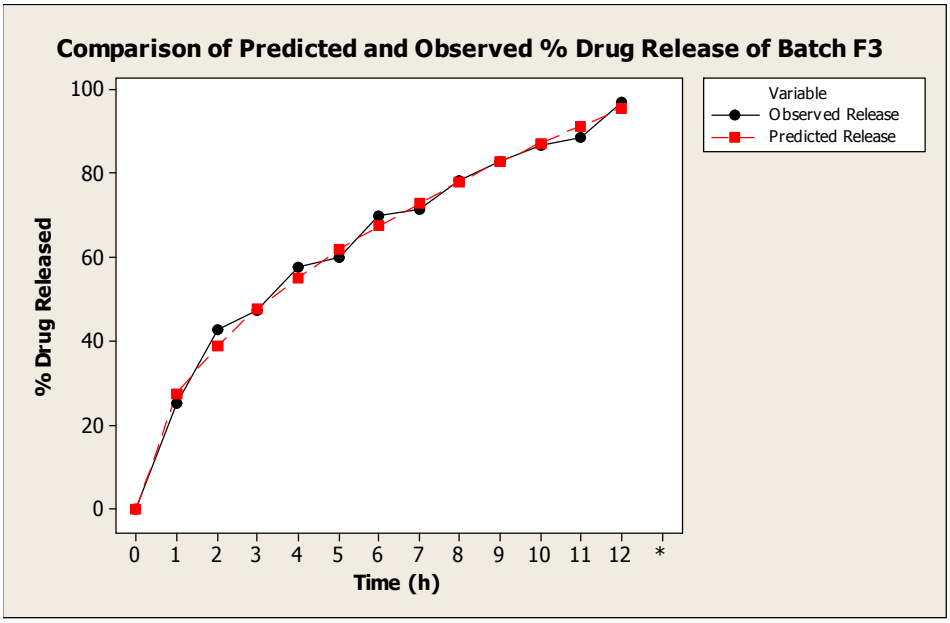

Figure 7: Comparison of Predicted and Observed % Drug Release of Batch F3

Tablets floating in the dissolution medium

RESULTS

Drug – Excipient Compatibility Studies

It was found that there was no chemical interaction between Nizatidine and the polymers used. The drug mainly exhibits two peaks for two NH stretches, one peak for thiazole ring, one peak for CH stretch in thiazole ring, two peaks for CH stretches in NCH_3 groups and, two peaks for CH stretches in CH_2CH_2. One peak each for C=C and NO_2 stretches. Two peaks for CH deformation in NCH_3 and CH_2, two peaks for CN stretch, one peak for CH stretch in $CH\text{-}NO_2$. There was no discernable shift or appearance or disappearance of these peaks indicating that there was no sort of chemical interaction.

Flow Properties of Powdered Blend

The angle of repose values were found to be in between $27^o50'$ to $31^o29'$. The poured density values were found to range from 0.532 - 0.585gms/cc, the tapped density values were found to range from 0.619-0.691gms/cc. Carr's index and Hausner's ratio were in the range of 13.50–17.78% and 1.16-1.22 respectively.

Post Compression Parameters

The mean thickness of the tablets was in the range of 4.81-5.06mm. The measured hardness of the tablets was in the range of 4.42-5.10 kg/cm^2. The % friability was in the range of 0.53 – 0.69. The mean % drug content was found to be in the range of 96.30 – 98.32% of Nizatidine. The average weight of the formulated tablets was in the range of 395 – 406 mg. The percent deviations were within the acceptable range.

Floating Characteristics

The tablets showed acceptable lag time which were in the range of 10 – 364 seconds. All batches except F1, F6 and F7 floated for more than 12h and showed good matrix consistency. Batches F1 and F7 floated for 8h with good matrix consistency. Batch F6 floated for about 6h and the matrix eroded with time.

***In-Vitro* Drug Release**

Batches F1, F2, F3, F4, F5, F7, F8, and F9 showed mean cumulative % drug release of 83.06, 89.17, 96.82, 84.90, 88.60, 67.88, 70.73 and 71.62% respectively by the end of 12h. Batch F6 released 96.62% of drug by the end of 8h.

Swelling Index

The swelling index of the formulations was in the range of 40.61 – 55.64% by the end of 3h.

DISCUSSION

The tablets on contact with 0.1N HCl medium, the hydrochloric acid in the medium reacted with sodium bicarbonate in the tablet matrix inducing the formation of CO_2 gas. This CO_2 was trapped in the matrix by the gel formed by hydration of polymers, which contributed the buoyant force required for floating of the tablets. Tartaric acid was used instead of citric acid because of its better compressibility. The powdered blend exhibited good flow properties and the angle of repose, bulk and tapped densities increased with the increase in lactose concentration.

The tablets were of uniform shape, size and thickness. The hardness set was optimum as the floating lag time was decent and % drug release in the initial hours was as predicted. Friability of all the batches was less than 1%. All the batches formulated contained acceptable amount of Nizatidine. The weight variation was within acceptable limits.

The floating lag time increased with the increase in polymer concentration. Except batches F1, F6 and F7 all others floated for more than 12h and their matrices remained consistent without erosion. Batches F1 and F7 floated for about 8h and their shorter floating times in comparison with other batches was attributed to the increased weight gain and swelling caused by the excessive uptake of liquid by high amount of polymers present in the matrix. The matrix of the batch F6 started to disintegrate causing erosion and formed a viscous gel like layer on the top of the dissolution medium which to an extent retarded the drug release.

The swelling index increased with the increase in the polymer concentration. The combination of polymers had more swelling index than with individual polymer. Xanthan gum swelled more than HPMC K100M.

During *in-vitro* dissolution study, the outer matrix got hydrated by the dissolution medium and formed into a viscous gel like layer around the tablet. The thickness of this layer varied with time and this retarded the drug release as a function of the polymer concentration. Tablets with both xanthan gum and HPMC K100M showed higher drug retardation than when either of the polymers was used. The burst release of drug in the first few hours was attributed to the time needed by the polymer to get hydrated and form as a release retarding gel layer. This was evident in case of batch F6 where the inconsistent eroding matrix caused the burst release of drug throughout the dissolution time causing total drug release in about 8h. Batch F3 exhibited highest amount of drug release with 96.82% at end of 12h and the obtained release was in agreement with predicted values. The predicted release and obtained release were shown in figure 7; t_{50} and t_{80} for F3 were 3.3h and 8.44h respectively and were almost as predicted. Thus this was selected as the best batch among the formulated ones.

The dissolution data was fitted into different data models and based on the correlation coefficient (R) values the best fit model was determined. Batches F1, F2 and F3 followed Higuchi-matrix release kinetics. Batch F6 followed Hixson-Crowell kinetics. Batches F4, F5, F7, F8 and F9 followed Korsmeyer-Peppas release kinetics. The diffusion exponent 'n' values were in the range of 0.488 to 0.705 indicating the drug release mechanism to be non-fickian anomalous transport by swelling/diffusion/erosion of the gel matrix formed by the hydrated polymer as shown in Table 7. The fitting of data into different kinetic equations and calculation of the release rate constants was done using PCP Disso and DD Solver. Minitab 16 statistical software was used to draw the graphs.

CONCLUSION

Floating tablets of Nizatidine were formulated using xanthan gum and HPMC K100M (alone and in 1:1 combination) as release modifying polymers. The amount of polymer and diluent used had a significant effect on many parameters like flow properties, floating properties, swelling index and drug release retardation. By carefully optimizing the amounts of the polymers and gas generating agents, the formulation with desired characteristics can be produced.

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