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Research Article

# Formulation and evaluation of floating mucoadhesive beads of Nizatidine

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**ABSTRACT**

An objective of the present study was to develop alginate/hydroxypropyl methylcellulose (HPMC)/chitosan based floating-mucoadhesive beads of Nizatidine to provide prolonged contact time of drug to treat gastric disorders. Floating-mucoadhesive beads were prepared and characterized for *invivo* performance in rabits. Beads were prepared by ionic gelation technique where calcium chloride used as gelating agent. Prepared beads were evaluated extensively for particle size, drug entrapment; swelling and surface morphology by using scanning electron microscopy, in vitro mucoadhesion using rat stomach mucosal membrane and *invitro* drug release studies were carried out. Alginate-HPMC-chitosan beads may be suitable floating-mucoadhesive drug delivery system for delivering Nizatidine to treat gastric disorders**.**

**Keywords:** Beads; alginate; hydroxyl propyl methyl cellulose; chitosan; floating- mucoadhesion; Nizatidine

## INTRODUCTION

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal.

Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. .Various approaches have been made to prolong the retention time of dosage form in the stomach. Retention of drug delivery system with prolonged overall gastrointestinal transit time and slow but complete release in the stomach improves bioavailability of drugs that have site specific absorption from stomach.The gastro-retentive formulation can be retained in the stomach to aid in improving oral prolonged delivery of the drugs that have an absorption window in particular area of gastrointestinal tract. Hence, such system helps in continuously releasing the drug while reaching the absorption window, ensuring maximum bioavailability. These considerations have led to the development of oral sustained release (SR) dosage forms possessing retention capabilities. There are different approaches such as bioadhesive system, swelling and expanding system, floating system and delayed gastric emptying system have continuously releasing the drug while reaching the absorption window ensuring maximum bioavailability (Brahmankar D et al., 2009; Chein Y.W).

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## MULTIPARTICULATE SYSTEM

Multiparticulate drug delivery system applies specially to multiple particles such as pellets, beads, microspheres, microcapsules. In recent years, multiparticulate dosage forms or micro particles have gained in popularity for a variety of reasons. Conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level. These have a disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. These single unit dosage forms have the disadvantage of a release all or nothing during emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro-retentive floating microspheres, floating beads

and floating granules. Multi- particulate drug delivery systems are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. The system is based on the expansion of the core (non effervescent FDDS or low density approach), which lead to floating due to low density. Also the air entrapped by the swollen polymer confers buoyancy to this dosage forms. Multiparticulate carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. The success of these microspheres is limited due to their short residence time at the site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling gastro retentive and bioadhesion characteristics to multiparticulates and developing gastro retentive bioadhesive multiparticulates. These multiparticulates have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.It is stated that, 'the multiparticulates' float on the stomach contents, and then adhere to the mucous linings as the stomach empties. The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the stomach. The floating multiparticulate oral sustained release drug delivery system have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site (Somwanshi S et al., 2011; Dhole A et al., 2011; Gattani S et al., 2012; Patel D et al., 2011).

## MATERIALS

Nizatidine was obtained from Lupine Ltd.,Pune Maharashtra as a gift sample. Hydroxy propyl methyl cellulose from Colorcon Ltd., Goa, India, chitosan from Research-Lab, Mumbai, Sodium alginate from FDC Pharma India.

## METHODS

### Experimental Design

A $3^2$ full Factorial design was constructed where the amounts of HPMC ($X_1$) & Chitosan ($X_2$) were selected as factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. All other formulation and processing variable were kept constant throughout the study (Narkar M et al., 2010; Vaithiyalingam S et al., 2002 ).

**Table 1: Factor combination as per the experimental design for Nizatidine**

| Formulations | Coded value | |
|---|---|---|
| | X1 | X2 |
| F1 | 0 | 1 |
| F2 | -1 | -1 |
| F3 | -1 | 0 |
| F4 | 0 | 0 |
| F5 | 1 | 0 |
| F6 | 1 | -1 |
| F7 | 1 | 1 |
| F8 | -1 | 1 |
| F9 | 0 | -1 |

**Table 2: Translation of experimental conditions into physical units for Nizatidine**

| Coded Levels | Actual Levels | |
|---|---|---|
| | $X_1$ (%) | $X_2$ (%) |
| -1 | 0.25 | 0.25 |
| 0 | 0.50 | 0.5 |
| 1 | 1 | 1 |

X1= Conc. of HPMC; X2= Conc. of chitosan

### Method of Preparation of Floating-Mucoadhesive Beads

Beads were prepared (Table 3) by ionotropic gelation method. Sodium alginate (3% w/v) was dissolved in 50 ml of distilled water with agitation and HPMC K4M (0.25/0.5/1%w/v) was added with slow stirring.

Simultaneously Nizatidine (3%) added to the above solution. Solution containing drug was added dropwise into calcium chloride solution containing chitosan and left at room temperature for 30min. The resultant hydrogel beads were washed twice with 50 ml of distilled water and dried at room temperature for 24 h. Coagulation fluid was prepared by mixing in an equal volume of chitosan (0.25/0.5/1%w/v) dissolved in 1% (v/v) acetic acid and 2% (w/v) calcium chloride solution (Gattani S et al., 2010; Teerawat S et al., 2010; Fursule R et al., 2009).

## EVALUATION OF FLOATING-MUCOADHESIVE BEADS

### Size Analysis

Alginate/HPMC/chitosan containing Nizatidine beads were evaluated for particle size. The bead sizes were taken for particle size analysis and average particle size was determined (Gattani S et al., 2010).

### Morphological Analysis/SEM

Surface and cross-sectional morphologies of beads were examined with the Scanning Electron Microscope (SEM) (JSM- 5310LV, Joel,). Beads were mounted on metal grids using double-sided tape and gold coated under vacuum (Gattani S et al., 2010; Patil A et al., 2010).

**Table 3: Formulation Composition for drug loaded beads**

| Sr No. | Ingredient | Quantity in % (w/v) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | Nizatidine | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 2 | Sodium alginate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 3 | HPMC | 0.5 | 0.25 | 0.25 | 0.5 | 1 | 1 | 1 | 0.25 | 0.5 |
| 4 | Chitosan | 1 | 0.25 | 0.5 | 0.5 | 0.5 | 0.25 | 1 | 1 | 0.25 |
| 5 | Calcium chloride | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

**Table 4: Results of batches of Nizatidine loaded floating-mucoadhesive beads**

| Batch | % Entrapment efficiency * | % Mucoadhe-sion | % Drug Release * | % Buoyan-cy | % Sweling Index * |
|---|---|---|---|---|---|
| F1 | 87.17±1.53 | 98 | 83.14±1.93 | 91 | 147±1.76 |
| F2 | 79.02±1.07 | 95 | 95.14±2.08 | 88 | 137±2.11 |
| F3 | 83.28±1.88 | 92 | 96.41±2.10 | 90 | 132±2.08 |
| F4 | 86.99±1.56 | 99 | 98.16±1.34 | 99 | 150±1.87 |
| F5 | 85.43±2.08 | 96 | 85.15±1.05 | 97 | 158±1.09 |
| F6 | 77.18±1.96 | 95 | 88.41±1.26 | 94 | 162±1.14 |
| F7 | 88.48±1.55 | 99 | 74.55±2.09 | 90 | 153±1.25 |
| F8 | 87.09±1.34 | 98 | 91.57±2.11 | 88 | 130±1.88 |
| F9 | 80.08±1.56 | 94 | 92.68±1.63 | 93 | 152±1.23 |

*All values are expressed as Mean ±SD, n = 3

**Table 5: Result of optimized batch F4 after three months storage**

| Days | % Drug release* | % mucoadhesion | Floating duration (hrs.) |
|---|---|---|---|
| Before Storage | | | |
| 0 | 98.16±1.34 | 99% | >12 |
| After Storage | | | |
| 30 | 97.89±1.08 | 96% | >12 |
| 60 | 97.87±1.84 | 97% | >12 |
| 90 | 96.06±2.08 | 95% | >12 |

**Buoyancy Study**

Buoyancy test was carried out using USPXXII dissolution test apparatus. Each dissolution jar was filled with 0.1 M HCl solution (pH 1.2, 900 ml) and maintained at temperature 37±0.5°C. Fifty beads were added in each jar and stirred with paddle at 50 rpm for 12h, floating lag time & beads remaining buoyant in 0.1 M HCl solution are observed visually and calculated the % buoyancy (Fursule R et al., 2009).

**Drug Loading and Encapsulation Efficiency**

The beads (100 mg) loaded with Nizatidine were added in 0.1 M HCl solution (pH 1.2) under stirring. The mixture was filtered with the Whatman filter paper and the amount of Nizatidine was determined spectrophotometrically at 313.5nm. The concentration in the sample was used to calculate the loading by dividing the weight of beads initially added. The Nizatidine encapsulation efficiency was estimated according to the formula (Teerawat S et al., 2010).

$$\% \, Drug \; content = \frac{DW}{TW} \times 100$$

Where, DW – amount of drug found in total dried beads; TW - Total weight of dried Beads.

$$\% \, Entrapment \; efficiency = \frac{AQ}{TQ} \times 100$$

Where, AQ- Actual amount of drug found in the beads; TQ- Theoretical amount of drug found in the beads

**Swelling Study**

Swelling behaviour of beads can be determined by their water absorbing capacity. Swelling study was done by using USP XXII dissolution test apparatus. Two-fifty milligrams of the dry beads kept in muslin cloth and tied to the lower end of the paddle and immersed in acid buffer (pH 1.2). One and two hours time interval beads were withdrawn from muslin cloth and wiped gently with tissue paper and weighted. Same procedure was continued up to 10 h. to calculate percentage erosion. After 10 h. beads were separated from the medium using stainless steel grid, wiped gently and dried for 24 h. at 30 °C and weighted. The percentage swelling was calculated according to the equation given below (Narkar M al., 2010).

$$Swelling \; index = \frac{(Wg - Wo)}{Wo} \times 100$$

Where, $W_o$ is the initial weight of beads; $W_g$ is the weight of beads at equilibrium swelling in the medium.

### *In Vitro* Drug Release Study

The drug release profiles of Nizatidine loaded beads were carried out in 0.1 M HCl solution (pH 1.2, 900 ml) at 37±0.5 °C using a USP XXII dissolution test apparatus (Electrolab, EDT08, India, paddle method). The rotation speed of the paddle was adjusted to 100 rpm for homogenous dispersion of gel beads in dissolution medium. An aliquot of 5 ml was withdrawn periodically from test solution and replaced with 5 ml of fresh medium maintained at 37±0.5°C and assayed spectrophotometrically at 313.5 nm (UV-1800, Shimadzu, Japan) for 12h. All drug release profiles were performed in triplicate. Percentage drug release was calculated using PCP Disso Software (Poona College of Pharmacy, Pune). In order to investigate the drug release mechanism, the release data were fitted to models representation zero order, first-order, Higuchi and Peppas–Korsemeyer equation (Narkar M et al., 2010; Gattani S et al., 2010).

### *In Vitro* Mucoadhesion Studies

In vitro mucoadhesion studies were carried out using rat stomach mucosa by the reported method with necessary modifications. Overnight fasted male rats (200—250 g) were sacrificed and stomach mucosa was excised and washed with physiological saline at the rate (5 to 10 ml/min for 10 min, then 20 to 30 ml/min for ca. 20 min) by using peristaltic pump. About 500 ml of physiological saline was used for cleaning the mucosa. After 15 min the mucosa was held in inclined position. Mucosa was fixed to the glass slide with the cynoacrylate glue and about 50 beads ($N_0$) hydrated with little amount of water and dispersed on the mucosal tissue and left on it for 20 min for the interaction with the mucosal surface. During this period whole system was placed in a constant humidity chamber which was adjusted to 90% relative humidity. At the end, the system was washed with 0.1 M HCl solution (pH 1.2) at the rate of 22 ml/min using a peristaltic pump. After 20 min beads detached from the mucosa (Ns) were observed visually and percent mucoadhesion was calculated by the following equation (Gattani S et al., 2010; Teerawat S et al., 2010).

$$\%\, mucoadhesion = \frac{N0 - Ns}{N0} \times 100$$

Where, $N_0$= amt of beads taken; $N_s$= amt of beads detached from mucosa.

### X-ray powder diffraction

To understand XRD pattern of pure drug and optimized formulation, a Philips 1710 X-ray Diffractometer (XRD) with a copper target and nickel filter was used to obtain XRD result for the samples. Powder were mounted on aluminum stages with glass bottoms and smoothed to a level surface. The XRD pattern of each sample was measured from 10- $50^0$ (2θ) using a step increment of $0.1^0$ (2 θ) and a dwell time of 1 second at each step (Patil A et al., 2010).

### Differential scanning calorimetry

The physical state of the Nizatidine encapsulated in microbeads was characterized using a differential scanning calorimetric (DSC) thermogram analysis (Shimadzu, DSC-50). Each sample (~10 mg) was sealed separately in a standard aluminum pan, the samples were purged in DSC with pure dry nitrogen set at a flow rate of 10 ml/minute, the temperature speed was set at 10°C/minute, and the heat flow was recorded from 0 to 250°C (Patil A et al., 2010).

### Stability study

The stability studies for beads were done by keeping the sample beads from optimized batches for 3 months. The beads were pack in container and kept in humidity chamber maintained at 40˚C ± 2˚C temperature and 75% ± 5% relative humidity for 3 months. At the end of 3 months the sample were analyzed for different parameters like physical appearance, % drug release, floating duration, % mucoadhesion.

## RESULTS AND DISCUSSION

### Characterization of Nizatidine

In the present study, an attempt was made to formulate the floating-mucoadhesive beads of Nizatidine using HPMC, chitosan and sodium alginate polymers. The characterization of drug was done by the melting point, UV, IR Spectroscopy and Differential Scanning Calorimetry.

### Melting point determination

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

### Determination of $\lambda_{max}$ of Nizatidine

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

### Calibration curve of Nizatidine

Standard calibration curve of Nizatidine at the wavelength 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.

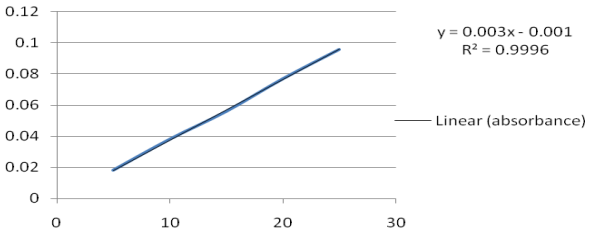


**Figure 1: Standard calibration curve of Nizatidine in 0.1 N HCl**

### Differential Scanning Calorimetry (DSC)

The results of DSC study are shown in figure 2. DSC thermograms showed endothermic peak of Nizatidine at 133$^0$C, which corresponds to its melting point. DSC is a fast and reliable method for understanding polymorphic transitions when screening drugs and excipients for compatibility, obtaining information about possible interactions. The absence of detectable crystalline domains of Nizatidine loaded microbeads clearly indicates that Nizatidine was dispersed completely in the formulation, thus modifying the microbeads to an amorphous, disordered-crystalline phase. DSC analysis was performed on native Niztidine, Placebo microbeads and Nizatidine loaded microbeads. The DSC heating curves were recorded as a plot of enthalpy (m/w) *vs.* temperature. The results are shown in Fig.2 for native Nizatidine, Fig.3 for placebo microbeads, Fig.4 for Nizatidine loaded microbeads. The endothermic peak of native Nizatidine was found approximately at 133$^0$C. This characteristic peak was not observed in Nizatidine loaded microbeads. The absence of detectable crystalline domains of Nizatidine in drug-loaded microbeads clearly indicates that Nizatidine encapsulated in microbeads is in the amorphous or disordered-crystalline phase or in the solid-state solubilized form in the polymer matrix.

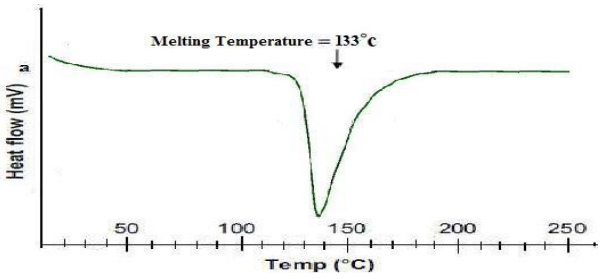


**Figure 2: DSC thermogram of Nizatidine**

The endothermic peak of Polymer was found approximately at ~52ºC in placebo microbeads and ~56ºC drug-loaded microbeads due to glass transition temperature (Tg) of Polymer.

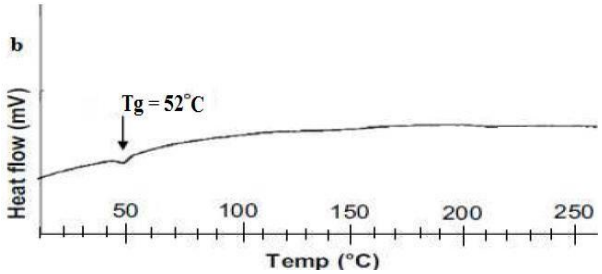


**Figure 3: DSC curve of Placebo microbeads**

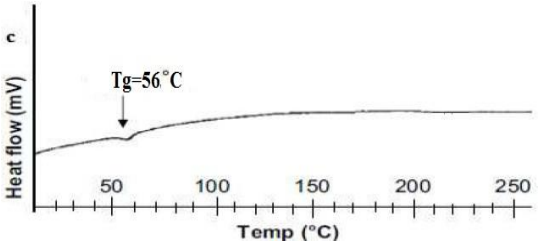


**Figure 4: DSC curve of Nizatidine loaded microbeads**

**XRD analysis**

XRD analysis provides the crystal lattice arrangements and produces important information regarding the degree of crystallinity in the formulations. The XRD pattern of free Nizatidine (A), Placebo microbeads (B), physical mixture of Nizatidine and placebo microbeads (C) were obtained as shown in Fig.5. Therefore, it can be anticipated that Nizatidine is present in an amorphous state in the microbeads formulations.

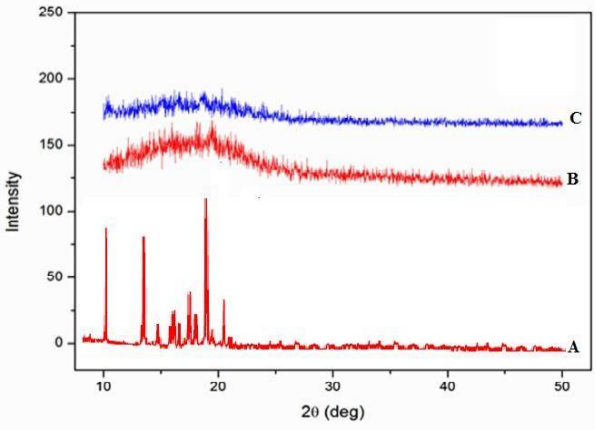


**Figure 5: XRD of A) pure drug Nizatidine B) Placebo microbeads C) Nizatidine loaded microbeads**

**Drug and Excipient compatibility study**

The IR spectra of drug and various polymers is recorded in combination with each other. IR spectra showed in Figure 6. There was no any evidence of interaction between drug and excipients.

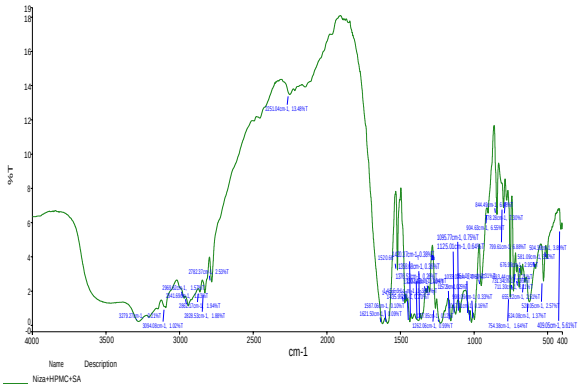


**Figure 6: FTIR spectrum of drug and excipients**

**Formulation and evaluation of floating mucoadhesive beads**

Total nine batches of Nizatidine loaded floating-mucoadhesive beads were prepared and these batches were evaluated for % Entrapment efficiency, % mucoadhesion, % drug release as shown in Table 4.

**Size analysis**

There was significant variation in particle size among the different batches of dried beads. Beads showed size range from 1mm- 1.5mm.

**Buoyancy study**

Alginate beads coated with chitosan showed high floating ability (88%-99%), with an optimal chitosan concentration of 0.5% (w/v) with 99% floating beads. The lower chitosan concentration may be insufficient to protect air bubbles inside the beads from the surrounding medium, leading to sinking. Higher (1% w/v) chitosan showed similar floating ability to 0.25% (w/v) chitosan due to a higher concentration of coagulation fluid, which yielded larger, thicker beads. The thicker chitosan skin may cause solution uptake, resulting in a higher bulk density than the external medium and sinking (Table 4). Formulation F2, F3, F8 contains less conc. of HPMC therefore they show less buoyancy.

**Drug Entrapment efficiency**

Drug encapsulation efficiency was 77.18 % to 88.48%. Concentration of chitosan had impact on drug entrapment. Chitosan concentration increases then entrapment efficiency increases because of gel structure. Chitosan combination with HPMC increases drug entrapment efficiency. It was due to the higher degree of firmness in the alginate-chitosan complex during the gelation process caused by ionic interactions between the carboxylate groups in the alginate and the protonated amine groups in the chitosan. Varying chitosan levels (0.25% -1.0% w/v) also affected EE with higher chitosan concentrations causing a higher EE. Higher levels of chitosan probably increased coagulant viscosity and reduced the diffusion rate of the drug trapped in the beads. Therefore F1, F7, F8 show high entrapment efficiency (Table 4).

**%Swelling Index**

Swelling of the beads was measured on the basis of the water absorbing capacity. Formulation F5, F6, F7 showed higher swelling might be due to HPMC. Formulation F1, F8 show less swelling due to high concentration of chitosan. HPMC increases the swelling of beads and chitosan decreases the swelling (Table 4).

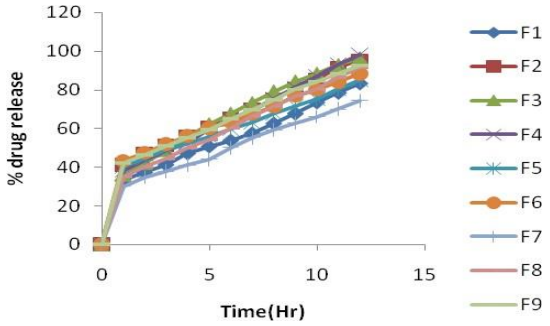


**Figure 7: Drug release profile of Nizatidine from bead formulations F1-F9**

***In vitro* drug release study**

It was found that formulations F4 showed highest release 98.16%, and F7 show less release (Table 4). Release rate depend on both chitosan as well as HPMC polymer. Dissolution study shows that as the concentration of chitosan increased the % drug release of drug decreased HPMC sustain the drug release. Chitosan concentration increases then decrease the initial burst release of the drug from beads and retard the release of drug (Figure 7).

***In Vitro* Mucoadhesion Study**

Mucoadhesive drug delivery can improve drug effectiveness by targeting them at a specific site. Mucoadhesion study was done as shown in figure 8. HPMC and chitosan both show Mucoadhesive property. Formulation F7 shows 99% mucoadhesion. Beads with 1% (w/v) chitosan (F1 and F7) remained on the gastric mucosa indicating that chitosan facilitates gastric adherence, as reported previously, due to the strong electrostatic attraction between the positively charged chitosan and the negatively charged mucal glycoproteins. HPMC increases the mucoadhesive property of the beads.

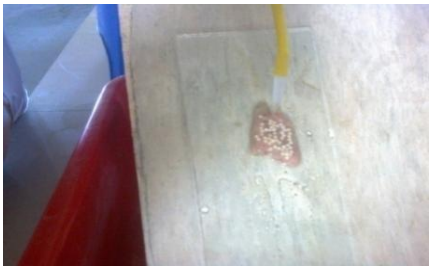

**Figure 8: In Vitro mucoadhesion test**

**Morphology of beads**

Careful examination of representative beads of formulation using SEM microscopy revealed more detail information regarding their external and internal morphological features. As it can be seen from the SEM images (Figure 9) the beads presented a rough surface with characteristic large wrinkles and micropores due to chitosan.

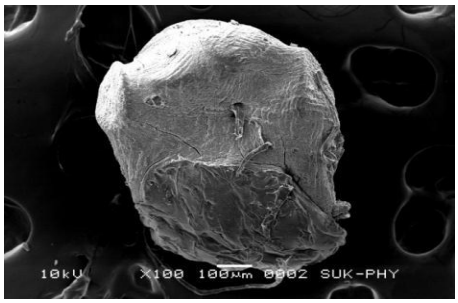


**Figure 9: Scanning electron microphotographs of F4 Beads**

**Stability study**

The stability studies for beads were done by keeping the sample beads from optimized batches for 3 months. The beads were pack in container and kept in humidity chamber maintained at 40˚C ± 2˚C temperature and 75% ± 5% relative humidity for 3 months. At the end of 3 months the sample were analyzed for different parameters like physical appearance, % drug release, floating duration, % mucoadhesion.

## CONCLUSION

From the experimental results it can be concluded that Infrared spectroscopy studies of Nizatidine, sodium alginate, chitosan, HPMC K4M alone and their physical mixture revealed that, Nizatidine was compatible with all the polymers used. From *in-vitro* mucoadhesion study it was evident that the F4 and F7 formulation showed better mucoadhesion effect. Sodium alginate beads prepared with 0.5% HPMC and 0.5% chitosan showed better floating and Mucoadhesive property. *In-vitro* release study of F4 indicated that Nizatidine was released in sustained manner up to 12 hours. So sodium alginate/HPMC/chitosan beads of Nizatidine were potential candidate to prolong the residence time in stomach.

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