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Research Article

Formulate gastroretentive floating bioadhesive drug delivery system of nizatidine by direct compression technique

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ABSTRACT

Nizatidine is a gastroprotective drug with a short biological half-life and narrow absorption window. This study aimed at developing floating tablets of nizatidine using various HPMC viscosity grades, namely K4M, K15M, Carbopol 934P, Sodium alginate and sodium carboxy methyl cellulose. Directly compressed tablets revealed an excellent uniformity in hardness, thickness and weight and nizatidine was evenly distributed within the matrix floating tablets. Buoyancy study revealed the tablets remain buoyant for more than 12 h. Among all the formulations, F12 formulation containing 3:1 ratio of HPMC K15M and Carbopol 934P was found to be promising, which showed a floating lag time less than 5min and floating duration of more than 12 hours. It showed constant drug release up to 12 hours and good bio adhesion strength. All the designed formulations displayed zero order release kinetics and drug release follows non-Fickian diffusion mechanism.

Keywords: Nizatidine, Hydroxy propyl methyl cellulose, Gastro-retentive, Floating, Carbopol

INTRODUCTION

In recent years, gastric retentive drug delivery systems are more effective drug delivery system. When, some of the drugs were formulated as controlled release dosage forms they can't attain the sufficient bioavailability and effective plasma level due to its less gastro intestinal transit time[1]. By retention of such drugs in the stomach, we can prolong the overall gastrointestinal transit time and increase the bioavailability. This would be particularly valuable for the drugs that exhibit an absorption window in the upper part of the small intestine[2]. There are a number of approaches that can be used to prolong gastric retention time, such as floating drug delivery systems, swelling and expanding systems, polymeric bio-adhesive systems, and modified shape systems, high density systems and other delayed gastric emptying devices. From the formulation considerations, FDDS appears to be the most flexible and potent approach to prolong gastric residence time of drug[3].

Nizatidine [N-2-2-(dimethylamino) methyl]-4-thiazolyl] methyl thio] ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine] is competitive, reversible inhibitor of the histamine H_2 receptors of the gastric acid secreting cells[4]. It is also used for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer and active

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duodenal ulcers. It has a very short biological half-life 1-2 hours and low absolute oral bioavailability. It does not have any demonstrable anti-androgenic effects and drug interactions compared to any other class of H_2- receptor antagonists[5]. It also finds applications in the field of local delivery of drug to the stomach and proximal small intestine and importantly in treating microorganisms (Helicobacter pylori), which colonize the stomach because the major factors governing reduced luminal drug delivery are gastric acidity, gastric emptying and the epithelial mucus layer and therefore it helps to provide better availability of new products with new therapeutic possibilities and increased patient compliance[6].

The aim of the present study is to design and evaluate the effervescent floating tablets of Nizatidine by using different polymers like Chitosan, HPMC and Carbopol940 and gas generating agents like sodium bicarbonate and calcium carbonate.

MATERIALS AND METHODS

Nizatidine was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad. HPMCK100M was purchased from SD Fine Chem. Ltd. Mumbai. Carbopol 940 was purchased from Loba chem. Mumbai. Chitosan was purchased from India Sea Food, Cochin. Lactose, Sodium bicarbonate, Calcium carbonate, magnesium stearate and talc are purchased from Qualigens fine chemicals, Mumbai. All excipients were analytical grade[7,8].

Formulation of floating-bioadhesive tablets of Nizatidine:

Procedure for floating-bioadhesive tablet preparation: Sustained release bioadhesive-floating tablets were prepared by direct compression method. Accurately weighed quantities of hydrophilic polymers, bioadhesive polymer, microcrystalline cellulose were taken in a motar and required quantity of Nizatidine was added and mixed slightly with pestle. This mixture was passed through 40# mesh and later collected in a plastic bag and blended for 5min. To this required amount of sodium bicarbonate was added and again mixed for 5 min . Later 1% of magnesium stearate was added and final blend was again passed through 40# mesh. Thus obtained blend was mixed thoroughly for 10min and compressed into tablets[9,10].

Table.1: Composition of Nizatidine floating-bioadhesive tablets

Formula code	Drug	HPMC K15M	HPMC K4M	Carbopol 934P	Sodium CMC	Sodium alginate	$NaHCO_3$	MCC
F1	150	-	125	25	-	-	60	36
F2	150	-	120	30	-	-	60	36
F3	150	-	112.5	37.5	-	-	60	36
F4	150	-	125	-	25	-	60	36
F5	150	-	120	-	30	-	60	36
F6	150	-	112.5	-	37.5	-	60	36
F7	150		125	-	-	25	60	36
F8	150		120	-	-	30	60	36
F9	150		112.5	-	-	37.5	60	36
F10	150	125	-	25	-	-	60	36
F11	150	120	-	30	-	-	60	36
F12	150	112.5	-	37.5	-	-	60	36
F13	150	125	-	-	25	-	60	36
F14	150	120	-	-	30	-	60	36
F15	150	112.5	-	-	37.5	-	60	36
F16	150	125	-	-	-	25	60	36
F17	150	120	-	-	-	30	60	36
F18	150	112.5	-	-	-	37.5	60	36

All the ingredients are in mg and total weight of each tablet is 400mg.

Evaluation parameters[11-15]:

Precompression parameters:

Angle of Repose: Angle of repose has been defined as the maximum angle possible between the surfaces of pile of powder and horizontal plane. It is performed to determine the flow rate of powder done by the funnel method. 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:

Bulk Density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

Tapped density: It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

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

Hausner's ratio: Hausner Ratio is the measure of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Hausner Ratio, which are calculated using the following formulae:

Post compression parameters:

Weight variation: To study weight variation individual weights (W_I) of 20 tablets from each formulation were weighed using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Tablet hardness: Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 3 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness and standard deviation were calculated.

Tablet thickness: The thickness of tablets was determined by using vernier calipers. Three tablets from each batch were used, average thickness and standard deviation were calculated.

Friability: From each batch, 3 tablets were accurately weighed. Each group of tablets was rotated in the Friability test apparatus (Roche friabilator) at 25 rpm for 4 minutes (100 rotations). The tablets were then dedusted and reweighed to determine the loss in weight. The friability was calculated as the percent weight loss from actual weight of tablets.

Content uniformity: The formulated Nizatidine floating-bioadhesive tablets were assayed for drug content.

Buoyancy / Floating Test: The in vitro buoyancy was determined by floating lag time, as per the method described by a Rosa et al., 1994. Here, the tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and to float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Swelling characteristics: The swelling properties of matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml 0.1N HCl at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured.

Bioadhesive strength: Mucoadhesive strength of the tablet was measured on the modified physical balance. The design used for measuring the mucoadhesive strength. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCl pH 1.2, which was then placed below right side of the balance.

***In-vitro* Drug Release :**

Procedure

The *in-vitro* dissolution studies were performed for the formulated floating-bioadhesive tablets of nizatidine over a period of 12 hours, using USP dissolution test apparatus 2 (paddle method) at 50 rpm, [Electro lab, TDT – 082].A minimum of 3 tablets per each batch was tested. The dissolution medium consists of 900 ml of 0.1 N HCl and temperature was maintained at 37 $\pm$ 0.5 °C. The tablets were placed inside the dissolution vessel.

An aliquot (5ml) of sample was withdrawn at specific time intervals of 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660 and 720 minutes. The volume of dissolution fluid adjusted to by replacing 5ml of dissolution medium after each sampling. Each sample was analyzed at 315nm using double beam UV and Visible Spectrophotometer against reagent blank.

Kinetic Analysis of Dissolution Data:

To analyze the *in-vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

RESULTS & DISCUSSION

Drug-excipient Compatibility studies:

Fourier Transform Infrared spectroscopic studies (FT-IR):

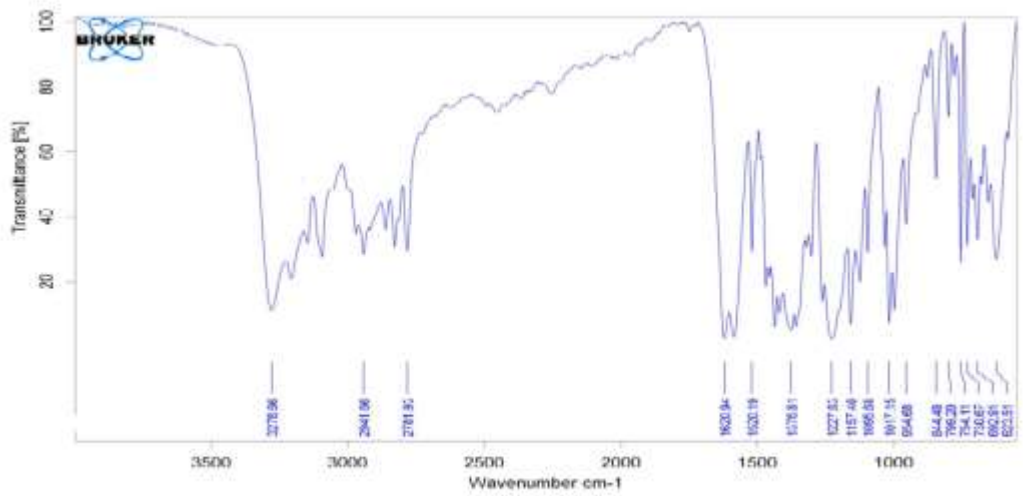

Figure 1. FT-IR spectrum of Nizatidine pure drug

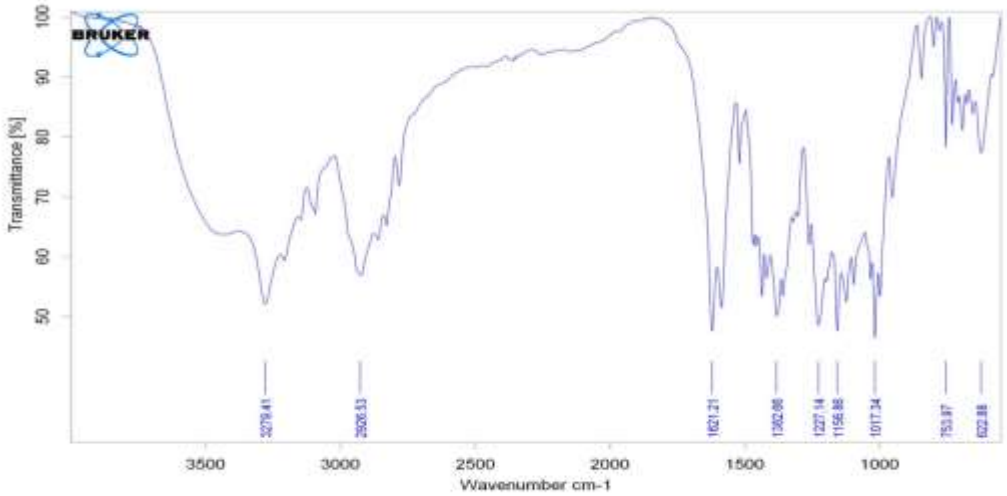

Figure 2: FT-IR spectrum of Nizatidine + HPMC K4M+ Sodium CMC

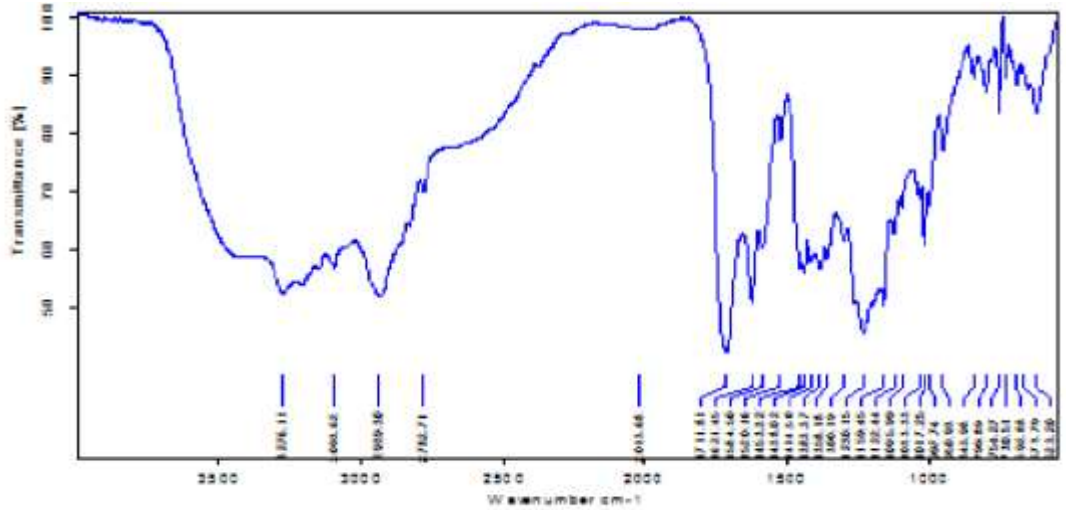

Figure 3: FT-IR spectrum of Nizatidine + HPMC K4M +Carbopol 934P

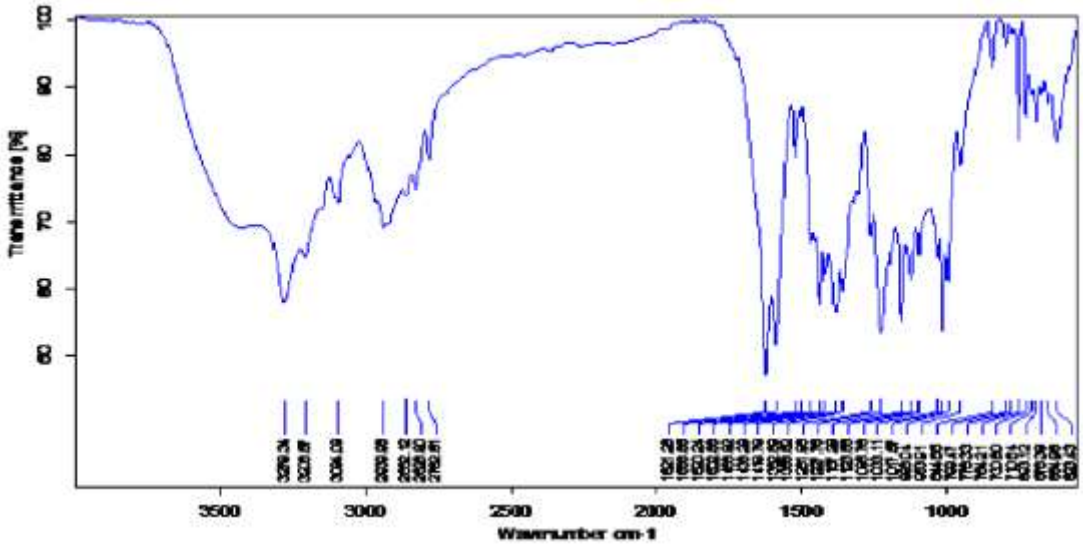

Figure 4: FT-IR spectrum of Nizatidine+ HPMCK4M+ Sodium alginate

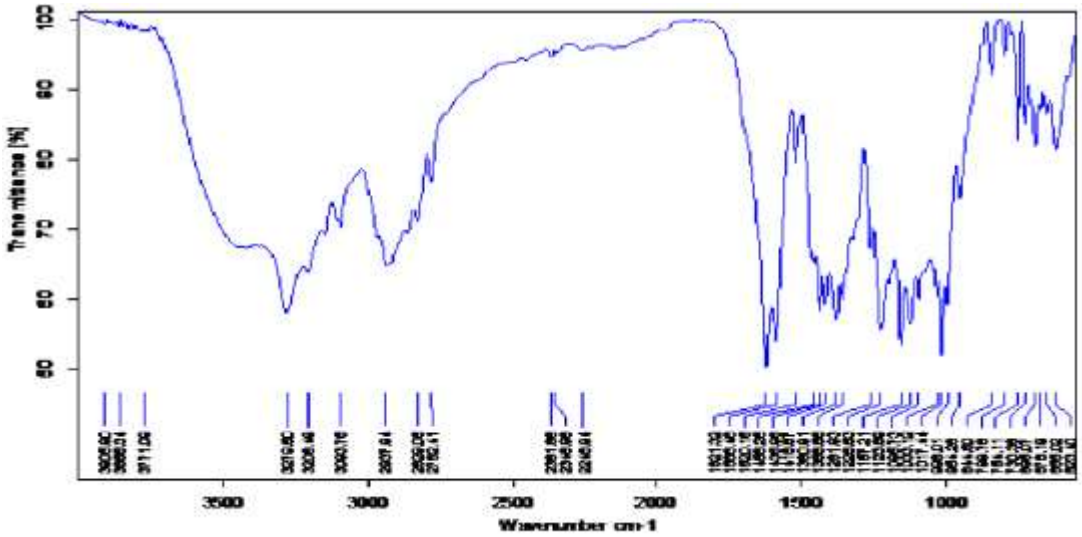

Figure 5: FT-IR spectrum of Nizatidine + HPMCK15M +Sodium CMC

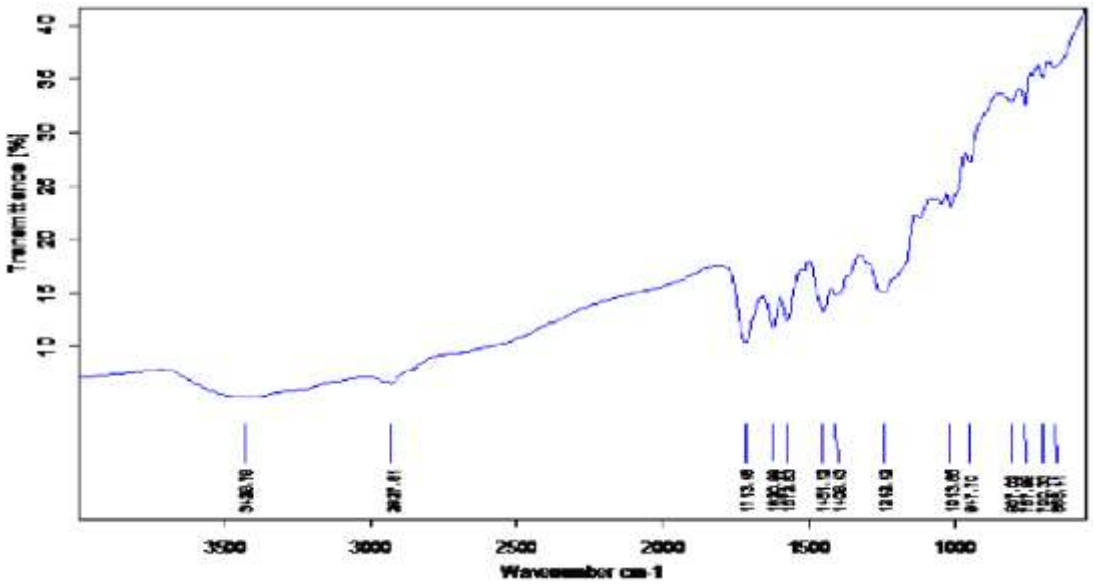

Figure 6: FT-IR spectrum of Nizatidine + HPMC K15M+ Carbopol 934P

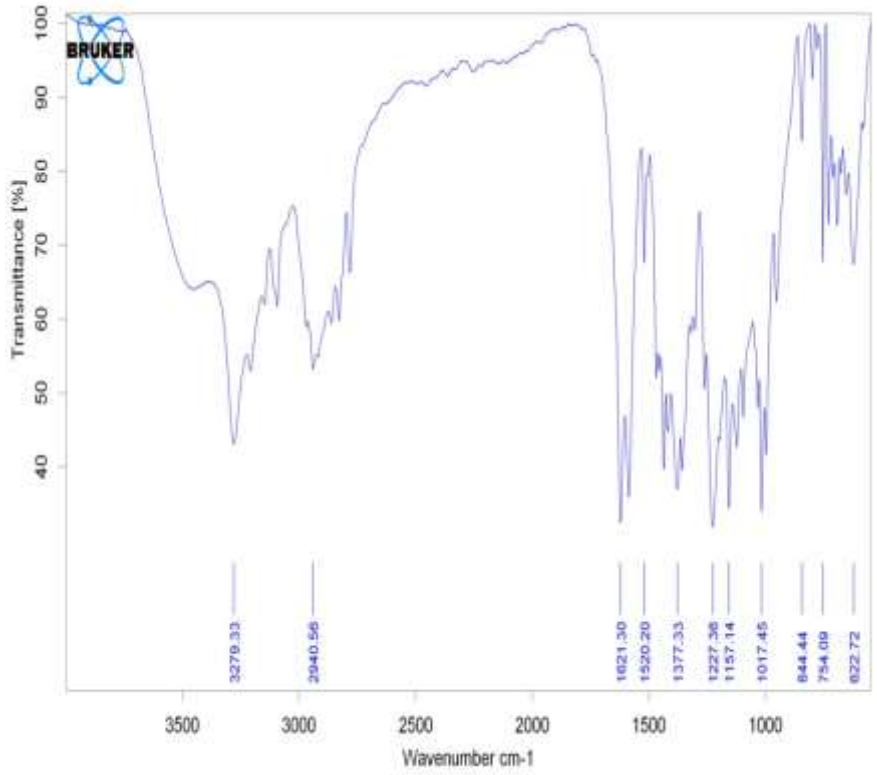

Figure 7: FT-IR spectrum of Nizatidine + HPMC K15M+ Sodium alginate

Thermographs obtained by DSC studies, revealed that the melting point of pure drug is 136.8^{0}C and that formulation F12 shows sharp endothermic peak at 136 ^{0}C as there is no much difference in melting point of the drug in the thermographs and that of in the formulation. It may be concluded that, the drug is in the formulation without interacting with the polymer and excipients.

Precompression parameters:

Table 2: Precompression parameters of tablets using powder blend

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (◦)	Compressibility Index (%)	Hausner's ratio
F1	0.434 ±0.001	0.519 ±0.001	26.5±0.5	16.3	1.19
F2	0.487 ±0.002	0.563 ±0.003	27.4±0.8	13.4	1.15
F3	0.426 ±0.003	0.489 ±0.002	25.1 ±0.2	12.8	1.14
F4	0.506 ±0.004	0.597 ±0.001	28.3 ±0.2	15.2	1.17
F5	0.500 ±0.003	0.579 ±0.002	28.3 ±0.1	13.6	1.15
F6	0.510 ±0.008	0.592 ±0.007	27.9 ±0.8	13.8	1.16
F7	0.500 ±0.001	0.579 ±0.002	29.2 ±0.5	13.6	1.15
F8	0.487 ±0.002	0.555 ±0.004	26.5 ±0.5	12.2	1.13
F9	0.484 ±0.005	0.568 ±0.006	27.2 ±0.2	14.7	1.17
F10	0.487 ±0.002	0.563 ±0.002	27.9 ±0.4	13.4	1.15
F11	0.502 ±0.002	0.576 ±0.003	25.1±0.2	12.8	1.14
F12	0.487 ±0.004	0.563 ±0.006	27.4 ±0.3	13.4	1.15
F13	0.500 ±0.001	0.579 ±0.003	28.3 ±0.4	13.6	1.15
F14	0.504±0.002	0.582 ±0.003	25.6±0.2	13.4	1.15
F15	0.512 ±0.001	0.596 ±0.006	25.1 ±0.8	14.0	1.16
F16	0.487±0.002	0.555 ±0.003	26.5±0.1	12.2	1.13
F17	0.489 ±0.001	0.562±0.006	28.3 ±0.1	12.9	1.14
F18	0.503±0.002	0.586 ±0.003	27.4 ±0.3	14.1	1.16

Values are mean±SD, n=3

The data's were shown in table. The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.426 ±0.003 to 0.510 ±0.008(gm/ml) and 0.489 ±0.002 to 0.596 ±0.006 (gm/ml) respectively. Carr's index of the prepared blends fall in the range of 12.2% to 16%. The Hausner ration fall in range of 1.13 to 1.19. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Post compression parameters:

Table 3: Post compression parameters

Formulation Code	Weight Variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	401±0.4	6.1±0.1	4.11 ±0.01	0.3 ± 0.01	97.23±0.510
F2	399 ± 0.5	6.5± 0.1	4.22 ± 0.02	0.4 ± 0.02	98.55±0.470
F3	398±0.6	6.0±0.3	4.10 ±0.03	0.4 ± 0.02	98.16±0.330
F4	401 ± 0.2	5.4 ± 0.1	4.14 ± 0.01	0.2 ± 0.01	99.34±0.420
F5	400 ± 0.3	5.7±0.2	4.13±0.01	0.5 ± 0.02	98.16±0.330
F6	399 ± 0.1	5.1 ± 0.3	4.11 ±0.04	0.2 ± 0.01	98.55±0.470
F7	398 ± 0.7	5.8 ± 0.1	4.20 ± 0.01	0.3± 0.01	98.16±0.330
F8	400 ±0.4	5.6 ± 0.2	4.18 ± 0.01	0.6 ± 0.01	99.25±0.670
F9	399 ± 0.3	5.7 ± 0.1	4.17 ± 0.02	0.3 ± 0.01	99.25±0.670
F10	398 ±0.2	6.8 ± 0.4	4.21 ± 0.01	0.4 ± 0.02	97.12±0.280
F11	399 ± 0.3	6.5±0.2	4.20 ± 0.01	0.2 ± 0.01	98.56±0.760
F12	400 ± 0.4	6.9 ± 0.1	4.11 ± 0.01	0.3 ± 0.02	99.34±0.420
F13	399 ± 0.5	5.6 ± 0.2	4.13 ± 0.04	0.5 ± 0.01	98.16±0.330

F14	402± 0.3	5.2 ±0.3	4.10 ± 0.03	0.6 ± 0.01	101.5±0.470
F15	399 ± 0.2	5.0 ± 0.1	4.17 ±0.02	0.4± 0.02	98.16±0.330
F16	397 ± 0.3	5.7 ± 0.2	4.16 ± 0.01	0.3± 0.01	99.25±0.670
F17	398 ± 0.4	5.9 ±0.3	4.19±0.02	0.5 ± 0.01	102.5±0.670
F18	400 ± 0.4	5.8 ± 0.1	4.18 ±0.01	0.2 ± 0.02	97.12±0.280

Values are mean ± SD n=3

Results revealed that all the formulated tablets were of good quality with regard to hardness ((5 ± 0.1 - 6.9 ± 0.1 kg/cm^2), thickness (4.1 ± 0.01 – 4.2± 0.01mm), weight variation (397± 0.3 - 402 ± 0.3mg) and drug content (97.1±0.2 – 102.5± 0.6 %).

Floating properties

Table 4: Floating properties of all formulations

Formulation code	Floating lag time(sec)	Floating duration(hrs)
F1	70 ±2.8	>12
F2	76 ± 2.0	>12
F3	84 ±2.1	>12
F4	79 ± 2.3	>12
F5	86 ± 3.4	>12
F6	95 ± 2.0	>12
F7	72 ± 2.5	>12
F8	85 ± 4.0	>12
F9	87 ± 1.5	>12
F10	78 ± 4.6	>12
F11	90 ± 2.0	>12
F12	92 ±2.6	>12
F13	139 ± 3.0	>12
F14	143± 2.5	>12
F15	160 ± 3.5	>12
F16	78 ± 2.5	>12
F17	104 ± 4.1	>12
F18	125 ± 2.6	>12

Values are mean ± SD n=3

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for more than 12 h in dissolution medium subjected to rotation. The floating lag time for all the formulations was found to be less than five minutes. From the results it was clearly observed that the reduction in concentration of HPMC in each batch resulted in increased floating lag time.

Swelling characteristics:

Table 5: Swelling index of all formulations

Formulation Code	Swelling index (%WU)					
	Time (hrs)					
	2	**4**	**6**	**8**	**10**	**12**
F1	45 ±0.9	100 ±0.5	107.5±0.1	125 ±0.7	77.5 ±0.6	72.5±0.5
F2	45 ±0.1	97.5 ±0.3	110 ±0.6	125 ±0.7	87.5 ±0.4	70 ±0.6
F3	50 ±0.6	102.5±0.5	115 ±0.4	127.5±0.4	90 ±0.8	72.5±0.4
F4	22.5±0.5	30 ±0.4	40 ±0.2	30± 0.8	27.5±0.3	22.5±0.5
F5	27.5±0.3	32.5±0.3	42.5±0.5	35±0.1	25 ±0.9	15±0.1
F6	30 ±0.4	37.5± 0.3	42.5±0.3	40±0.8	27.5±0.3	17.5±0.4
F7	30±0.8	52.5±0.5	50±0.6	45±0.9	42.5±0.5	25±0.9
F8	37.5±0.3	55±0.9	52.5±0.5	47.5±0.4	37.5±0.3	27.5±0.4
F9	40±0.2	60 ±0.8	55±0.9	52.5 ±0.5	40±0.2	30 ±0.8
F10	70 ±0.6	102.5±0.5	125±0.7	172.5±0.5	195±0.7	190±0.8
F11	77.5±0.3	107.5±0.4	127.5±0.4	175±0.7	210±0.8	197.5±0.4
F12	87.5±0.4	112.5±0.5	130±0.2	190 ±0.8	217.5±0.4	205±0.4

F13	52.5±0.4	100±0.6	125±0.7	147.5±0.3	162.5±0.4	162.5±0.4
F14	57.5±0.4	105±0.7	130±0.6	152.5±0.4	172.5±0.5	170±0.6
F15	62.5±0.5	105±0.7	132.5+0.5	157.5±0.3	180±0.8	177.5±0.4
F16	55±0.9	80±0.8	130±0.4	160±0.8	167.5±0.4	165±0.9
F17	57.5±0.4	85±0.9	130±0.8	165±0.9	185±0.1	182.5±0.4
F18	60±0.8	97.5±0.3	132.5±0.5	182.5±0.5	200±0.8	202.5±0.5

Values are mean ± SD n=3

The swelling index of all formulations was found to be ranging in between 22.5± 0.5% to 217.5 ± 0.4 %. All formulations containing HPMC K4M and HPMC K15M have exhibited good swelling and tablet integrity. Swelling is also a vital factor to ensure buoyancy and drug dissolution of the tablet. As reported by Bertram and Bodmeier, 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 chains. It was observed that the swelling index of the tablets increases with an increase in the polymer viscosity grades.

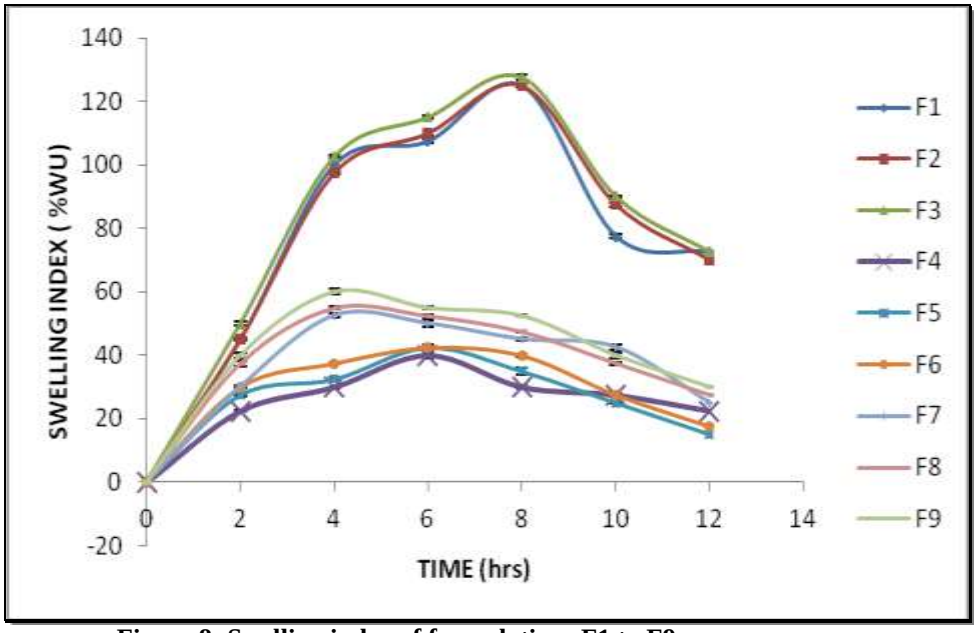

Figure 8: Swelling index of formulations F1 to F9

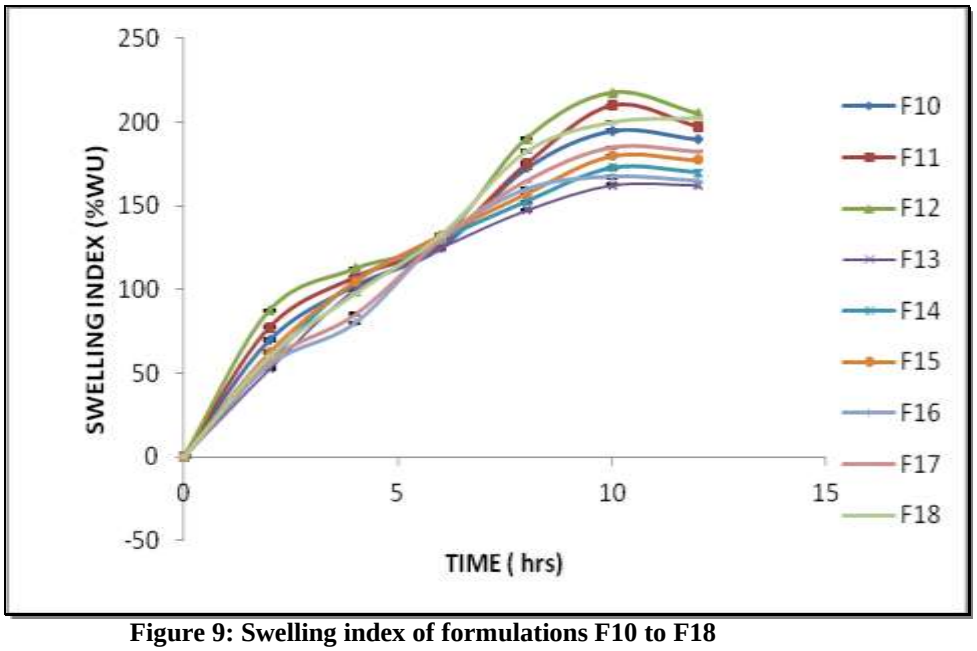

Figure 9: Swelling index of formulations F10 to F18

Bioadhesive strength:

Table 6: Bioadhesive strength of all formulations

Formulation code	Bioadhesive strength (gm)
F1	17 ± 0.8
F2	20 ± 0.5
F3	22 ± 0.7
F4	15 ± 0.2
F5	17 ± 0.2
F6	19 ± 0.7
F7	16 ± 0.6
F8	19 ± 0.1
F9	21 ± 0.2
F10	23 ± 0.8
F11	25 ± 0.2
F12	29 ± 0.4
F13	20 ± 0.6
F14	23 ± 0.5
F15	25 ± 0.7
F16	22 ± 0.8
F17	24 ± 0.3
F18	26 ± 0.4

Values are mean ± SD n=3

All formulations showed bioadhesive strength in the range of 15 ± 0.2 to 29 ± 0.4g. Bioadhesive strength depends on the viscosity and concentration of the polymer. Formulations F1 to F9 have shown low bioadhesion strength due to the lower viscosity of HPMC K4M. While formulations F10 to F18 containing HPMC K15M have shown higher bioadhesion strength due to higher viscosity. It was found that as the concentration of the bioadhesive polymer increases the bioadhesion strength also increases.

***In-vitro* drug release:**

Table 7: Cumulative % drug release of formulations F1 to F6

TIME (hrs)	CUMULATIVE % DRUG RELEASE					
	FORMULATION CODE					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0.5	16.5±0.1	16±0.2	15.7±0.4	19±0.3	18.7±0.2	16±0.1
1	22.8±0.2	21.3±0.3	20±0.05	25.1±0.3	24.6±0.1	24.8±0.3
2	30.7±0.7	30.2±0.4	30.4±0.1	32.7±0.2	33.9±0.5	33.9±0.3
3	42.6±0.3	40.3±0.2	41.3±0.1	48.6±0.7	45.6±0.3	45.1±0.4
4	53.1±0.5	53.3±0.5	52.8±0.4	61.4±0.2	60.4±0.5	61.1±0.3
5	51.9±0.1	58.8±0.6	58.6±0.3	73.2±0.7	68.7±0.4	68.2±0.4
6	71.2±0.2	69.2±0.4	68.7±0.5	87.4±0.5	80.1±0.5	80.3±0.5
7	80.1±0.2	79±0.3	78.8±0.4	99.4±0.2	93.5±0.1	95.8±0.4
8	92±0.2	90.7±0.4	89.7±0.2	108.9±0.6	107±0.2	106±0.2
9	102.3±0.3	101.5±0.5	101±0.5	_	_	_
10	-	-	-	_	_	_
11	-	-	-	_	_	_
12	-	-	-	_	_	_

Table 8: Cumulative % drug release of formulations F7 to F12

TIME (hrs)	CUMULATIVE % DRUG RELEASE					
	FORMULATION CODE					
	F7	F8	F9	F10	F11	F12
0.5	16.2±0.2	15.5±0.4	15.2±0.4	9.5±0.5	12.2±0.1	9±0.2
1	24.5±0.1	24±0.3	24.3±0.1	16.3±0.2	14.3±0.4	13.5±0.3
2	36.2±0.6	35.2±0.3	34.9±0.3	25.1±0.3	26.6±0.5	23.8±0.5
3	47.6±0.4	44.9±0.1	45.4±0.4	34.7±0.3	32.2±0.4	32±0.4
4	60.4±0.6	60.1±0.3	59.4±0.3	43.7±0.5	38.9±0.6	41.4±0.1
5	70.2±0.3	70.4±0.3	69.2±0.3	53.4±0.1	45.1±0.5	45.4±0.5
6	81.8±0.4	82.3±0.2	81.8±0.4	62.3±0.1	57±0.1	53±0.1
7	95.6±0.5	95.3±0.5	95.3±0.5	67.8±0.1	66.2±0.3	60.9±0.2
8	106±0.1	104±0.1	104±0.1	71.7±0.2	68.8±0.4	66.5±0.3
9	_	-	-	74.8±0.6	75.2±0.8	72.1±0.2
10	-	-	-	87.2±0.3	86.6±0.6	80.2±0.1
11	-	-	-	97.7±0.2	94.3±0.6	90.2±0.5
12	-	-	-	102.9±0.3	98±0.4	97.1±0.2

Table 9: Cumulative % drug release of formulations F13 to F18

TIME (hrs)	CUMULATIVE % DRUG RELEASE					
	FORMULATION CODE					
	F13	F14	F15	F16	F17	F18
0.5	5.7±0.2	5.7±0.2	8.7±0.5	8±0.2	12.5±0.1	9.2±0.2
1	10.2±0.4	7±0.4	9.8±0.4	10.7±0.4	17.7±0.3	12.8±0.1
2	18±0.2	20±0.3	20.6±0.3	18.8±0.2	25.9±0.3	20.3±0.4
3	30.1±0.4	27.9±0.5	27.9±0.6	28.2±0.4	36.5±0.6	25.7±0.3
4	41.3±0.3	40±0.2	40.8±0.2	39.3±0.4	43.5±0.2	32.8±0.4
5	54.8±0.1	46.5±0.5	50.8±0.5	50.8±0.3	52.2±0.4	45.5±0.5
6	60.7±0.3	54.1±0.1	59.9±0.2	56.7±0.1	56.6±0.1	59.4±0.1
7	69.2±0.3	58.6±0.6	63.7±0.1	68.6±0.4	61.8±0.1	65.3±0.4
8	75.8±0.6	64.9±0.3	70.8±0.3	80.3±0.2	68.6±0.4	71.4±0.2
9	87.5±0.5	84±0.4	83.6±0.4	86.7±0.3	83±0.3	79.8±0.3
10	92.9±0.2	91.7±0.2	89.3±0.2	92.2±0.2	91±0.3	88.8±0.2
11	100±0.3	98.9±0.4	98.8±0.4	98.9±0.2	97.9±0.2	97.5±0.2
12	106.7±0.1	105±0.1	105±0.1	104±0.4	103±0.4	103±0.5

Value are mean ± SD n=3

In-vitro dissolution studies of all the formulations were carried out in 0.1N HCl. The release of Nizatidine from floating bioadhesive tablets varied according to the type and concentration of polymer. Formulations F1 to F9 containing HPMC K4M showed faster drug release and entire drug was released within 8 h this might be due to the low viscosity of HPMC K4M polymer. While formulations F10 to F18 containing HPMC K15M showed constant drug release up to 12h. Formulation F14, F15, F16 containing HPMC K15M and Sodium CMC showed faster release than formulations F16, F17, F18 containing HPMC K15M and sodium alginate and F10, F11, F12 containing HPMC K15M and carbopol 934 this might be due to low viscosity of the sodium CMC polymer. And formulations F16, F17, F18 containing HPMC K15M and sodium alginate showed faster release than F10, F11, F12 formulations due to the low viscosity of sodium alginate when compared to carbopol 934p. It was also observed that as the concentration of carbopol 934p was increased drug release was decreased. Thus as the concentration and viscosity of the polymer increases and release rate of the drug from the drug delivery system decreases.

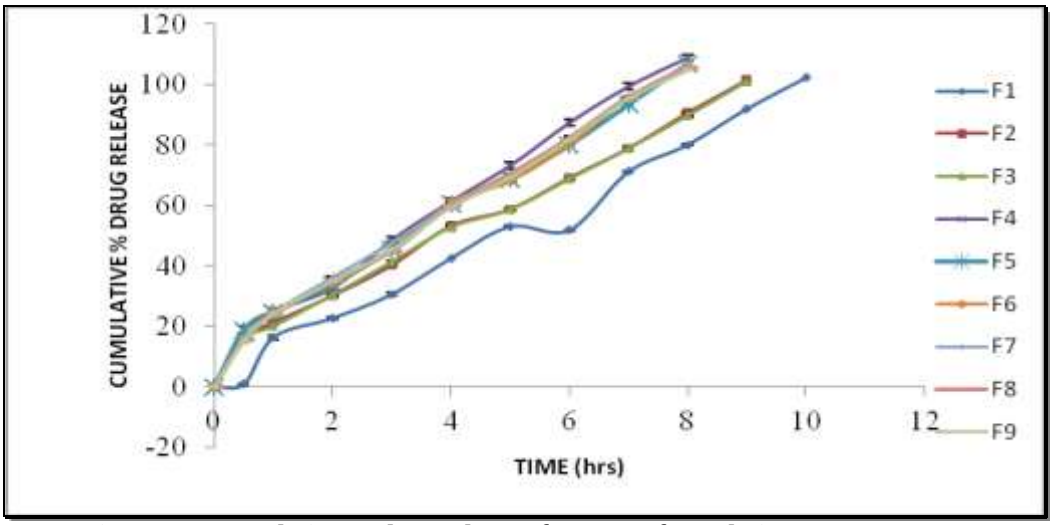

Figure 10: Cumulative % drug release of F1 to F9 formulations

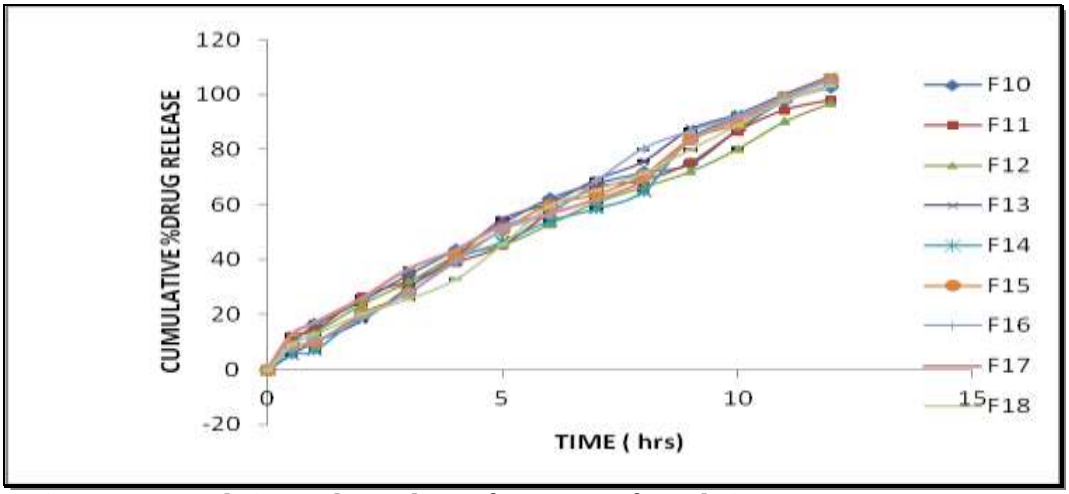

Figure 11: Cumulative % drug release of F10 to F18 formulations.

Kinetic release studies:

Table 10: Kinetic release data of all formulations

FORMULATION CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSMEYER PEPPAS	
	R^2	R^2	R^2	R^2	n
F1	0.989	0.762	0.970	0.983	0.638
F2	0.990	0.741	0.966	0.981	0.649
F3	0.990	0.733	0.969	0.983	0.650
F4	0.990	0.792	0.966	0.970	0.656
F5	0.989	0.797	0.962	0.975	0.637
F6	0.990	0.811	0.968	0.987	0.677
F7	0.990	0.822	0.976	0.992	0.674
F8	0.991	0.826	0.974	0.990	0.691
F9	0.991	0.818	0.974	0.991	0.690
F10	0.985	0.771	0.981	0.997	0.743
F11	0.991	0.863	0.970	0.9824	0.696
F12	0.992	0.908	0.977	0.997	0.750
F13	0.992	0.795	0.985	0.997	0.940
F14	0.993	0.722	0.962	0.986	0.960
F15	0.995	0.738	0.742	0.982	0.853
F16	0.990	0.811	0.968	0.987	0.677
F17	0.990	0.822	0.976	0.992	0.674
F18	0.991	0.826	0.974	0.990	0.691

The kinetics of drug release was examined by plotting the data obtained from *in-vitro* drug dissolution studies in various kinetic models such as Zero-order, First order, Higuchi release model and Korsmeyer and Peppas model. From results it is concluded that *in-vitro* drug release followed zero order release kinetics and the drug release mechanism was found to be of non-Fickian type**.**

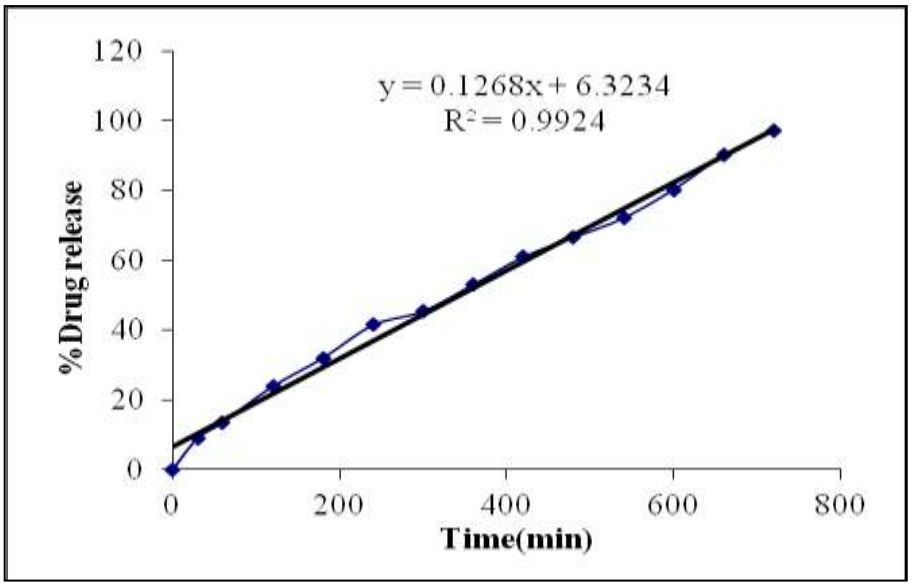

Figure 12: Cumulative % drug released v/s Time for the optimized formulation (Zero order rate)

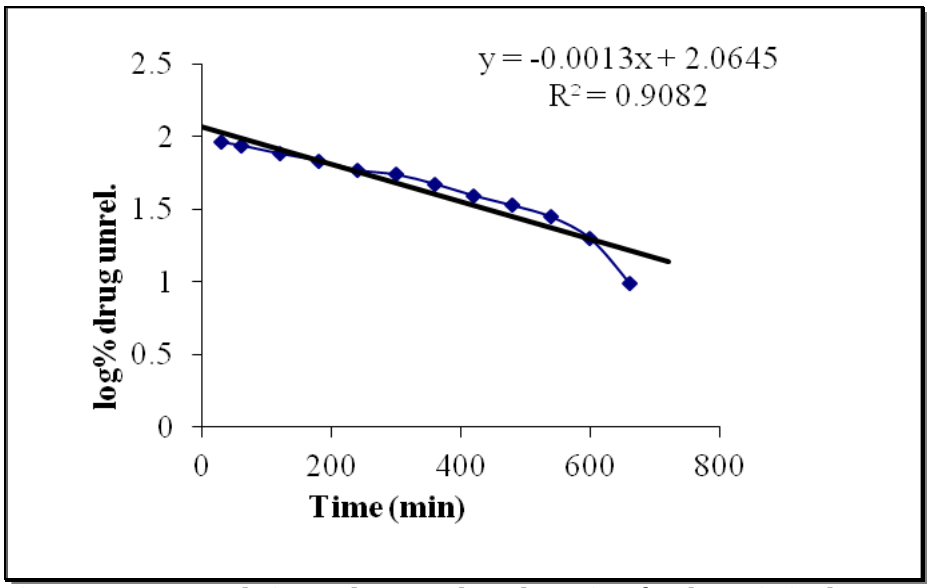

Figure 13: Log cumulative % drug unreleased v/s Time for the optimized formulation (First order rate)

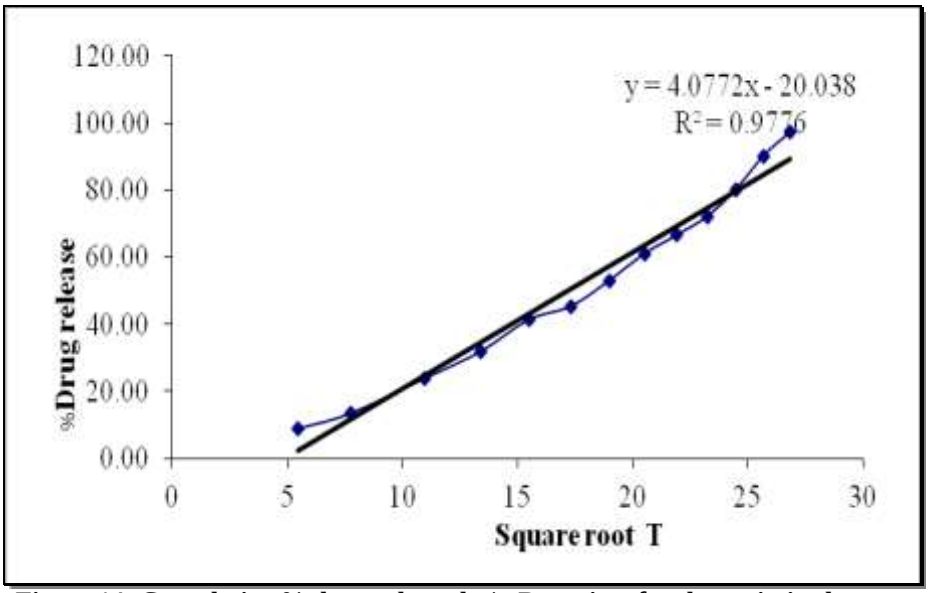

Figure 14: Cumulative % drug released v/s Root time for the optimized formulation (Higuchi matrix)

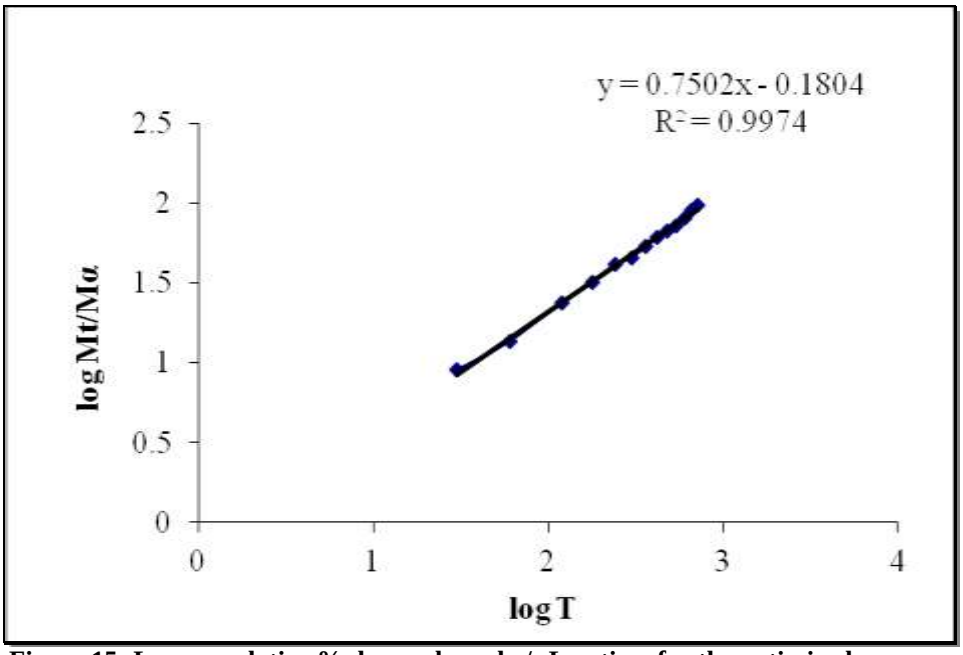

Figure 15: Log cumulative % drug released v/s Log time for the optimized formulation (Peppas model)

CONCLUSION

Floating-bioadhesive tablets of Nizatidine can be prepared by direct compression method using HPMC K4M, HPMC K15M, Sodium CMC, Sodium alginate and Carbopol 934P polymers. IR spectroscopic studies indicated that there are no drug- excipient interactions.As the concentration of HPMC K4M and HPMC K15M decreases, the floating lag time increases. As the concentration and viscosity of polymer in the tablet increases, the drug release rate decreases, whereas swelling index and the bioadhesion strength increases.All the designed formulations displayed zero order release kinetics and drug release follows non-Fickian diffusion mechanism. Among all the formulations, F12 formulation containing 3:1 ratio of HPMC K15M and Carbopol 934P was found to be promising, which showed a floating lag time less than 5min and floating duration of more than 12 hours. It showed a constant drug release upto 12 hours and good bioadhesion strength. Hence, this F12 formula can be brought to the market successfully.

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