WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 3, 1198-1221. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION STUDIES OF FLOATING DRUG DELIVERY SYSTEM CONTAINING NIZATIDINE ANTI ULCER DRUG

S. Chandra*, S. Kavi Bharathi*, S. Sangeetha, A. Sheikalisha, B. Nandhini and Dinesh Kumar R.

Department of Pharmaceutics, JKKMMRF's College of Pharmacy, Komarapalayam, Dr.M.G.R. Medical University.

Article Received on
21 Dec. 2020,

Revised on 11 Jan. 2021,
Accepted on 01 Feb. 2021

DOI: https://doi.org/10.17605/OSF.IO/Z3RYD

***Corresponding Author**
Dr. S. Chandra* and
S. Kavi Bharathi*
Department of Pharmaceutics, JKKMMRF's College of Pharmacy, Komarapalayam, Dr.M.G.R. Medical University.

ABSTRACT

In the present study the floating tablet of nizatidine were prepared by GRDDS by using polymers. In this preparation was done to increase the anti ulcer activity of nizatidine by formulating floating core tablet. Totally 5 formulation are developed when in this formulation used to the two different polymers like HPMC K4, HPMC K100 individually.

KEYWORDS: GRDDS (Gastero retentive drug delivery system), HPMC, HPMC K.

INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades mainly because of their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.

Nizatidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastroesophageal reflux disease (GERD). Its oral bioavailability is about 70% and biological half life is about 2hrs.

One novel approach in this area is GRDDSs (gastro retentive drug delivery system).Dosage forms that can be retained in the stomachare called GRDDs. GRDDSs can improve the controlled prolonged delivery bycontinuously releasing the drug for a period of time before it reaches its absorptionsite. Prolonging the gastric retention of the drugs issometimes desirable for achieving therapeuticbenefits of drug that are absorbed from theproximalpart of the GIT (gastro intestinal tract) or those are less soluble in or are degraded byalkaline pH or they encounter at the lower part ofthe GIT.

Drugs that are easily absorbed from GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequently dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time After oral administration, such a drug delivery would be retained in the stomach and release the drug in controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT.

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. Therefore the timing of administration of ulcerative medications can significantly influence the therapeutic effects. 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. 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 H2 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.

Approaches to achieve gastric retention

High density (sinking) system or non- floating drug delivery system

This approach involves formulation of dosage forms with the density that must exceed density of normalstomach content (~ 1.004 gm/cm3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc.[22] The materials increase density by up to 1.5-2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time.[23] But, effectiveness of this system in human beings was not observed[24] and no system has been marketed.

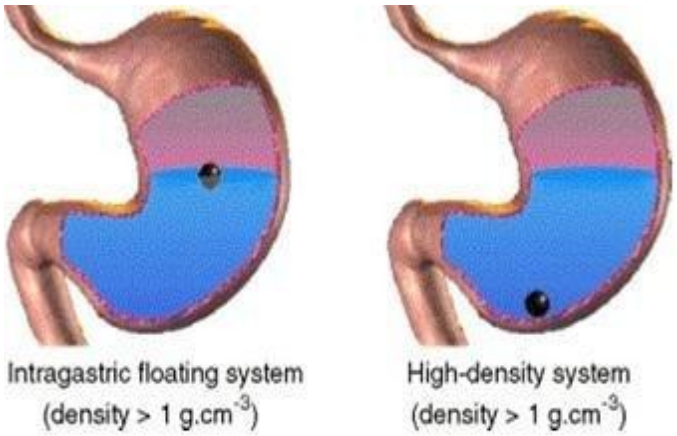

Figure 1: High density system.

Floating drug delivery systems

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability.[25] This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine.[26] This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate fora prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder). These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system waspproposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as stickingtogether or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be anattractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping.Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

Non-effervescent systems

Non-effervescent floating drug delivery systems arenormally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity ofshape and a bulk density less than unity within thegastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into the sub-types:

Hydrodynamically balanced systems

Sheth and Tossounia first designated these ‘hydrodynamically balanced systems’. These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the

stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LP®, based on the system was marketed during the 1980's.Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigatedto improve efficiencies of the floating hydrodynamically balanced systems.

Swelling system

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems', since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state. The balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross – linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

Factors controlling gastric retention of dosage forms

1. **Particle size**

Should be in the range of 1-2 mm to pass through the pyloric valves into the small intestine.

2. **Density**

Density of dosage form should be in range of 1g/cm3 to 2.5g/cm3.

3. **Size**

Size should be greater than 7.5 mm in diameter.

4. Shape of dosage forms

Ring and tetrahedron devices with flexural modulus of 22.5-48 KSI (keto pound/ inch2 show 90-100 % gastric retention times (GRT).

5. Single unit/multiple unit

Multiple units are preferable because of predictable release profile, coadministration of different units, larger safety margins.

6. Food intake

GRT is longer in fed states.

7. Nature, calorie content

Indigestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, Fat and protein meal increases GRT.

8. Frequency of intake

GRT increases 400 times due to low frequency of **MMC**

9. Posture

Varies between spine and upright ambulatory states.

10. Gender

Females have shorter GRT than males.

11. Age

Age > 70 shows longer GRT.

12. Nature of drug

Drugs with impact on gastro intestinal transit time e.g. Codeine and pharmacokinetic agents e.g. metclopramide, cisapride increases GRT.

13. Other factors

- Diseased states of the individual (chronic disease, diabetes etc.)
- Body mass index
- Physical activity
- Molecular weight and lipophilicity of the drug depending on its ionization state.

Advantages of gastroretentive drug delivery systems

1. Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

2. Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

3. Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological halflife, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

4. Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

5. Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

6. Minimization of fluctuations in drug concentration

It makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

7. Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

8. Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

9. Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

10. Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Disadvantages of gastroretentive drug delivery systems

1. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin
2. Unsuitable for drugs that are unstable in acidic environment. E.g. Erythromycin
3. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin & NSAID's
4. Drugs that absorb selectively in colon. E.g. Corticosteroid
5. Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifidipine
6. Floating drug delivery systems require high fluid level in stomach to float and work effectively.

METHODS

Description of nizatidine

5.0 mg of sample was taken in a petri dish and was spread carefully and recorded its colour, odour and texture.

Preformulation study of nizatidine

Preformulation studies were primarily performed to investigate the physicochemical properties of drug and to establish its compatibility with polymers and other excipients. DSC and FTIR spectra of pure drug; and physical mixtures containing drug, polymers and other excipients were produced and compared with each other.

FTIR studies of nizatidine

The FTIR technique can be used to recognize the functional groups in the pure drug and drug-excipient compatibility. Pure Nizatidine FTIR spectra and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and excipients were taken in the ratio 100:1 and mixed by mortar.[11] The samples were made into pellet by the application of pressure. Then the FTIR spectra were recorded between 4000 -400cm−1.

DSC of nizatidine

Calorimetric response of the sample was measured using a DSC instrument (821e Metler-Toledo GmbH) operating with STARe software version 9.1 and equipped with an intra cooler. The instrument was calibrated by using indium. The sample 5.1240 mg were analyzed under dry nitrogen purge (50ml/min) in a sealed and pinhole aluminum pan. The sample is heated from room temperature to 1470C and held for 5 minutes, then the sample is cooled to (- 500C) and held for 15 minutes, and then the sample is again heated to 1520C a constant heating and cooling rate of 100C/min is used. Thermograms were collected during heating. Melting point was determined as the onset of the endothermic peak, where as glass transition temperature is measured as the onset of the glass transition.

Melting point determination

Melting point of Nizatidine was determined by capillary method.Fine powder of Nizatidine was filled in a glass capillary tube. The drug filled capillary tube was inserted into the melting point apparatus and observed the temperature at which drug started to melt by using the thermometer.

Angle of repose

The angle of repose, or critical angle of repose, of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding. The angle of repose can range from 0° to 90°. The morphology of the material affects the angle of repose; smooth, rounded sand grains cannot be piled as steeply as can rough, interlocking sands. The angle of repose can also be affected by additions of solvents. If a small amount of water is able to bridge the gaps between particles, electrostatic attraction of the water to mineral surfaces will increase the angle of repose, and related quantities such as the soil strength.

When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles, and the coefficient of friction of the material. Material with a low angle of repose forms flatter piles than material with a high angle of repose.

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

Where, θ- angle of repose;

h- height of granule above flat surface

r- radius of circle formed by the granule pile. The limit has been presented in table

Table 1.

Flow ability	Angle of repose
Excellent	<25
Good	25-30
Passable	30-40
poor	>40

Bulk density

Bulk density, also called apparent density or volumetric density, is a property of powders, granules, and other "divided" solids, especially used in reference to mineral components (soil, gravel), chemical substances, (pharmaceutical) ingredients, foodstuff, or any other masses of corpuscular or particulate matter. It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume, and internal pore volume. It is expressed in g/ml is given by

$D_b = M/V_0$

Where, M is the mass of powder and V_0 is the bulk volume of powder

Tapped density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample to constant volume is expressed in g/ml and is given by

Dt = M/VT

Where, m is the mass of powder and Vt is the tapped volume of powder

Carr" s compressibility index

The Carr index (also: Carr's index or Carr's Compressibility Index) is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr. The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder.

C=100(1-ρB/ρT)

ρB is the freely settled bulk density of the powder, and ρT is the tapped bulk density of the powder after "tapping down".

Table 2.

Carr's index	
% compressibility	Relative flowability
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Slightly poor
28-35	Poor
35-38	Very poor
>40	Extremely poor

Hausner's ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner (1900–1995). is the tapped and bulk density of the powder.

Hausner's Ratio = p_t / p_0

Where,p_t is the tapped density and p_0 is the bulk density.

Formulation of floating tablet of nizatidine by direct compression technique

Nizatidine was mixed manually in polybags with gastro retentive polymers separately as per formulae and MCC was added as diluent and sodium bicarbonate, citric acid were added as effervescent agents and mixed for 10 mins. The blend was lubricated with magnesium stearate for 3-5 minutes and talc was added as glidant. The mixed blend was then compressed into tablets by direct compression method.

Composition of nizatidine floating tablets

Table 3.

Formulation	F1	F2	F3	F4	F5
Nizatidine	150mg	150mg	150mg	150mg	150mg
Hpmc k15m	100mg	100mg-	100mg	-	-
Hpmc k100m	-	-	-	100mg	100mg
Mcc	45mg	48mg	54mg	48mg	46mg
Nahco3	65mg	60mg	48mg	58mg	62mg
Citric acid	29mg	30mg	35mg	32mg	30mg
Mg. Stearate	7mg	8mg	9mg	8mg	8mg
Talc	4mg	4mg	4mg	4mg	4mg

Post compression parameters

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (600 mg) was extracted in 100 mL of 0.1N HCl. The solution was centrifuged at 3000 rpm for 15 min. The drug content was analysed at 242 nm using a UV/ visible spectroscopy after suitable dilution with 0.1 N HCl.

Weight variation test

Weight variation was carried outto ensure that, each of tabletscontains the proper amount of drug. The test was carried out by weighing the 20 tablets individually using analytical balance, then calculating the average weight, and comparing the individual tablet weights to the average. The percentage of weight variation is calculated by using the following formula.

$$\text{Percentage deviation} = \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$$

Hardness

The resistanceof tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Tablet hardness is defined as the load required crushing or fracture a tablet placed on its edge. Sometime it is also

termed as tablet crushing strength. The hardness test was performed using Monsant type (Make: Singhla) hardness tester. The instrument measures the force required to break the tablet when the force generated by anvils to the tablet. The tablet was placedbetween two anvils; force appliedto the anvils, and the crushing strength that just causes the tablet to break wasrecorded. The crushing strength test was performed on 20 tablets from each formulation.

Friability

For each formulation, the friability of 20 tablets was determined using Roche type friabilator. 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dusts, tablets were re-weighed and friability percentage was calculated usingthe following equation.

$$\text{Friability} = \frac{\text{w intial} - \text{w final}}{\text{w intial}} \times 100$$

Where, $W_{initial}$ = weight of the tablets before test (mg).
W_{final} = weight of the tablets after test (mg).
% Friability of tablets less than 1% is considered acceptable.

In vitro buoyancy studies

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies.

In vitro dissolution studies

The performance of floating formulations has been reported to be greatly affected by physiological conditions such as food transport, gastrointestinal motility, and so on. A study25 on floating mini tablets of atenolol has indicated lower bioavailability of drug. The reason for this lower bioavailability is attributed to small size of the dosage form, causing too short of a residence time and a premature exit from the stomach. The tablets in this investigation are much larger in size and are expected to be retained for longer duration in upper GIT. *In vitro* dissolution studies of all the formulations of floating tablets of nizatidine

were carried out in 0.1N HCl. The study was performed for 24 h and cumulative drug release was calculated at every one hour time interval. *In vitro* dissolution studies of all the formulations are shown in figure 2, 3 and 4. It was observed that the type of polymer influences the drug release pattern. All the formulations contained equal amount of gas generating agent (sodium bi carbonate) and citric acid.A significantly higher rate and extent of drug release was observed from the batches based on HPMC K4M. Varying the amount of HPMC K100M affect the drug release.

Determination of swelling

Previous literature suggested that high swelling results in formation of a good polymer network which in turn may cause retention of tablet in stomach for longer period of time along with uniform drug release. So, it is necessary to study the swelling behavior of the prepared tablets. Tablets (n = 3) were initially weighed, then immersed into beakers containing 150 ml 0.1N HCl at 37 ± 0.5 ºC. After predetermined intervals the tablets were withdrawn blotted to remove excess water and reweighed.[20] Swelling characteristics of the tablets were expressed in terms of weight gain.

$$\% \text{ SI} = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

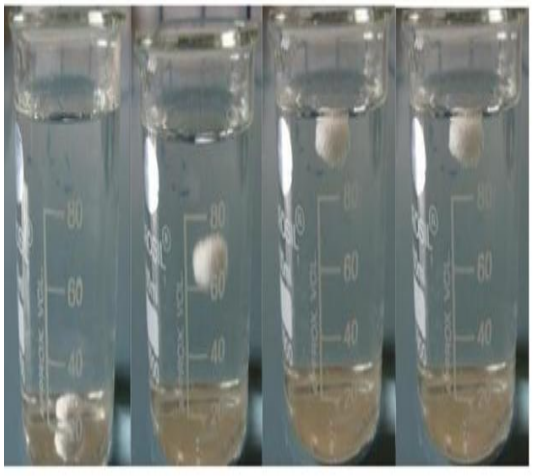

Figure 2: Floating behavior of nizatidine.

Drug release kinetics

To analyze the mechanism of release and release rate kinetics from floating tablets, the obtained dissolution data were fitted into various mathematical models viz., Zero order, First

order, and Higuchi equation. Korsmeyer- Peppas model was also applied to find out the mechanism of drug release.

$Q_t = K_H t^{½}$ (Higuchi equation)

$\log M_t / M_\infty = \log k + n \log t$ (Koresmeyer's Peppas equation)

Where Q_t is the amount of drug released at time t, K_H is the Higuchi dissolution constant, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, k is a constant incorporating structural and geometric characteristics of the drug dosage form and n is the different exponent indicative of the drug release mechanisms. When n is 0.45, the diffusion phenomenon dominates and when n value reaches 0.89 and above, it may be characterized by the case II relaxation release transport and super case II transport. Values of n between 0.45 and 0.89 can be regarded as indicators of anomalous transport.

Moisture uptake studies

Moisture uptake studies for odt should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic.

Moisture uptake studies were carried out by weight method

Method

- ✓ Clean and dry petriplates were taken and their empty weights were recorded.
- ✓ 10 tablets were placed into each petriplates and the total weight of each petriplate with the test substance was recorded.
- ✓ Finally the petriplates were placed in desiccators saturated 75% relative humidity at 25^0 using various standard salt solution.
- ✓ The weights of all petriplates were recorded at the end 1,2,4,6,8,24,48,72 hr.
- ✓ The petriplates were carefully wiped with tissue paper to remove any adhering moisture before the weight was recorded.
- ✓ The percentage of moisture absorption was determined using the formula

$$\left(\frac{wt_1 - wt_2}{wt_2} \right) \times 100,$$

where: wt_1 = weight of initial dried sample

wt_2 = weight of secondarily dried sample

Stability studies

Stability studies are performed in life sciences, chemical, and food and beverage industries to determine the effects of environmental conditions on product quality. Stability studies provide the supporting data that companies use to establish product storage requirements and expiration dating. Common factors that affect this stability include temperature, light, pH, oxidation and enzymatic degradation. Special considerations are also required when dealing with chiral molecules, deuterated internal standards and large biomolecules.

RESULTS AND DISCUSSION

Characterization of Nizatidine

In the present study, an attempt was made to formulate the floating-tablets of Nizatidine.The characterization of drug was done by the melting point,IR Spectroscopy and Differential Scanning Calorimetry.

Melting point determination

The melting point of Nizatidine was found to be 133^0C as measured by melting point apparatus. The reported melting point range for Nizatidine 133-135^0C.

Determination of λ_{max} of Nizatidine

λ_{max} of Nizatidine in 0.1N HCl was found to be 313.5 nm.

Calibration curve of Nizatidine

Standard calibration curve of Nizatidine at the wave- length 313.5 nm is shown in Figure1. It was observed that Nizatidine showed good linearity (r^2 =0.9996) over the range of 5-25µg /mL Hence, calibration curves of Nizatidine were found to obey Beer-Lambert's law over this range.

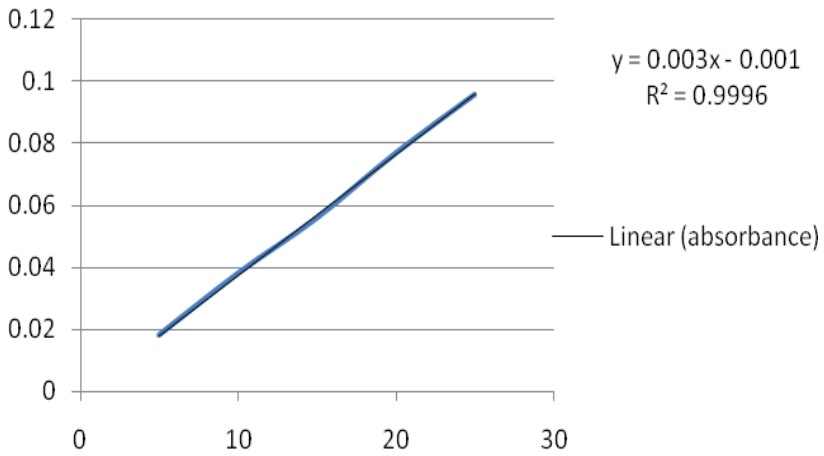

Figure 3.

Calibration curve

Differential scanning calorimetry (DSC) The DSC thermogram of Nizatidine displayed the characteristic peak at 135.91^{0}C compare to its melting point 132^{0}C. Similarly the Eudragit E100 thermogram showed peak at 62.40^{0}C. The physical mixture of the drug and Eudragit E100 showed the DSC thermogram at 132.02^{0}C which reveals that drug is complexed with Eudragit E100. There is a slight shift in melting point because of moisture content.

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.

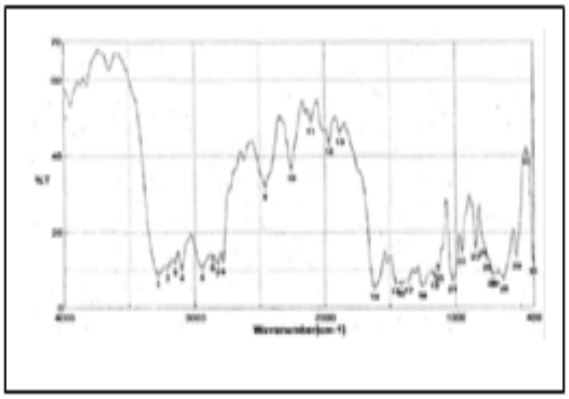

Figure: FTIR spectra of Nizatidine pure drug.

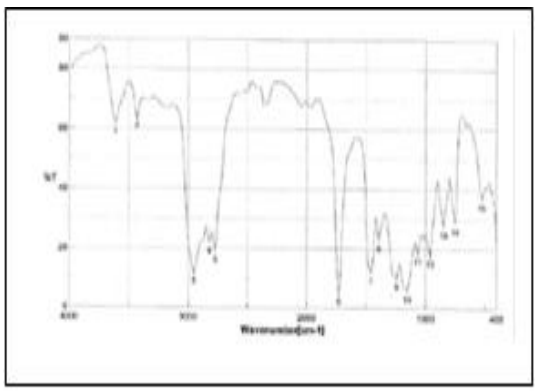

Figure 13: FTIR spectra of optimized formulation.

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 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.

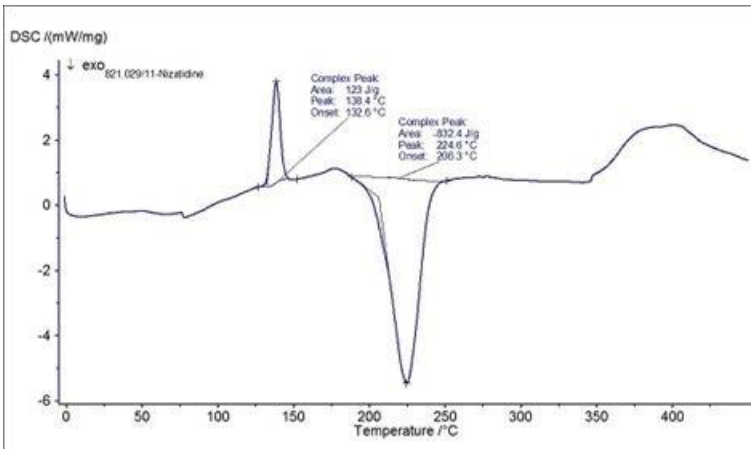

Figure 14: DSC thermogram of pure drug Nizatidine.

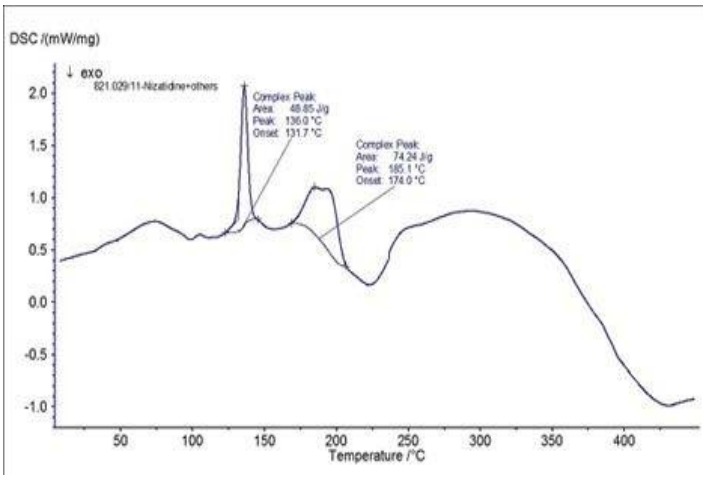

Figure 15: DSC thermogram of optimised formulation.

Table 7: Results of flow properties of core and compression coated tablet blends.

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cc) gm/ cm3) (gm/cm3)	Tapped density (gm/cc)	Carr's index (%)	Hausner ratio (HR)
F1	27.89	0.558	0.654	13.93	1.15
F2	26.79	0.543	0.652	27.24	1.22
F3	24.32	0.524	0.589	14.74	1.15
F4	22.13	0.613	0.674	17.33	1.14
F5	25.33	0.630	0.623	19.22	1.27

Table 8: Mean weight, thickness, friability and drug content of floating tablets.

Formulation	Mean weight	Thickness	Friability	Drug content
F1	392.80 ± 1.00	4.24 ± 0.70	0.50	93.52 ± 0.36
F2	394.70 ± 0.76	4.29 ± 1.20	0.25	94.05 ± 0.47
F3	398.10 ± 0.69	4.30 ± 0.82	0.32	91.03 ± 0.59
F4	390.40 ± 0.75	4.20 ± 0.79	0.98	107.3 ± 1.01
F5	392.40 ± 1.24	4.18 ± 0.62	0.87	109.8 ± 0.75
F6	392.00 ± 0.89	4.26 ± 1.00	0.51	114.8 ± 0.36

Table 9: Floating lag time and floating duration of tablet.

Formulation	Lag time (Sec)	Duration (hrs)
F1	26	More than 12 hrs
F2	134	6.5hrs
F3	34	More than 12 hrs
F4	18	7.5hrs
F5	27	More than 12 hrs

Table no. 9: Results of *in vitro* dissolution studies of Nizatidine floating core tablets.

Time(min)	F1	F2	F3
0	0	0	0
60	44.03± 0.85	41.7 ± 0.63	35.4 ± 0.57
120	54.49 ± 0.93	48.42 ± 0.69	45.60 ± 0.72
180	70.32 ± 0.79	59.31 ± 0.78	56.14 ± 0.82
240	88.82 ± 0.89	75.33 ± 1.04	68.66 ± 0.85
300	98.06 ± 0.63	86.46 ± 0.83	80.83 ± 0.92
360		98.23 ± 0.95	87.09 ± 0.62
420			99.39 ± 0.47

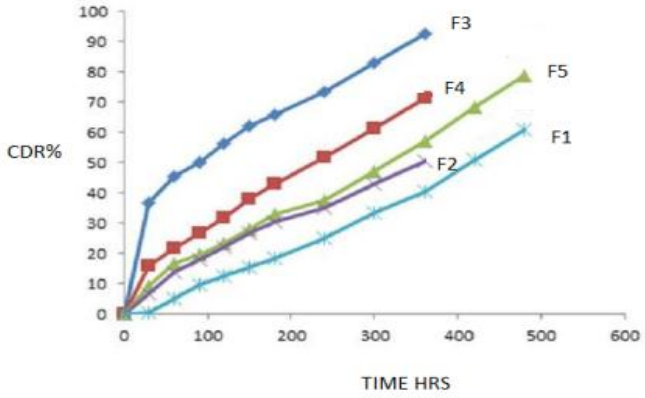

Figure No. 16: Dissolution profile forlmulation.

Drug release kinetic data

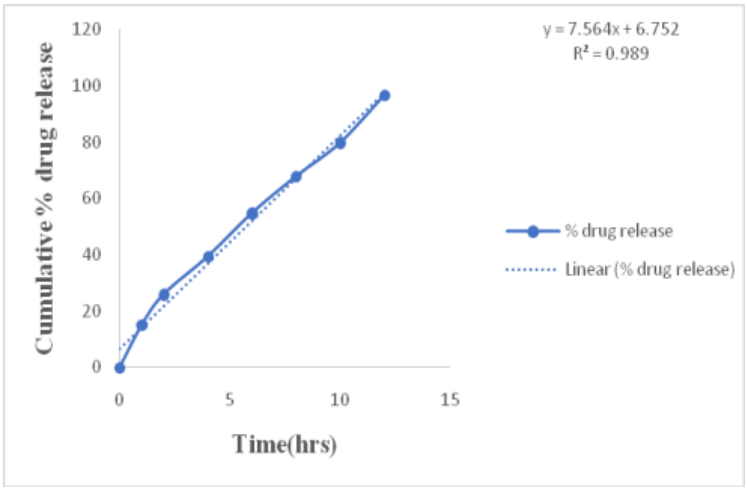

Figure 17: Zero order kinetics of optimized formulation.

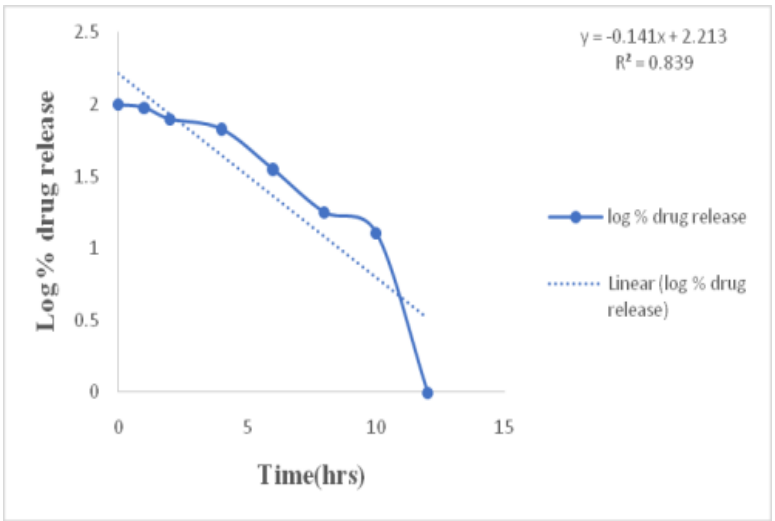

Figure 18: First order plot for the optimized formulation.

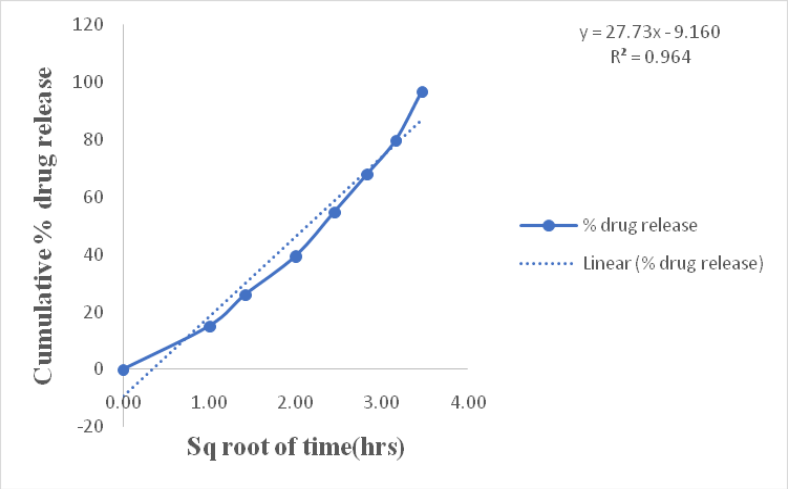

Figure 19: Higuchi model for the optimized formulation.

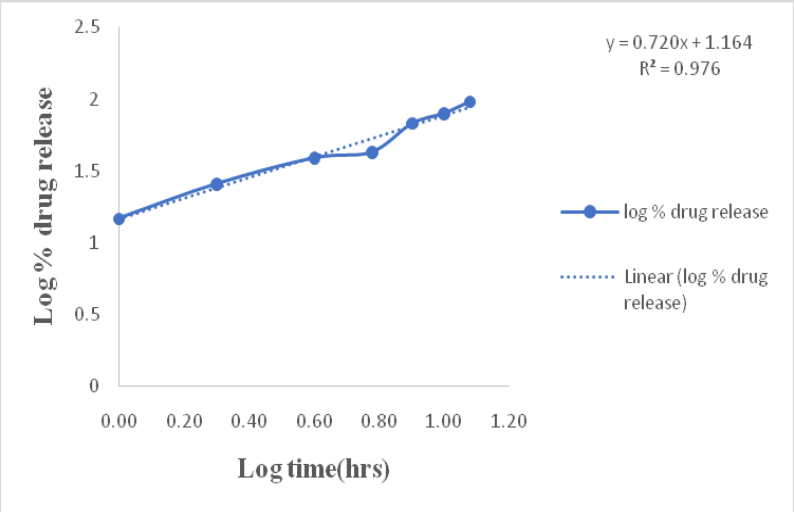

Figure 20: Korsmeyer Peppas model for the optimized formulation.

SUMMARY AND CONCLUSION

The novel gastro retentive delivery systems for Nizatidine were developed and evaluated. The results propose that synthetic polymers like HPMC K15M and HPMC K100M can increase the retention time of formulation in stomach and also can control the drug release from formulation due to matrix formation there by reducing the dose frequency.

It can be concluded that the local action of Nizatidine may be increased in the stomach due to increased retention and absorption by using formulations F1, F3 and F5. The present study demonstrates that Nizatidine could be successfully delivered to provide relief of gastric acidity.

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. The floating tablets containing HPMC K100M (F3) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability and sustained drug release properties.

The optimized formulation F3 followed Higuchi kinetic model and the mechanism of drug release was found to be non-fickian according to krosmeyer- peppas kinetic model. *In vivo* studies conducted on healthy volunteer supported prolonging of the gastric residence time.

BIBILIOGRAPHY

1. Singh BN, Kim KH. "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention", J Control Release, 2000; 63: 235-259.
2. Wells J; Pharmaceutical Preformulation: Aulton ME; Pharmaceutics: The Science of dosage form design. Edinburg, London, Melbourne, Newyork, 1998; 3: 247.
3. Banker GS, Anderson NR; Tablets: Lachman L, Lieberman HA, Kanig JL; The Theory and Practice of Industrial Pharmacy Varghese Publication House, Bombay, 1987; 3: 296-303.
4. Newman AW. Micromeritics: Brittain HG; Physical Characterization of Pharmaceutical Solids. Marcel Dekker Inc, Newyork; Basel, 1995; 70: 271-275.
5. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site specific delivery. Int J Pharma. 1996; 136: 117-139.
6. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv, 2006; 3(2): 217-233.
7. Singh BN and Kim. Floating drug delivery systems: an approach to controlled drug delivery via gastric retention. J. Control. Release, 2000; 63: 235-239.
8. S.J. Hwang, H Park and K Park, "Gastric Retentive Drug Delivery Systems," Critical Reviews in Therapeutic Drug Carrier Systems, 1998; 15(3): 243-284.
9. Streubel A, Siepmann J, Bodmeier R. Multiple unit Gastroretentive drug delivery: a new prepration method for low density microparticle. J Microencapsule, 2003; 20: 329-347.
10. Dehghan Mohamed HG, Khan FN. Gastroretentive Drug Delivery Systems: A Patent Perspective. International Journal of Health Research. March, 2009; 2(1): 23-44.
11. Reynolds, J. E. F. Martindale: The Extra Pharmacopoeia, The Royal Pharmaceutical Society: London, 1996: 1218-1220.

12. Singh BN, Kim KH. "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention", J Control Release, 2000; 63: 235259.
13. Abdul W, Basit A, Michael J, Lacey L.F. International Journal of Pharmaceutics. 2002; 237: 23–33.
14. The British Pharmacopoeia, British Pharmacopoeia Commission, HMSO, LONDON. 2007.
15. Korsmeyer RW, Gurny R, Docler E, Buri P, Peppas NA. J. Pharm. 1983; 15: 25-35.
16. Higuchi.T. J. Pharm. Sci. 1963; 52: 1145-1149.
17. "Stability Testing of New Drug Substances and Products", Eur Medicines Agency, 2003; 1-20.
18. Kumar R, Patil MB, Patil SR, Paschapur MS. "Formulation and Evaluation of Effervescent floating tablet of Famotidine", Int J Pharm Tech Res, 2009; 1(3): 754-763.
19. Costa P, Lobo JMS. "Modeling and Comparison of Dissolution profiles", Eur J Pharm Sci, 2001; 13: 123133.
20. Ninan M, Lu X, Qifang W, Xiangrong Z. Development and evaluation of new sustained-release floating microspheres. Int J Pharm, 2008; 358: 82–90.
21. Garg S, Gupta GD. Progress in controlled gastro retentive delivery systems. Trop. J Pharm Res, 2008; 7(3): 1055-66.
22. Abdul A, Varun J. Formulation, development and in vitro evaluation of candesartan cilexetil mucoadhesive microbeads. Int J Curr Pharm Res, 2012; 4(3): 109-18.
23. Jia-Qing HMD, Richard HH. Pharmacological and pharmacodynamic essentials of H2-receptor antagonists and proton pump inhibitors for the practicing physician. Best practice Res clingastroenterol, 2001; 15(3): 355-70.
24. Takeuchi K, Kawauchi S, Araki H, Ueki S. Stimulation by nizatidine, a histamine H2 – receptor antagonist, of duodenal HCO3- secretion in rats: relation to anti- cholinesterase activity. World J. Gastroenterol, 2000; 6(5): 651-8.
25. Patil JS, Kamalapur MV, Marapur SC, Kadam DV. Ionotropic gelation and polyelectrolyte complexation: The novel techniques to design hydrogel particulate sustained, modulated drug delivery system: A review. Dig J Nanomat Biostruct, 2010; 5(1): 241-8.
26. Patil JS, Kamalapur MV, Marapur SC, Shiralshetti SS, Kadam DV. Ionotropically gelled chitosan-alginate complex hydrogel beads: Preparation, Patil et al., Mucoadhesive Hydrogel Beads of Nizatidinecharacterization and in vitro evaluation. Indian J Pharm Edu Res, 2012; 46(1): 248-52.

27. Patil JS, Kamalapur MV, Marapur SC, Shiralshetti SS. Ionotropically gelled novel hydrogel beads: Preparation, characterization and in vitro evaluation. Indian J. Pharm. Sci, 2011; 73(5): 504-09.
28. Bhanja S, Sudhakar M, Neelima V, Roy H. Development and evaluation of mucoadhesive microspheres of Irbesartan. Int J Pharm Res Health Sci. 2013; 1: 17-26.
29. Higuchi WI. Analysis of data on the medicament release from ointments. J Pharm Sci. 1962; 51(8): 802-4.
30. Costa P, Lobo JS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci, 2001; 13(2): 123-33.
31. Sherina VM, Santhi K, Sajeeth CI. Formulation and evaluation of sodium alginate microbeads as a carrier for the controlled release nifedipine. Int J Pharm Chem Sci, 2012; 1: 699-710.
32. Farhana Y, Talukdar MU, Islam MS, Laila S. Evaluation of aceclofenac loaded agarose beads prepared by ionotropic gelation method. Stamford J Pharm Sci, 2008; 1(1): 10-7.
33. Ghareeb MM, Issa AA, Hussein AA. Preparation and characterization of Cinnarizine floating oil entrapped calcium alginate beads. Int J Pharm Sci Res, 2012; 3: 501-8.
34. Verma A, Sharma M, Verma N, Pandit JK. Floating alginate beads: studies on formulation factors for improved drug entrapment efficiency and in vitro release. Farmacia, 2013; 61(1): 143-61.
35. Murali N, Rao G, Reddy VP. AAPS Pharm Sci Tech, 2008; 9: 1.
36. Bertram U, Bodmeier R. Eur. J. Pharm. Sci, 2006; 27: 62–71.
37. Barzegar-Jalali M, Maleki N, Garjani A, Khandar AA, Haji-Hosseinloo M, Jabbari R, Drug Dev Ind Pharm, 2002; 28: 681-686.
38. Mohammed FA, and Khedr H. Drug Dev. Ind. Pharm, 2003; 293: 321–337.
39. Susan R, Orenstein MD, David A, Gremse MD, Carmela D. Pantalem BS, Douglas F. Kling MBA, Keith S. Rotenburg. Clinical therapeutics, 2005; 27: 4.
40. Abdul W, Basit A, Michael J, Lacey L.F. International Journal of Pharmaceutics. 2002; 237: 23–33.
41. Hwang SJ, Park H, Park K. Drug Carrier Syst, 1998; 15: 243–284.
42. Ray NC, Hsiu OH, Chiao YY, Ming TS. Eur. J. Pharm. Sci, 2010; 39: 82-89.