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Formulation and Evaluation of Floating Osmotic Tablets of Nizatidine

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Abstract

This study was conducted to develop floating osmotic tablets of Nizatidine, a H2 receptor antagonist, to release the drug as two distinct pulses separated by a lag time that achieve plasma concentration profiles varying in a circadian rhythm fashion, for the chronotherapy of ulcer. Floating osmotic tablets were developed using effervescence method consisted of three different steps viz, preparation of floating sustained release drug containing tablets followed by time-lagged (4 hrs) coating with hydrophobic rupturable polymer, ethyl cellulose (EC), and finally compression coating with immediate release dose of nizatidine and supporting buoyant layer. Three ratios of Ethyl cellulose to HPMC E15 (32.5:67.5, 50:50, and 67.5:32.5) at three coating levels (5%, 10%, 15%) were used to optimize the lag time (4 hrs). Carbopol 934P, cross povidone and sodium bicarbonate were used in buoyant layer. The developed floating osmotic tablets by effervescence method were evaluated for preformulation parameters, weight variation, thickness, hardness, friability, drug content, content uniformity, *In-vitro* floating properties, and *In-vitro* drug release. The optimized formulation provided expected two-phase release pattern of Nizatidine with initial immediate dose release in 30 min and then lag time 4 hrs of no drug release followed by sustained release for 8hrs in stomach during floating.

Keywords: Pulsatile drug delivery systems; Gastric retention; Chronopharmacokinetics; Nizatidine

Introduction

Chronotherapeutic drug delivery system is one of advanced approach used to increase effectiveness of the drug [1]. Human body physiological functions vary with time in a day, these variations cause fluctuations in plasma drug concentration. Circadian variation in most of the diseases such as Asthma, Hypertension, and Gastric Ulceritis lead to the development of site specific drug delivery associated with time–scheduled drug release shown in Figure 1; For example in early hours of the day patients encountered with more chances of heart stroke than in the other timings of the day ,asthma aggravates in early morning and in midnight than in the rest of the day as well as body stiffness associated with inflammation in early hours of morning [2-4]. To benefit from the drug therapy dosage form were taken by the patient before sleep, enabling the dosage forms to release drug completely.

Anti-ulcer therapy

As the acid gastric acid secretion is highest at the night, patients suffering with peptic ulcer diseases experience greater degree of pain when compared with the day time intervals [5,6]. Therefore the timing of administration of ulcerative medications can significantly influence the therapeutic effects [7,8]. Conventional pulsatile release dosage forms release drug after a log period of 5-6 hours and the viscous environment of lower part of G.I tract obstructs the drug diffusion and microbial flora also retards the drug release which results in bioavailability and in-vivo variability problems [9,10]. Due to the absorption window in the stomach Nizatidine is developed in combination of floating and pulsatile technologies, which will be a suitable drug delivery for the onset and extent of symptoms which show a circadian variation required the time scheduled drug release for effective drug action. Floating pulsatile Nizatidine drug delivery system, a H_2 receptor antagonist used as a model drug to provide right time relief from gastric acid breakthrough where patient suffers a sudden gastric pH reduction below 4 at least once or twice in the midnight [11,12].

Materials

Nizatidine was obtained as gift sample from hetero formulations jadcherla unit Hyderabad and other excipients HPMC K4M, Lactose, Magnesium stearate, Talc, Sodium bicarbonate, Carbopol 934P, Cross povidone, Ethyl cellulose 50Cps, HPMC E 15, Dibutyl phthalate, Iso propyl alcohol, Conc. Hydrochloric acid, carbopol 934, Aerosil were obtained from S.D. Fine Chemicals, Mumbai.

Methodology

Floating osmotic tablets of Nizatidine were prepared using Effervescence method Here floating osmotic tablets of Nizatidine were formulated in 3 steps. They are:

Step 1: Formulation of floating tablets (Direct compression)

The composition of different formulations of Nizatidine floating core tablets are shown in Table 1. Three formulations were prepared and coded them from F1 to F3.

Step 2: Formulation of floating osmotic tablets (Spray coating)

Coating solution formula (8%w/w polymer solution):

Ethyl cellulose
Hpmc E15
} 8% w/w

Dibutyl phthalate - 20% w/w (based on dry weight of polymer)

Talc - 5% w/w (based on dry weight of polymer)

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NaHCO3 -5 gm

Isopropyl alcohol q.s

Water

Coating procedure

8% (w/w) coating solutions of ethyl cellulose along with hydroxypropyl methyl cellulose (erodible polymer) and sodium bicarbonate were prepared in isopropyl alcohol and water. The weight ratios of ethyl cellulose (Aqualon EC N50) to hydroxypropyl methyl cellulose (Methocel E15) were 37.5:62.5%, 50:50% and 67.5:37.5% (w/w). The solution was plasticized with dibutyl phthalate (20%, w/w, with respect to dry polymer), and then talc was added as glidant (5%, w/w, related to dry polymer). The homogeneous dispersion was gently stirred throughout the coating process. The polymer solution was sprayed onto the core tablets in a conventional pan coating apparatus (Pharma R & D Coater, VJ instruments Pvt. Ltd., Mumbai, India) till the desired weight gain (5%, 10% and 15%, w/w). At each stage the coated tablets were further dried in the coating pan for 15 min. at 40°C. The tablets were then placed in the oven at 40°C for 2 hr to remove the residual solvent (Table 2).

Step 3: Formulation of floating osmotic tablets of nizatidine with immediate release dose (Compression coating)

All the ingredients in the Table 3 were accurately weighed and to this sodium bicarbonate as a gas generating agent, passed through sieve no. 20 was added and blended thoroughly. 50% w/w (of the tablet) of the above powder was added to the die cavity and then the optimized floating osmotic release tablet (CF8) was placed exactly at the centre of the die on the powder. To it remaining 50% w/w (of tablet) of the above powder was added as shown in such a way that the osmotic release tablet was fully covered on its upper crown, encapsulating rest of the tablet in the powder. It was then compressed using multi station tablet punching machine using 12 mm punches (Table 3).

Evaluation of Floating Osmotic Tablets of Nizatidine

Preformulation studies (drug-excipient interaction studies, flow properties) were carried out for powder blends to detect any interaction between drug and excipients and to determine the flow properties of ingredients. Prepared tablets were evaluated for post compression parameters like various quality control tests such as Tablet thickness and Diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and drug release and other specific evaluation tests for GFDDS like floating lag time and total floating time.

Drug-excipient interaction studies

Fourier transforms infrared spectroscopy: The Infrared spectra of Nizatidine pure drug, exipients, physical mixture of drug and excipients (Optimised formula-CCF3) were recorded between 400 to 4000 cm^{-1}. The IR spectra were obtained using KBr disk method using an FTIR spectrophotometer [13].

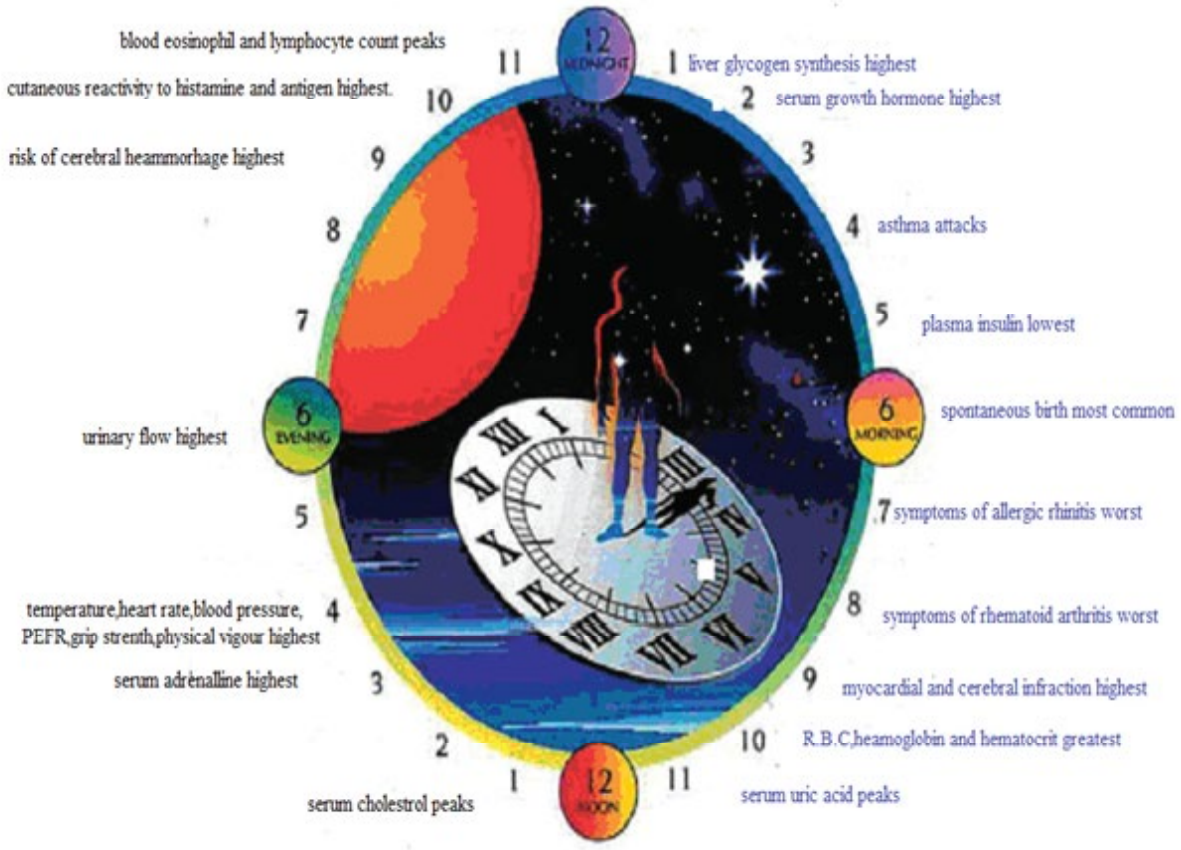

Figure 1: Display in the form of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep routine, when symptoms or events of diseases are worst or most frequent [4].

S. No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
1.	Nizatidine	75	75	75
2.	HPMC K4M (D:P)	75 (1:1)	112.5 (1:1.5)	150 (1:2)
3.	NaHCO3 (10%)	35	35	35
4.	Aerosil (1%)	3.5	3.5	3.5
5.	Magnesium stearate (1%)	3.5	3.5	3.5
6.	Lactose	158	120.5	83

Total Weight- 350 mg

Table 1: Composition of nizatidine floating tablets prepared with HPMC K4M.

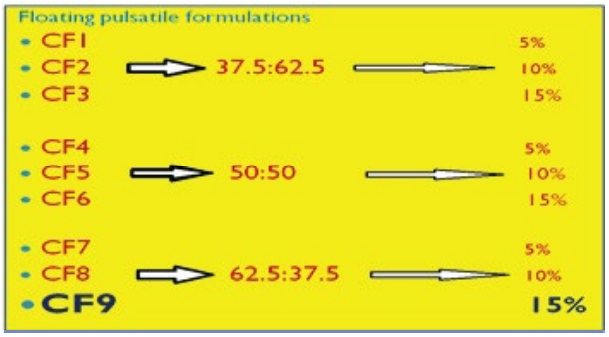

Table 2: Formula of different coating formulations- polymer ratios- coating levels.

S. No.	Ingredients	CCF1	CCF2	CCF3
1	Nizatidine	75	75	75
2	Carbopol 934P	30	25	20
3	Cross povidone	-	5	10
4	NaHCO3	40	40	40
5	Magnesium stearate	15	15	15
6	Lactose	40	35	30

Total weight- 200 mg

Table 3: Composition of compression coating with buoyant immediate dose layer.

Differential scanning calorimetry: Thermal properties of pure drug and the optimised formulation were evaluated by Differential scanning calorimetry (DSC) using a diamod (DSC) (Mettler's).sample of 5-15 mg was taken in a pierced dsc aluminum pan and scanned in the temperature range 50-250°C with a heating rate 10°C; nitrogen served as a purged gas and the system was cool down by liquid nitrogen [14,15].

Flow properties [16]

Angle of repose: The powder mass was allowed to flow through the funnel orifice kept vertically to a plane paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation:

$\Theta=\tan^{-1} H/R$

Bulk density: Bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. It was calculated by using equation given below:

$Df=M/Vp$

Where, Df=Bulk Density

M=Weight of sample in grams

Vp=Final volume of powder in cm^3

Tapped density: It is the ratio of total mass of the powder to the tapped volume of the powder. It is expressed in g/ml and is given by

$Do=M/Vp$

Where,

Do=Tapped density

M=Weight of sample in grams

Vp=Final volume of powder after tapping in cm^3

Carr's index: Carr developed an indirect method of measuring powder flow from densities. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated by

$\%\ Compressibility=Do-Df/Df \times 100$

Where,

Df=Fluff or poured bulk or bulk density

Do=Tapped or consolidated bulk density

Hausner's ratio: Hausner Ratio is the measure of the propensity of a powder to be compressed which is calculated using the following formulae:

$Hausner\ ratio=Do/Df$

Df=Fluff or poured bulk or bulk density

Do=Tapped or consolidated bulk density

Post compression parameters

Tablet thickness and diameter: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier callipers.

Hardness: This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability: The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. The percent loss in weight or friability (F) was calculated by the formula

$F= (1-W/Wo) \times 100$

F=Friability

Wo=Initial weight

W=Final weight

Weight variation: This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This is done by sampling randomly and weighing 20 tablets and average weight is calculated.

Content uniformity: This test is performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. This test is performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equal to 150 mg of Nizatidine was dissolved in 0.1 N HCl in 100 ml volumetric flask. It was diluted

and the absorbance was measured at 314 nm using 0.1 N HCl as blank and the % drug content was estimated using the following formula.

Note: the Regression equation for Nizatidine from standard graph is

Y=0.004x

R2=0.998

In-vitro **buoyancy determination:** The floating characteristics of the GFDDS are essential, since they influence the in vivo behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter's complication.

a) Floating lag time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium at pH 1.2, temperature 37 ± 0.5°C, paddle rotation at 50 rpm.

b) Total floating time: The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37 ± 0.5°C, paddles rotation at 50 rpm.

In-vitro **dissolution studies:** Dissolution studies were carried out using USP XXIV dissolution apparatus (rotating paddle method-2). The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed for the Nizatidine at 314 nm by using a double beam UV spectrophotometer. Each dissolution study was performed three times and the mean values were taken [17].

Kinetic modeling of dissolution data: To analyze the *In-vitro* release data and to determine the release mechanism various kinetic models were used. Only for floating tablets of Nizatidine the kinetic models applied. In floating osmotic tablets there is no drug release for certain time which does not need determination of kinetics. The *In-vitro* drug release data was fitted in to different kinetic models in order to explain the mechanism of drug release [18].

Results and Discussion

Standard graph of Nizatidine in 0.1 N HCl

The scanning of the volumetric solution of Nizatidine in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 314 nm. The standard concentrations of Nizatidine (50-250 µg/ml) prepared in 0.1 N HCl showed good linearity with R^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law (Figure 2).

Drug-excipient interaction studies

7.2.1 Fourier transforms infrared spectroscopic studies (FTIR): The FTIR spectra of drug and optimized formulation were recorded and shown in Figure 3 and 4. The major peaks were obtained at 754.5, 1017.8, 1229.8 and 3000-2850/cm^{-1} for pure drug and the same characteristic bands of the drug in optimized formulation also shown without any significant spectral changes, thus there is no interaction between drug and excipients used in the formulation.

Differential scanning calorimetric study (DSC): DSC study was conducted for Nizatidine and optimised formulation (CCF3). DSC thermogram of pure Nizatidine shows sharp exothermic peak at 138.4°C. Similar exothermic peak was obtained at 136°C for the optimised formulation. The DSC thermograms were given in Figure 5 and 6 indicates the minor change in the melting endotherm of drug could be due to the mixing of the drug and polymer, which indicates no potential incompatibility with polymers used in the optimized formulation (Figure 5 and 6).

Flow Properties of floating core and compression coated tablet blends: The powder blends of floating tablets (F1-F3) and compression coated tablets were evaluated for their flow properties, the results were shown in Table 4. Angle of repose was in the range from 21.8 to 28.14 which indicates good flow of the powder for all formulations. The values of bulk density were found to be in the range from 0.51 to 0.623 gm/cc; the tapped density was in the range of 0.597 to 0.684 gm/cc. The Carr's index was found to be in the range from 11.10 to 17.25. The Hausner ratio was found to be in the range from 1.16 to 1.37. These results indicate that the powdered blends exhibited good flow properties and have good compressibility.

Post compression parameters of floating core and compression coated tablets of Nizatidine: The final tablets were white, smooth, and flat, round shaped in appearance. The thickness was measured by vernier calipers and was ranged between 4 ± 0.20 and 4.1 ± 0.09 mm. The diameter was measured and ranged between 11.04 ± 0.11 to 11.12 ± 0.11 mm. The weight variation for different formulations (F1 to F3) showed satisfactory results as per United States Pharmacopoeia (USP) limit (average weight ± 5%). The hardness was measured by Monsanto tester and was found to be ranged from 4.66 ± 0.28 to 5.16 ± 0.28 kg/cm^2. The friability was found to be ranged from 0.472 to 0.76 which was below 1% indicating good mechanical resistance of the tablets. The percentage of drug content for all formulations was found to be in between 98.1 ± 1.21 to 103.03 ± 0.45 of Nizatidine, it complies with official specifications (95 to 110%) (Table 5).

In-vitro buoyancy studies core and compression coated tablets of Nizatidine

All the tablets were prepared by effervescent approach. On immersion in 0.1 N HCl solution pH (1.2) at 37°C, the tablets floated, and remained buoyant without disintegration. Sodium bicarbonate was used as the effervescent base. When the floating matrix tablets

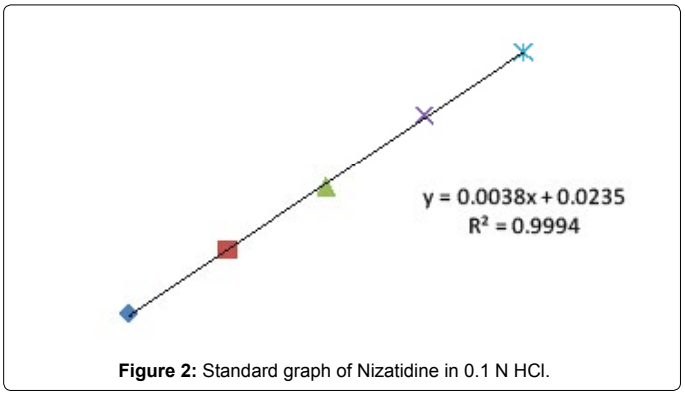

Figure 2: Standard graph of Nizatidine in 0.1 N HCl.

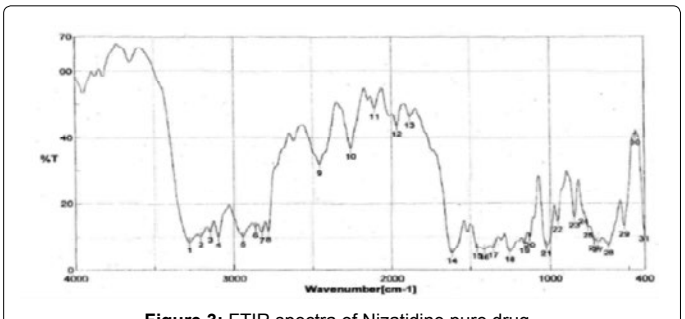

Figure 3: FTIR spectra of Nizatidine pure drug.

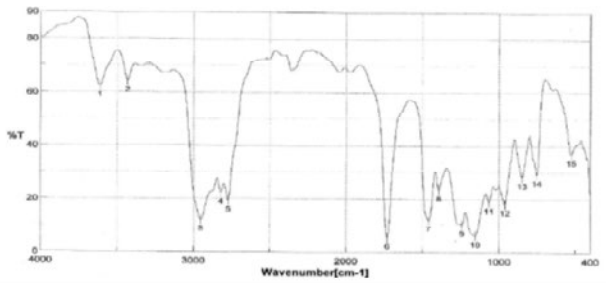

Figure 4: FTIR spectra of optimized formulation (CCF3).

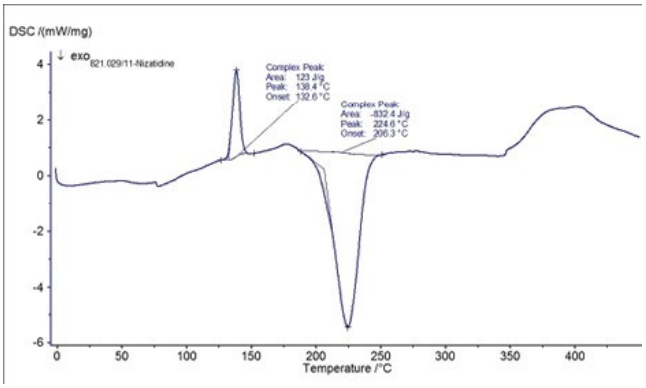

Figure 5: DSC thermogram of pure drug Nizatidine.

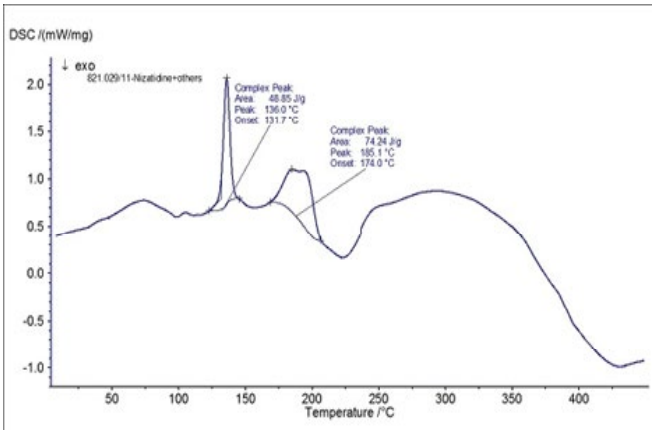

Figure 6: DSC thermogram of optimised formulation.

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cc) gm/ cm3) (gm/cm3)	Tapped density (gm/cc)	Carr's index (%)	Hausner ratio (HR)
F1	28.14	0.561	0.652	13.95	1.16
F2	26.89	0.542	0.655	27.25	1.20
F3	24.22	0.514	0.598	14.71	1.17
CCF1	23.14	0.623	0.684	17.36	1.15
CCF2	25.23	0.610	0.624	19.25	1.25
CCF3	26.45	0.596	0.634	18.34	1.37

Table 4: Results of flow properties of core and compression coated tablet blends.

containing gas generating agent were exposed to 0.1 N HCl, hydrochloric acid reacted with sodium bicarbonate in the floating tablet inducing CO_2 formation. The generated gas was entrapped into the matrix of swollen polymer matrix and was well protected by gel formed by hydration of polymers, which led to floating of the dosage forms (Table 6).

In core tablet formulations as the HPMC K4M level increasing the FLT increased. As the polymer concentration increases it takes more time for the polymer matrix to hydrate and swell and then float, so FLT increased. In compression coated formulations, FLT decreased in the order CCF1>CCF2>CCF3. This is due to addition of cross povidone to CCF2 and CCF3 which has higher swelling index than carbopol and helps in floating along with carbopol. So floating lag time is decreased.

In-vitro dissolution studies of core, spray coated, and compression coated tablets of Nizatidine

In-vitro dissolution studies of all the formulations of Nizatidine were carried out in 0.1 N HCl and percentage drug release was calculated. RDC indicates released drug content in all the displayed figures (Table 7) (Figure 7).

(RDC release drug content)

By increasing the amount of HPMC K4M the drug release was decreased proportionately in the following order F1<F2<F3. Among these formulations F3 was selected for further development as it has sustained the release of Nizatidine up to 7 hrs which is near to the desired release profile (8 hrs) (Table 8).

The amount of ethyl cellulose was increased from CF1 to CF9. The increase in lag time from CF1 to CF9 was due to decreased permeability and increased hydrophobicity of coating membrane because of the increasing concentration of insoluble polymer (ethyl cellulose-37.5-50-62.5) as well as increased coating thickness (5-10-15%). Both the factors (weight ratio of polymers and coating thickness) have antagonistic effect on total drug release with drug release decreasing on elevating the level of either of the factors. However the effect of weight ratio of ethyl cellulose to HPMC seems to be more pronounced as compared with that of coating level. Release rate decrease was also due to more tortuous diffusional path length due to increase in coating thickness (Figure 8) (Table 9).

In CCF1 only carbopol was used. The floating lag time and floating time were good for CCF1 but took two hours to release the immediate release dose of Nizatidine. So to enhance fast release of immediate dose the super disintegrant, cross povidone was added in CCF2 (5mg), CCF3 (10mg). Target release of immediate dose within 30min was achieved with CCF3 followed by lag time up to fourth hour and sustained release up to 8hrs. Cross povidone worked both to enhance the release of Nizatidine immediately and also decreased the floating lag time due to its instant high swelling (Figure 9).

Kinetic modeling of drug release from Nizatidine floating core tablets: Kinetics were applied only to floating core tablets (matrix) because there is no drug release for certain time in floating osmotic tablets. The *In-vitro* dissolution data were fitted in different kinetic models viz. zero order, first order, Higuchi and Korsemeyer-Peppas equation. Correlation coefficients of all formulations showed higher correlation with zero order plots than first order. So, predominant drug release order is controlled release. To confirm the exact mechanism of drug release from these tablets, the data were fitted to Higuchi and Korsemeyer- Peppas equation. All three formulations showed higher regression values for Higuchi model indicating the release mechanism

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Weight variation (%)
F1	3.90 ± 0.05	8.9 ± 0.09	4.76 ± 0.25	0.503	99.89 ± 1.75	4.1%
F2	3.85 ± 0.03	8.9 ± 0.1	5.23 ± 0.25	0.543	99.93 ± 2.71	3.5%
F3	3.89 ± 0.04	8.8 ± 0.15	5.16 ± 0.28	0.488	102.63 ± 2.1	2.8%
CCF1	4.10 ± 0.02	12.01 ± 0.12	5.12 ± 0.29	0.622	98.33 ± 2.41	4.6%
CCF2	4.12 ± 0.04	11.95 ± 0.16	5.24 ± 0.35	0.569	101.22 ± 1.25	3.9%
CCF3	4.09 ± 0.01	12.18 ± 0.24	5.36 ± 0.22	0.658	99.56 ± 1.42	2.2%

Table 5: Results of post compression properties core and compression coated tablets of Nizatidine (n=3).

Formulation code	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	120	>5
F2	154	>6
F3	180	>7
CCF1	256	>12
CCF2	189	>12
CCF3	129	>12

Table 6: Results of *In-vitro* buoyancy study

Time(min)	F1	F2	F3
0	0	0	0
60	44.4 ± 0.88	41.7 ± 0.6	35.4 ± 0.57
120	54.55 ± 0.96	49.43 ± 0.73	44.6 ± 0.72
180	71.35 ± 0.83	59.31 ± 0.87	58.04 ± 0.82
240	85.84 ± 0.88	77.63 ± 1.1	69.76 ± 0.75
300	97.11 ± 0.6	85.56 ± 0.87	81.85 ± 0.9
360		98.49 ± 0.95	89.09 ± 0.92
420			98.39 ± 0.57

Table 7: Results of *in vitro* dissolution studies of Nizatidine floating core tablets (n=3).

Time	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
0	0	0	0	0	0	0	0	0	0
60	13.50	6.00	3.00	2.40	1.8	0.00	0.00	0.00	0.00
120	25.28	12.03	7.52	6.61	5.71	4.80	2.70	0.30	0.30
180	32.32	19.90	16.56	14.75	10.54	9.33	6.32	3.60	3.61±
240	37.29	23.91	23.55	25.93	16.00	12.68	11.45	10.52	4.83
300	45.3	31.54	29.68	35.08	24.79	17.25	13.91	20.48	20.45
360	49.45	43.12	41.84	41.27	30.93	22.74	20.59	30.79	28.37
420	59.45	52.57	49.81	51.31	38.91	30.46	28.32	40.89	40.86
480	68.94	63.79	58.85	59.48	46.61	37.44	41.26	55.19	53.05
540	81.62	74.89	66.37	65.80	52.27	42.74	54.69	65.39	69.54
600	87.46	84.90	74.23	75.76	69.65	49.88	72.69	78.95	84.02
660	97.54	94.06	86.94	84.87	75.13	62.45	87.19	92.28	98.27

Table 8: Results of *in vitro* dissolution studies of Nizatidine floating osmotic tablets-spray coating (CF1-CF9).

Time (min)	CCF1	CCF2	CCF3
0	0	0	0
30	64.5 ± 0.98	82.5 ± 2.2	99.00 ± 2.03
60	82.56 ± 1.12	99.16 ± 3.29	1.45 ± 2.64
120	98.32 ± 1.66	2.40 ± 1.56	2.45 ± 1.56
180	4.81 ± 0.88	4.51 ± 0.94	3.61 ± 1.17
240	6.04 ± 1.15	6.34 ± 1.12	4.53 ± 1.44
300	21.37 ± 1.63	22.87 ± 1.34	21.96 ± 1.49
360	29.74 ± 2.04	31.54 ± 1.45	31.24 ± 1.55
420	44.16 ± 1.35	47.78 ± 1.81	45.05 ± 1.33
480	56.61 ± 1.28	59.25 ± 1.65	55.46 ± 1.38
540	72.31 ± 2.53	75.36 ± 2.08	72.90 ± 2.4
600	79.00 ± 1.7	80.57 ± 1.38	80.80 ± 1.35
660	86.93 ± 0.6	89.41 ± 1.13	89.35 ± 1.11
720	97.01 ± 0.81	98.60 ± 0.84	99.43 ± 1.04

Table 9: Results of *in vitro* drug release of Nizatidine floating osmotic tablets with immediate release dose-compression coating (CCF1-CCF3) (n=3).

Formulation code	Zero order	First order	Higuchi	Peppas	Peppas
	R^2	R^2	R^2	R^2	N
F1	0.994	0.878	0.978	0.97	0.498
F2	0.987	0.818	0.959	0.945	0.499
F3	0.993	0.833	0.988	0.983	0.545

Table 10: Results of kinetic modelling of nizatidine floating core tablets.

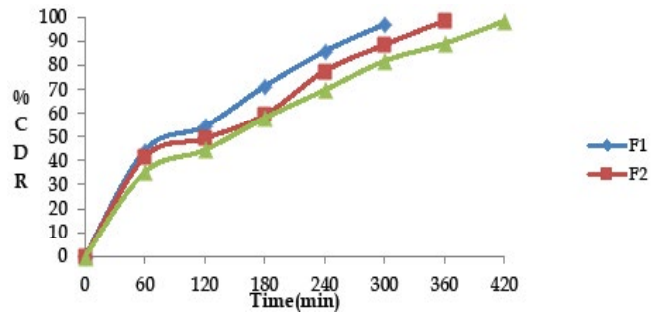

Figure 7: Comparative drug release profiles of Nizatidine core tablets.

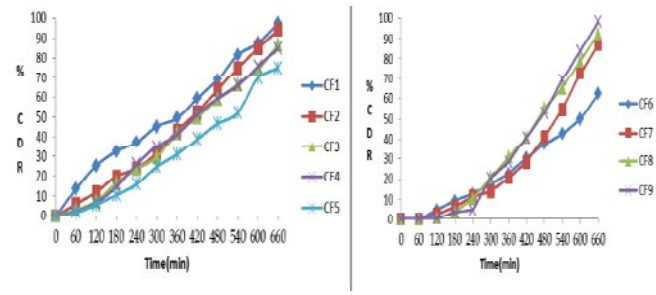

Figure 8: Comparative drug release profiles of Nizatidine floating osmotic tablets (CF1-CF9).

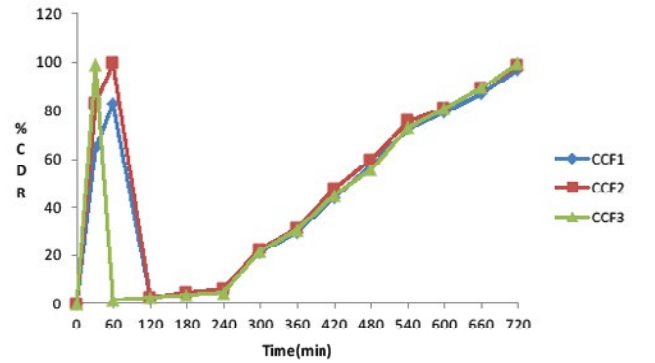

Figure 9: Comparative drug release profiles of Nizatidine floating osmotic tablets with immediate release dose-compression coating.

was Higuchi matrix diffusion. The causes for diffusion may be due to the swollen insoluble hydrogel matrix, which entrapped the drug. According to peppas kinetics based on n value the mechanism of drug release for F1, F2 was fickian diffusion and F3 was non fickian or anomalous transport (Table 10).

Conclusion

The present study demonstrates that Nizatidine could be successfully delivered to provide relief of gastric acidity in the mid night (nocturnal acid breakthrough) and in the afternoon by design of a floating osmotic chronopharmaceutical formulation. The formulation is to be taken after meal, where immediate release dose will provide relief from acid secretion in response to the meal, while timed osmotic release floating tablet with delayed "sustained" release will attenuate midnight and afternoon acidity. This will provide an ideal therapeutic regimen with enhanced patient compliance in the chronotherapy of ulcer. The final optimized formulation from compression coating (CCF3) exhibited release profiles which were close to the set targets (immediate dose release-30 min, lag time-3.30 hrs, sustained release-8 hrs). Thus the designed formulation can be considered as one of the promising formulation technique for preparing floating osmotic drug delivery systems and hence in chronotherapeutic management of ulcer by opening a "new therapeutic dimension" to an existing drug molecule.

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