Research Article CODEN: IJPRNK ISSN: 2277-8713
RK Venisetty, IJPRBS, 2014; Volume 3(1): 252-276 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

DEVELOPMENT AND EVALUATION OF GASTRIC RETENTIVE FLOATING TABLETS OF NIZATIDINE

MOTUKURI R[1], NAGESH P[2], RK VENISETTY[3]

1. MNR College of Pharmacy, Hyderabad, India.
2. Dr. Reddy's Laboratories Ltd, Hyderabad, India.
3. Chaitanya College of Pharmacy Education and Research, Warangal, India.

Accepted Date: 21/01/2014; Published Date: 27/02/2014

Abstract: Objective: The main objective of this study was to develop an optimal gastric floating drug delivery system (GFDDS) for Nizatidine that can target stomach and upper intestinal mucosa and increase drug availability. **Methods**: Gastro retentive tablets of Nizatidine were developed by direct compression method using HPMC K4M, HPMC K15M, xanthan gum, kondagogu gum and sodium bicarbonate. To investigate the interaction between drug and excipients FTIR and DSC were carried out. Formulations were evaluated for floating lag time, duration of floating, effect of hardness on buoyancy lag time, dimensional stability, drug content, swelling studies and *in vitro* drug release. The release mechanism of Nizatidine from floating tablets was evaluated on the basis of Korsemeyer-Peppas model. **Results**: FTIR and DSC studies indicated the absence of any significant chemical interaction between the drug and excipients. The formulations were found to have floating lag time equivalent to 95 sec. It was found that the dimensional stability of the formulations increased with increasing concentration of the swelling agent. Increasing the hardness of the tablet resulted in increase floating lag time. The 'n' value of the formulations ranged from 0.5 to 0.8 which indicated anomalous (non-Fickian) transport mechanism. **Conclusion:** Among the various formulations studied, the formulation prepared with combination of HPMC K4M and HPMC K15M (F11) showed the best result in terms of the quicker lag time, floating duration and drug release. F11 is considered as the ideal formulation. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolonged floating time.

Keywords: Floating tablets, gastric retention, nizatidine, swelling studies

PAPER-QR CODE

Corresponding Author: Mr. VENISETTY RAJ KUMAR

Access Online On:

www.ijprbs.com

How to Cite This Article:

RK Venisetty, IJPRBS, 2014; Volume 3(1): 252-276

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease. Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine [1-3].

To achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions, grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease [4].

Floating drug delivery systems or hydrodynamically balanced systems (HBS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the systems are floating in the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in plasma drug concentration. HBS system contains a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquires a bulk density of less than one thereby being buoyant on the gastric contents of stomach until all the drug was released. The various buoyant preparations includes tablets, pills, granules, powders, capsules, hollow, microspheres (micro balloons) and laminated films. Based on the mechanism of buoyancy, two distinctly different technologies i.e., noneffervescent and effervescent systems have been utilized in the development of GFDDS.

Oral treatment of gastric disorders with an H_2-receptor antagonist like Nizatidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion. This principle may be applied for improving systemic as well as local delivery of Nizatidine which would efficiently reduce gastric acid secretion. Nizatidine is absorbed only in the initial part of the small intestine and has 70% absolute bioavailability. Moreover, colonic metabolism of Nizatidine is partly responsible for the poor bioavailability of Nizatidine from the colon and short biological half-life of drug (1-2 hours) which favors development of a sustained release formulation.

The novel dosage forms can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastro-retentive dosage forms that will provide us with new and important therapeutic options. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. The present investigation is concerned about the development of effervescent floating drug delivery systems that generate CO_2, thus reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at desired rate. The floating drug delivery systems result in long lasting intra-gastric buoyancy which may not only provide a sustained site of specific therapeutic action but also may lead to reduction in side effects and better patient compliance.

MATERIALS AND METHODS

Nizatidine pure drug was a generous gift from Euro Labs, Hyderabad, India. HPMC K15M, HPMC K4M and Xanthan gum was purchased from Signet Chemical Corporation, Mumbai, India. Kondagogu gum and lactose was gifted by Zydus Cadila, Ahmedabad, India and all other chemicals of highest grade were purchased from S.D. Fine Chemicals, Mumbai, India

Experimental methodology

Analytical method development

A stock solution of Nizatidine (1000 µg/ml) was prepared in 0.1N HCl. The UV spectrum was recorded in the range of 200-400 nm. The solutions of 50 to 250 µg/ml were prepared from stock solution by appropriate dilution with 0.1 N HCl. The absorbance of each of solution was recorded using UV spectrophotometer at wavelength of maximum absorption.

Compatibility studies

Drug polymer interactions were investigated by FTIR & DSC. The infrared spectra of Nizatidine pure drug-excipients, physical mixture of drug and excipients were recorded between 400 to 4000 cm^{-1}. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer.

Thermal properties of pure drug and the formulation were evaluated by differrentential scanning calorimetry (DSC). The analysis was performed at a rate 200^0c temperature range under nitrogen flow of 60 ml/ min.

Tablet manufacturing

Nizatidine and all ingredients were accurately weighed and passed through sieve # 40. Nizatidine was well mixed with weighed quantity of polymer and then with remaining excipients i.e. sodium bicarbonate, micro crystalline cellulose in a geometric proportions. It is then mixed homogeneously in a poly bag for about 10 min then lubricants like Magnesium Stearate and Talc is added and then mix properly for remaining 10 min to obtain the blend for compression. Then the blend was subjected to compression by using tablet punching machine using 11mm circular standard flat faced punches.

The composition of different formulations of Nizatidine floating tablets are shown in table 1. Nizatidine, HPMC K4M, HPMC K15M, Xanthan gum andKondagogu gum were passed through sieve no.80 separately. Sodium bicarbonate was passed through sieve no.44. All the ingredients were mixed in proportion shown in table no.10. The powder blends were lubricated with magnesium stearate (1% w/w) and talc (2% w/w), and these lubricated blends were compressed into tablets using 9 mm flat faced round tooling on a multiple punch tablet machine (Rimek mini press II). The compression force was adjusted to obtain tablets with hardness in range of 4.5 to 6 kg/cm^2. Each tablet contained 150 mg of Nizatidine. Fifteen formulations were prepared and coded them from F1 to F15.

Table 1: Composition of different floating tablet formulations of Nizatidine

Ingredients	Formulations														
(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
HPMC K4M	90	120	150	187.5	-	-	-	-	75	75	100	100	-	-	-
HPMC	-	-	-	-	90	120	150	187.5	75	100	75	75	-	-	-

K15M															
Xanthan Gum	-	-	-	-	-	-	-	-	-	-	-	-	150	-	-
Kondagogu	-	-	-	-	-	-	-	-	-	-	-	-	-	150	120
$NaHCO_3$	35	35	35	40	35	35	35	40	35	40	40	60	35	35	35
Lactose	113	63	53	10.5	113	83	53	10.5	53	23	23	3	53	53	83

Evaluation

Precompression parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio were calculated according to the existing methods. Similarly post compression parameters like tablet thickness, diameter, hardness, friability, uniformity of weight and content uniformity were calculated based on pharmacoaepial methods.

In vitro buoyancy determination:

The floating characteristics of the GFDDS are essential, since they influence the *in vivo* behaviours of the drug delivery system. However there seemed to be no threshold value for the floating system to remain float under a physiological condition due to the latter's complication.

Floating lag time:

The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5^{0}C paddle rotation at 50 rpm it is measured using stopwatch.

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^{0}C, paddle rotation at 50 rpm, it is measured using stopwatch.

Determination of swelling index:

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablet was determined by placing the tablets in 200 ml beaker using 0.1 N HCl. After every one hour up to 12 hours, each tablet was removed and blotted with tissue paper to remove the excess water and weighed on the balance. The experiment was performed in triplicate for each time point.

The swelling index is expressedas a percentage and was calculated from the equation.

Swelling Index (S.I.) = {(Wt-Wo)/Wo} × 100

Where,

Wt = weight of tablet at time t

Wo= weight of tablet before immersion.

In vitro dissolution studies:

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (apparatus II). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900ml). It was maintained at 37 ± 0.5^0C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. 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 (Labindia-3000, Labindia, Mumbai, India). Each dissolution study was performed for three times and the mean values were taken.

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 equation rate describes the systems where the drug release rate is independent of its concentration. The first order Equation describes the release from system where release rate is concentration dependent [5]. The release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation is well reported [6]. The Hixson-Crowell cube root law equation describes the release from systems where there is a change in surface area and diameter of particles or tablets [7].

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant. Dividing this equation by W_0 and simplifying

$f_t = k_0 t$

Where $f_t = 1-(W_t / W_0)$ and f_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant in this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were full filled. In this way a graphical relationship between f_t versus time to get the Zero order constant from the slope. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems as well as matrix tablets with low soluble drugs [8], coated forms, osmotic systems, etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First order kinetics:

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model is,

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant. In this way a graphical relationship between log percent drug remaining versus time to get the First order constant from the slope. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such a way, that the amount of drug released by unit of time diminishes.

KorsmeyerPeppas model (power law):

Korsmeyer and Peppas [9-11] developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t)

$Q_t / Q_\alpha = K_k t^n$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism. For matrix tablets, an n value of ~0.5 indicates diffusion – controlled mechanism while an n value of ~1.0 indicates erosion [12]. Reports suggest that if the value of n is 0.5, it indicates Fickian transport, a value of 0.5 and 1.0 non-Fickian transport, and the values close to 1.0 indicate that the system is releasing drug in a zero-order manner regardless of the actual mechanism of release [13].

This type of analysis of release behavior is valuable to the formulator for comparative purposes. The release exponent can be obtained from the slope and the constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t. This model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon being involved.

Higuchi Model:

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between square root of time versus concentration indicates that the drug release follows strict Fickian diffusion. For purpose of data treatment, the above equation is usually reduced to:

$$Q = Kt^{1/2}$$

Therefore a plot of amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time. An important advantage of the above equations is its simplicity.

Hixson-crowell model:

The simplified equations is represented as

$$Q_0^{1/3} - Qt^{1/3} = kt$$

Where,Qt = amount of drug released in time (t)

Qo = initial amount of drug in solution

K = cube root constant

A graphic representation of cubic root of unreleased fraction of drug versus time will be linear if geometric shape of the formulation diminishes proportionally over time.

The following plots were made using the in-vitro drug release data:

Cumulative % drug release vs time (Zero order kinetic model);

Log cumulative of % drug remaining vs time (First order kinetic model);

Cumulative % drug release vs square root of time (Higuchi model);

Log cumulative % drug release vs log time (korsmeyer – peppas model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs time (Hixson-Crowell cube root law).

Results and Discussion

Determination of λ_{max} of Nizatidine in 0.1 N HCl:

The study started with the construction of standard calibration curve of Nizatidine. The scanning of the volumetric solution of Nizatidine in the ultraviolet range of 200 – 400 nm and the λ_{max} was found to be 314 nm (Fig 1).

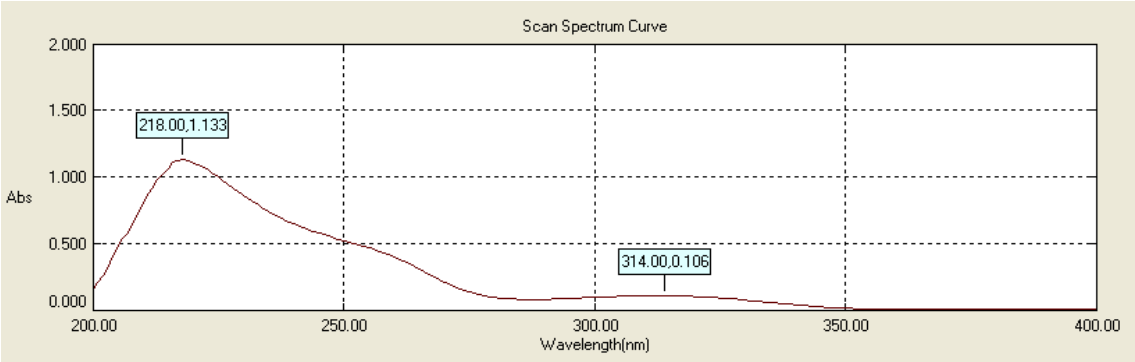


Figure 1: λ_{max} of Nizatidine in 0.1 N HCl

Standard curve for Nizatidine:

The standard graph of Nizatidine in 0.1N HCl was plotted by taking concentration ranging from 50 to 250 µg/ml and showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer's-Lamberts law.

The prepared floating tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling index, *in vitro* buoyancy studies and *in vitro* drug release studies. All the studies were performed in triplicate, and results were expressed as mean ± SD.

Drug-Excipient compatibility studies:

Fourier Transform Infrared spectroscopic studies (FTIR):

The FTIR spectra of drug, excepients, drug loaded formulation. The characteristic peaks of the optimized formulation followed the same trajectory as that of the drug alone with no change at different group frequencies indicating that there are no drug-excipient interactions (Fig 2, Table 2).

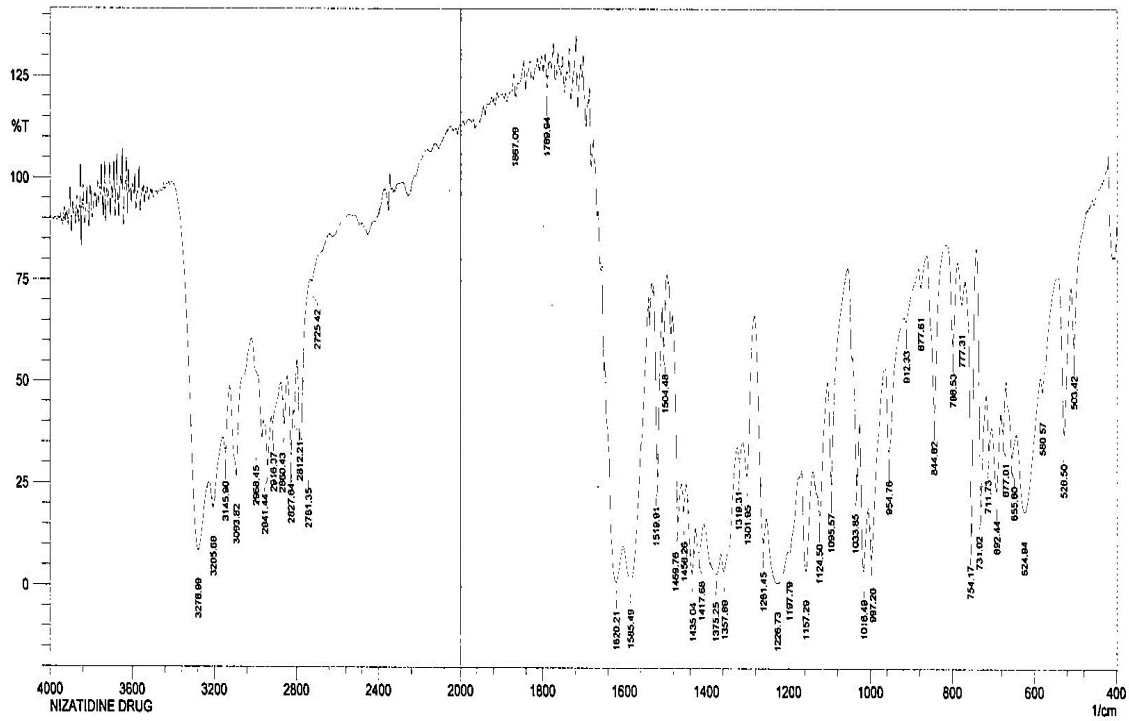


Figure 2: FTIR spectra of Nizatidine used in the preparation of floating matrix tablet

Table 2: FTIR peak positions (cm^{-1}) and assignments for Nizatidine drug and its combinations with excipients

Nizatidine	Nizatidine+HPMCK4M+HPMC	Frequency range	Mode of vibration
2941.44	2939.52	2950-2800	CH stretching
1469.76	1469.76	1454-1475	CH_2 stretching
2827.64	2827.64	2850-2815	CH_3 stretching
1469.75	1469.75	1475	C=C stretching
1261.45	1261.45	1360-1250	C-N stretching

3278.99	3278.99	3500-3180	N-H stretching
1375.25	1377.17	1380-1360	NO_2 stretching
_	3404.36	3400-3300	OH stretching
_	2351.23	2800-2340	OH stretching
_	1072.42	1260-1000	CO stretching
_	1058.92	1300-1000	C-O-C stretching

Differential Scanning Calorimetry(DSC):

DSC study was conducted on the selected formulation. DSC thermogram of pure Nizatidine shows sharp exothermic peak at 138.4°C. Similar exothermic peak was obtained at 136°C for the formulation prepared with combination of HPMC K4M & K15M. The DSC thermograms were given in the following section (Table 3, Fig 3, 4).

Table 3: DSC melting points of the selected formulations

Formulations	DSC melting point in °C
Pure Nizatidines	138.4
Nizatidine + HPMC K4M + K15M	136

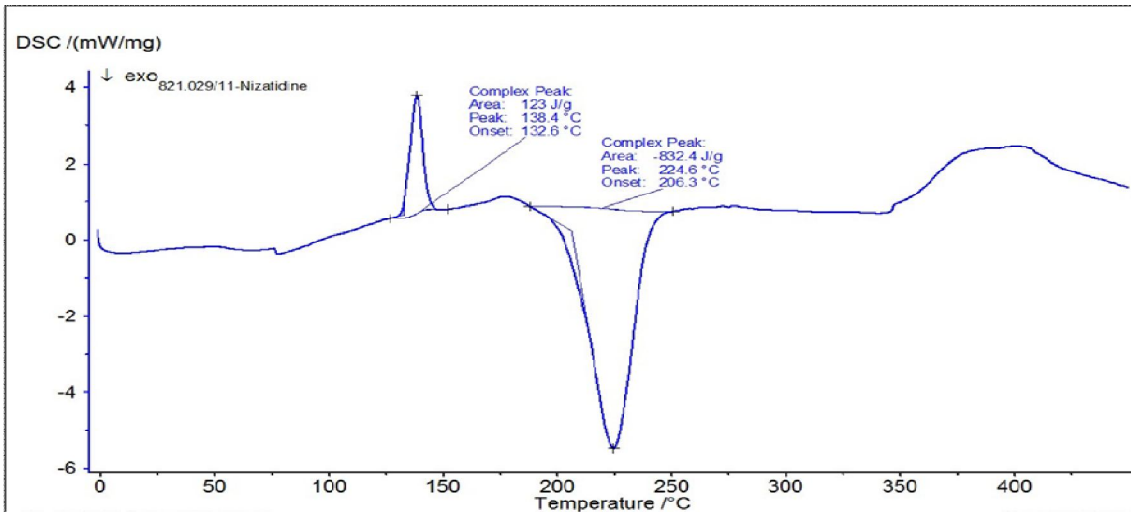


Figure 3: DSC thermogram of pure Nizatidine

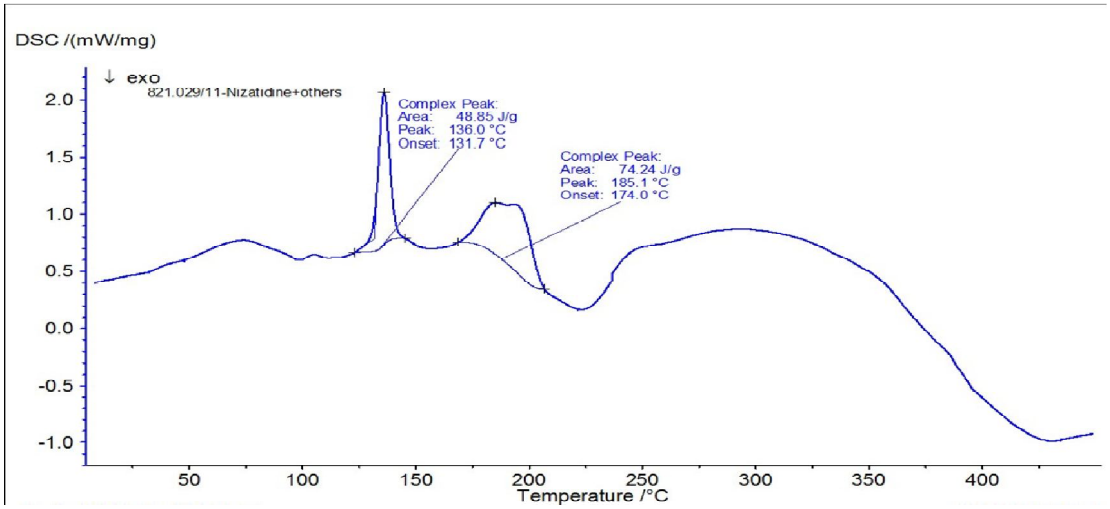


Figure 4: DSCthermogram of Nizatidine-polymer mixture

Pre and post compression evaluation of floating tablets:

Characterization of powder blend:

The powder blends were evaluated for their flow properties, the results were shown in table 4. Angle of repose was in the range from 24.2 to 27.69 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 0.591 gm/cc; the tapped density was in the range of 0.591 to 0.670 gm/cc. The Carr's index was found to be in the range from 11.10 to 16.64, the Hausner ratio was found to be in the range from 1.11 to 1.19, indicating compressibility of the tablet blend is good. These values indicate that the powdered blend exhibited good flow properties.

Table 4: Pre compression flow properties ofNizatidine floating tablets

Formulation	Angle of repose (Θ)	Bulk density(gm/cc)	Tapped density(gm/cc)	Carr's index (%)	Hausner's ratio (HR)
F1	24.22	0.51	0.598	14.71	1.17
F2	27.43	0.581	0.650	11.10	1.11
F3	27.6	0.576	0.651	11.52	1.13
F4	26.56	0.529	0.597	11.39	1.12

F5	25.27	0.512	0.598	14.38	1.16
F6	27.69	0.520	0.591	12.01	1.13
F7	26.91	0.512	0.611	16.2	1.19
F8	24.34	0.553	0.637	13.18	1.15
F9	27.69	0.526	0.631	16.64	1.19
F10	27.26	0.578	0.667	13.34	1.15
F11	27.1	0.591	0.670	11.79	1.13
F12	27.64	0.581	0.669	13.15	1.15
F13	25.97	0.530	0.631	16.0	1.19
F14	24.22	0.543	0.625	13.12	1.15
F15	27.09	0.545	0.620	12.09	1.13

Post compression evaluation of floating tablets:

Floating Nizatidine tablets were white, smooth, and flat shaped in appearance. The thickness of floating tablets was measured by verniercalipers and was ranged between 4.0 ±0.20 and 4.32±0.39 mm. The diameter of floating tablets was measured and was ranged between 8.8 ± 0.11 to 9.03 ± 0.11 mm. The weight variation for different formulations (F1 to F15) showed satisfactory results as per United States Pharmacopoeia (USP) limit (average weight ± 5%). The hardness of the floating tablets was measured by Monsanto tester and was found to be ranged from 4.66 ± 0.28to 6.16 ± 0.28kg/cm2. Friability was found in be ranged from 0.472 to 0.76 which was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F15 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).

Table 5: Post compression properties of Nizatidine floating tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content(%)	Weight variation (mg)
F1	4.2±0.04	8.8±0.15	6.16±0.28	0.488	102.63±2.1	399.8±0.78
F2	4.16±0.036	8.9±0.11	5.03±0.05	0.644	99.56±0.75	399.8±0.73
F3	4.19±0.025	8.9±0.05	5.06±0.11	0.488	99.96±0.56	399.7±1.08
F4	4.25±0.025	8.9±0.11	5±0.2	0.689	98.5±1.00	399.8±0.8
F5	4.17±0.092	8.9±0.05	5.16±0.35	0.472	101.7±1.60	400.05±1.14
F6	4.2±0.025	8.8±0.11	5.83±0.28	0.644	101.51±0.75	399.85±1.11
F7	4.03±0.134	8.9±0.05	5.3±0.17	0.555	102.03±1.5	400.0±0.62
F8	4.32±0.39	8.9±0.17	4.66±0.28	0.687	99±0.54	399.9±1.11
F9	4.2±0.31	8.83±0.05	5.33±0.28	0.592	103.03±0.45	399.17±1.48
F10	4.3±0.31	9.0±0.0	4.83±0.28	0.76	99.7±1.31	399.75±0.98
F11	4.2±0.09	8.93±0.05	4.66±.028	0.561	102.83±0.35	399.6±1.02
F12	4.25±0.09	8.93±0.05	5.5±0.3	0.503	98.6±1.4	398.9±1.39
F13	4.0±0.20	9.03±0.11	5.33±0.28	0.517	98.1±1.21	399.9±1.16
F14	4.13±0.15	9.0±0.05	4.93±0.11	0.484	98.9±0.45	399.9±1.11
F15	4.1±0.03	8.9±0	5±.0.2	0.638	100.46±0.96	399.6±0.98

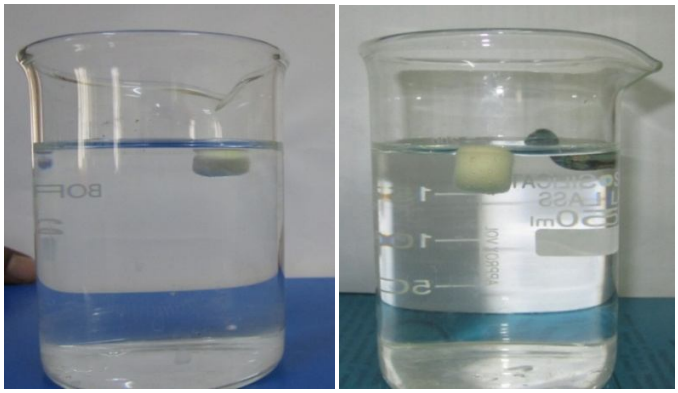
Floating characteristics

All the tablets were prepared by effervescent approach. On immersion in 0.1N HCl solution pH (1.2) at 37^{0}C, the tablets floated, and remained buoyant without disintegration. Sodium bicarbonate was used as the effervescent base. When the floating matrix tablets containing gas generating agent were exposed to 0.1N 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. All the prepared batches showed the total floating

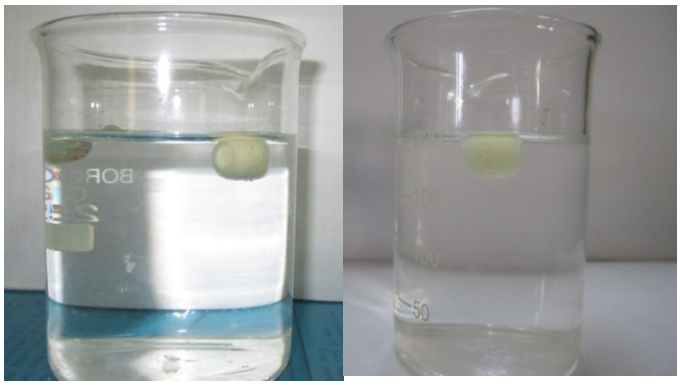
time more than 12 hours except the F1, F2, F5 and F6 batches showed only more than 6 hours [14-17].

The study shows that the batches containing HPMC polymer showed less floating lag time than the batches containing xanthan gum. In this study, penetration of water into tablets prepared with xanthan gum was rather slow, causing delayed gel formation and subsequent increase in the floating lag time compared to the tablets prepared with HPMC K4M, HPMC K15M. In this study, penetration of water into tablets prepared with Kondagogu gum was fast, causing fast gel formation and subsequent decrease in the floating lag time compared to the tablets prepared with HPMC K4M and HPMC K15M (Fig 5, Table 6) (Wu et al 1997; Joseph et al 2002).

At 0 sec At 90 sec



At 120 sec At 4 hrs



At 6 hrs At12 hrs

Figure 5: Photographs showing *in vitro* buyoancy study of optimized formula F11 in 0.1 N HCl at different time intervals

Table 6: Results of *in vitro* buoyancy study of Nizatidine floating tablets.

Formulation	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	82	6
F2	75	>8
F3	80	>12
F4	92	>12
F5	80	6
F6	72	>8
F7	94	>12
F8	180	>12
F9	65	>12
F10	120	>12
F11	95	>12
F12	58	>12
F13	756	>24

F14	120	>12
F15	70	>12

Effect of hardness on buoyancy lag time:

The effect of hardness on buoyancy lag time for batch F11 was studied. The results of floating lag time of tablets with hardness of 4 kg/cm^2, 6kg/cm^2, 8kg/cm^2 were 56, 132 and 186 sec (Fig 6). Buoyancy lag time (sec) vs hardness (kg/cm^2) plotted and shown in figure 6. Buoyancy of the tablet was governed by both swelling of the hydrocolloid particle on the surface when it contacts the gastric fluid that in turn results in an increase in bulk volume and the presence of internal void spaces in the dry center of the tablet (porosity). Increasing the hardness of the tablet results in increased floating lag time, which might be due to high compression resulting in reduction of porosity of the tablet. Moreover the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result of this, the capability of the tablet to float is significantly reduced [18].

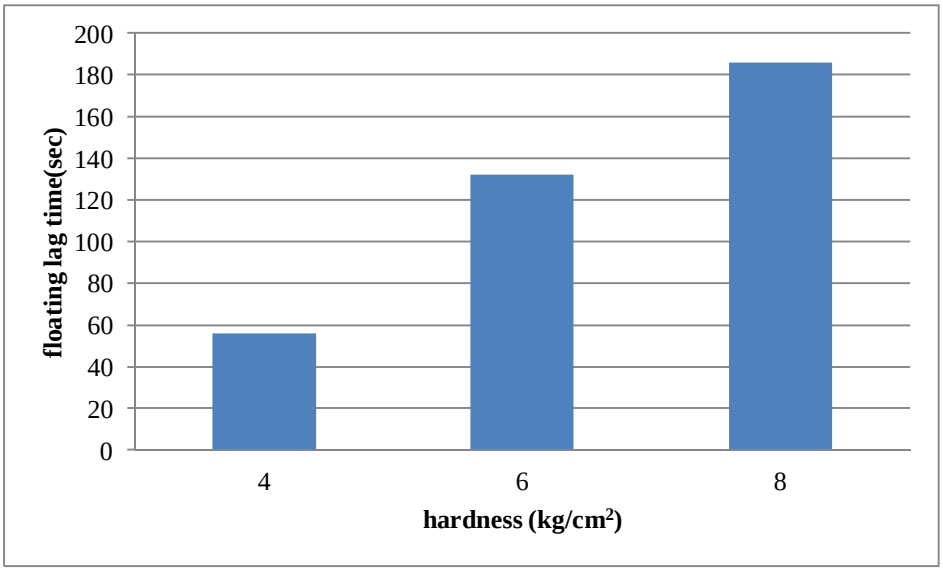


Figure 6: Effect of hardness on floating lag time

***In vitro* release study:**

In vitro dissolution studies of all the formulations of Nizatidine were carried out in 0.1 N HCl. Percentage drug release was calculated at one hour time intervals for 12 hours. The variation in

drug release was due to different types of polymers and different concentrations of polymer in all fifteen formulations. Among these formulations, formulation F11 showed most consistent drug release up to the end of 12 hours (98.03%). Formulation F11 floated with a lag time of 95 seconds; because of these reasons, the formulation F11 was considered as most promising formulation among all the fifteen formulations.

***In vitro* dissolution data of formulations with HPMC K4M:**

As the polymer concentration of HPMC K4M increases the drug release rate was retarded. F-1 formulation retards the drug release only for 7 hours. F-2 formulation retarded the drug release for about 9 hours, F-3 formulation containing drug: polymer ratio 1:1 retards the drug release for 11 hours. F-4 formulation retard the drug release up to 12 hours but it is having burst release at initial hours. Further the tablet integrity was also poor. So attempts were made to improve the retardation of drug release, total buoyancy time as well as tablet integrity by employing high viscosity grade polymer like HPMC K15 M (Fig 7).

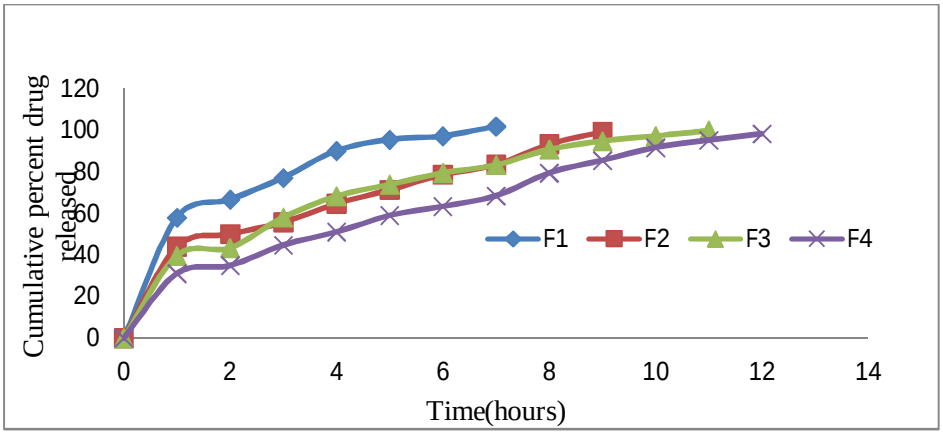


Figure 7: *In vitro* drug release curve of Nizatidine from formulations with HPMC K4M

***In vitro* dissolution data of formulations with HPMC K15M:**

As the polymer concentration of HPMC K15M increases the drug release rate was retarded. F-5 formulation has showed 99 % drug release in 9 hours. F-6 formulation has showed 100 % drug release in 11 hours, F-7 & F-8 formulations retarded the drug release up to 12 hours but did not give theoretical release in first hour (Fig 8).

From the dissolution profiles of tablets of HPMC K4M, HPMC K 15M formulations, the initial burst effect was observed to some extent which might be due to inherent characteristics of HPMC matrices which showed an initial burst of drug release, owing to the time required for

the formation of an efficient gel layer which was particularly evident for highly soluble drugs as Nizatidine which is highly soluble at low pH.

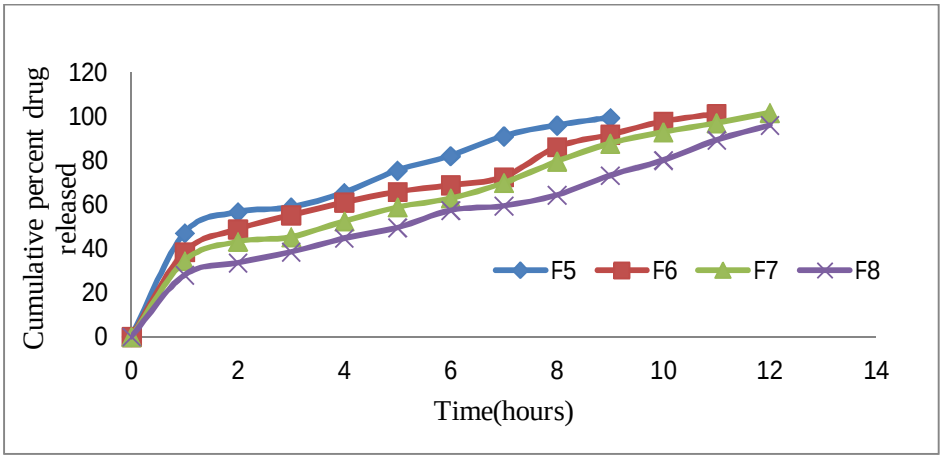


Figure 8: *In vitro* drug release curve of Nizatidine from formulations with HPMC K15M

***In vitro* dissolution data of formulations with HPMC K4 M & K 15 M:**

Drug release profiles of the formulations containing combinations of HPMC K4M and K15M (F9, F10, F11, F12) were reported. F9 formulation did not retard the drug release and gave initial burst effect. F10 formulation with more concentration of HPMCK15M than HPMC K4M takes more time to swell. There was an increase in floating lag time. Hence another combination was tried with more concentration of HPMC K4M than HPMC K 15M which decreased the floating lag time and it gave desired release in first hour. It also retarded the drug release for 12 hours. Next trail was done to still decrease the lag time. Hence the concentration of sodium bicarbonate was increased to 15%. The drug release was increased, hence F11 formulation was optimized (Fig 9).

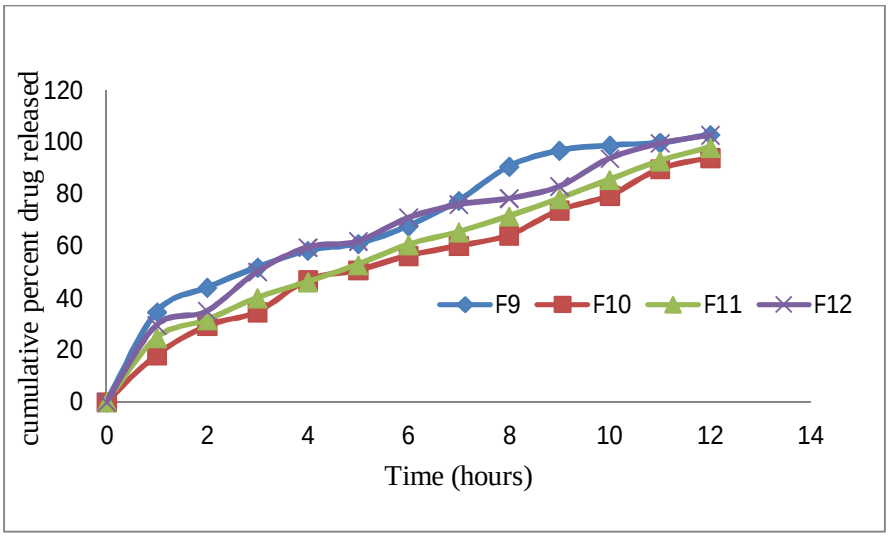


Figure 9: *In vitro* drug release curve of Nizatidine from formulations with combinations of HPMC K4M and K15M

From the overall dissolution profiles it was concluded that the drug release rate was decreased as the viscosity of HPMC increases. This can probably be attributed to the different diffusion and swelling behaviours of the polymer. With the increasing macromolecular weight, the degree of entanglement of the polymer chains increases. Thus the mobility of the macromolecule in a fully swollen system decreases. According to free volume of theory of diffusion, as the probability for a diffusing molecule to jump from one cavity into another, decreases. This leads to decreased drug diffusion coefficient and decreases release rate with increase in molecular weight or viscosity of the polymer [19].

***In vitro* dissolution data of formulations withdifferent natural polymers:**

The formulation with xanthan gum retards the drug release when compared to formulation with Kondagogu gum. It was observed that F14 formulation retarded the drug release. Hence the polymer concentration was decreased. F 15 formulation has less floating lag time and gave desired release in first hours along with drug retardation for 12 hrs (Fig 10).

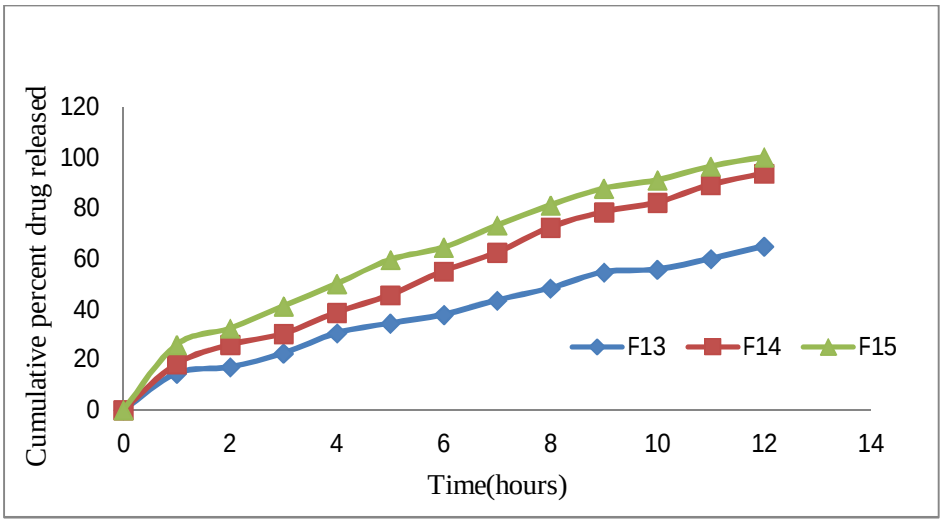


Figure 10: *In vitro* drug release curve of Nizatidine from formulations with xanthan gum and kondagogu gum

From the *in vitro* dissolution data it was found that formulation based on HPMC K4M have higher rate and extent of drug release than that of formulations based on HPMC K15M. Floating tablet containing HPMC exposed to dissolution medium, the medium penetrate between the free spaces of the macromolecular chain of the polymer after salvation of the polymer chain, the dimension of the polymer molecule increases due to polymer relaxation by the stress of penetrated solvent. This led to swelling which are characterized by formation of gel like network surrounding the tablets. Studies have shown that HPMC K4M have low viscosity and form a loose gel like network than that of HPMC K15M. Hence the tablet containing HPMC K4M have higher rate and extent of drug release as compared to that of tablet containing HPMC K15M.

An increase in polymer concentration causes increase in viscosity of the gel as well as the gel layer with longer diffusion path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate. The immediate release part for sustained release of Nizatidine was calculated and was found to be 34.4 mg (22.93%) of the drug in 1 hour.

Kinetic modeling of drug release:

The in vitro dissolution data were fitted in different kinetic models viz. zero order, first order, Higuchi and Korsemeyer-Peppas, Hixson-crowell equation [3]. Correlation coefficients of formulation F11 batch showed higher correlation with zero order plots than higuchi and first order. So, predominant drug release mechanism is controlled release. The zero order plots were found to be fairly linear as indicated by their high regression values (R^2= 0.943 to 0.998) [1]. To confirm the exact mechanism of drug release from these tablets, the data were fitted

according to Korsemeyer- Peppas equation. Slope values (0.5 < n < 1.0) suggested that the release of Nizatidine from the floating tablets followed the anomalous or non- Fickian transport mechanism which indicates release is controlled by both diffusion and erosion. The causes for diffusion may be due to the swollen insoluble hydrogel matrix, which entrapped the drug. The cause for good correlation for erosion may be due to the presence of the surface drug and due to the breakdown of the swollen matrix to smaller sizes. The R^2 value of Higuchi's model confirms diffusion (Table 7).

The dissolution data was also plotted in accordance with Hixson Crowell cube root law. Applicability of data (R^2 = 0.926) indicates a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time.

Table 7: Different kinetic models for Nizatidine floating tablets

Formulation	Zero order	First order	Higuchi	Korsemeyer-peppas		Hixoncrowell
	R^2	R^2	R^2	R^2	N	R^2
F1	0.943	0.973	0.975	0.986	0.813	0.839
F2	0.997	0.693	0.971	0.984	0.745	0.872
F3	0.953	0.683	0.985	0.97	0.701	0.946
F4	0.991	0.867	0.98	0.969	0.508	0.954
F5	0.988	0.785	0.969	0.947	0.355	0.924
F6	0.985	0.815	0.965	0.964	0.402	0.746
F7	0.992	0.838	0.96	0.949	0.457	0.752
F8	0.989	0.799	0.947	0.948	0.503	0.895
F9	0.97	0.807	0.969	0.969	0.469	0.867
F10	0.987	0.871	0.978	0.991	0.645	0.940
F11	0.998	0.812	0.981	0.984	0.571	0.926
F12	0.976	0.741	0.986	0.983	0.521	0.772
F13	0.992	0.990	0.981	0.976	0.65	0.994

F14	0.993	0.926	0.997	0.981	0.700	0.973
F15	0.987	0.860	0.990	0.987	0.588	0.838

Gastric emptying of the dosage forms is an extremely variable process and ability to prolong and control the emptying time which is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Nizatidine floating matrix tablets prepared with an aim to provide the drug for prolonged period of time in the stomach. Nizatidine was targeted to stomach because it has the absorption window in upper part of GIT, have colonic metabolism at the same time it has been provided for prolonged period of time for better therapeutic activity. The floatation was accomplished by incorporating gas generating salt, sodium bicarbonate into a swellable polymer. The physico chemical properties of all the formulations were found to be within the prescribed official limits. FTIR and DSC study of pure Nizatidine HCl and formulations showed that there is no drug polymer interaction.

The formulations containing HPMC K4 M did not show promising results, the drug release was poor, and the *in vitro* floating time was also found to be less. The increase in polymer concentration and viscosity causes retardation of the drug release. Formulations containing higher polymer concentration had slower drug release when compared to formulations with lower concentration of polymers. Comparing the three different grades of methocel (K4M and K15M), it was found that combination of polymers containing HPMC K4M with less concentration of HPMC K15M provided better-controlled release characteristics with excellent drug release and *in-vitro* buoyancy. The xanthan gum formulations showed increased floating lag time. Hence sodium bicarbonate concentration was increased. Formulation with Kondagogu gum gave sustained release characteristics for 12 hours. Formulation F11 and F15 gave better controlled drug release in comparison to the other formulations. But F11 formulation has shown more release than F15 formulation when compared with theoretical release profile. The drug release pattern from the optimized formulations followed zero order kinetics with non fickian diffusion mechanism.

CONCLUSION

In conclusion, the effervescent based FDDS is a promising approach to achieve *in vitro* buoyancy by using gel forming polymers HPMC K4M, HPMC K15M, Xanthan gum, Kondagogu gum and combination of HPMC K4M, HPMC K15M polymers by employing sodium bicarbonate as gas generating agent. Among the various FDDS formulations studied, the formulation prepared with combination of HPMC K4M and HPMC K15 M (F11) showed the best result in terms of the quicker lag time (95 sec) and floating duration of 12 h and releasing 98.03 ± 0.3% of the drug in

12 h and is considered as the ideal formulation. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolonged floating time. This dosage form holds promise for further *in vivo* studies which can be extrapolated for the development of other delivery system.

REFERENCES

1. Yang L, Fassihi R: Zero order release kinetics from self correcting floatable configuration drug delivery system. J. Pharm Sci.1996; 85: 170-173.

2. Talwar N, Sen H, Staniforth JN and inventors: "Orally administered controlled drug delivery system providing temporal and spatial control", US patent, 6 261 601, July 17, 2001.

3. Nur AO and Zhang JS: Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev Ind Pharm 2000; 26: 965-969.

4. Dave BS, Amin AF and Patel MM: Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation. AAPS Pharm. Sci Tech 2004; 5: E34

5. Bourne DW: Pharmacokinetics In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics. 4th ed, New York, NY: Marcel Dekker Inc, 2002:67-92.

6. Higuchi T: Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52: 1145–1148

7. Hixson AW and Crowell JH: Dependence of reaction velocity upon surface and agitation: I-theoretical consideration. Ind Eng Chem 1931; 23: 923-931.

8. Varelas CG, Dixon DG and Steiner C: Zero-order release from biphasic polymer hydrogels. J Control Release 1995; 34: 185-192

9. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA: Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15: 25–35.

10. Peppas NA: Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv 1985; 60, 110–111

11. Harland RS, Gazzaniga A, Sangalli ME, Colombo P and Peppas NA: Drug–polymer matrix swelling and dissolution. Pharm Res 1988; 5: 488-494

12. Ford JL, Mitchell K, Rowe P, Armstrong DJ, Elliott PNC, Rostron C and Hogan JE: Mathematical modeling of drug release from hydroxypropylmethylcellulose matrices: effect of temperature. Int J Pharm 1991; 71: 95–104

13. Yang GM, Kuo JF, Woo EM: Preparation and control-release kinetics of isosorbide dinitrate microspheres. J Microencapsul 2006; 23: 622–631.

14. Li S, Lin S, Daggy BP, Mirchandani HL and Chein YW: Efect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J Pharm 2003; 253: 13-22.

15. Sameer S, Kalpana P and Pathak AK: Formulation and Evaluation of Floating Tablet of Captopril. Int J Pharm Tech Res 2007; 3: 333-341.

16. Patil VS and Gaikwad PD: Formulation and evaluation of floating matrix tablet of locally acting H2-antagonist. Int J Pharm Tech. 2010; 2: 528-540.

17. Jadhav MN, Moorthy KS, Ayyappan T and Shanmugam S: Formulation and *in vitro* evaluation of gastro retentive floating matrix tablets of famotidine. Int J Pharm Bio Sci. 2010; 1: 548-560.

18. Wu W, Zhon Q, Zhang HB, Ma GD, and Fu CD: Studies on Nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric residence time. Yao Xue Xue Bao, 1997; 32: 786-790.

19. Joseph NJ, Lakshmi S and Jayakrishnan A: A floating type oral dosage form for piroxicam based on hollow poly carbonate microspheres: *in vitro* and *in vivo* evaluation in rabbits. J Control Rel 2002; 79: 71-79.