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Research Article

Design and *In Vitro* Evaluation of Mucoadhesive Floating Hollow Microspheres of Nizatidine with Gastroretentive Properties

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ABSTRACT

In the present investigation a novel oral drug delivery system was developed utilizing the concepts of controlled release and mucoadhesiveness, in order to obtain a unique drug delivery system which could remain in the stomach and control the drug release for an extended period of time. Nizatidine microspheres were prepared by emulsification-ionic gelation technique employing sodium alginate with mucoadhesive polymers such as Carbopol 934P and Hydroxypropyl methylcellulose. The prepared formulations were subjected to particle size and shape analysis, % drug entrapment efficiency, *in vitro* floatability, swelling rate, *in vitro* mucoadhesion and *in vitro* drug release studies. The prepared microspheres were discrete, spherical with a mean particle size in the range of 451 ± 1.21 µm to 645 ± 2.24 µm. Entrapment efficiency was found to be in the range of 77.4 ± 3.02% to 85.2 ± 0.56%. Formulations containing Carbopol 934P showed increased *in vitro* mucoadhesion compared to formulations with Hydroxypropyl methylcellulose. The % *in vitro* floating decreased and swelling rate increased with increase in the mucoadhesive polymer content at the end of 12 h. *In vitro* drug release for all the formulations in 0.1N HCl was diffusion controlled gradually over a period of 12 h and followed First order kinetics. The *in vitro* drug release mechanism was non-fickian type controlled by swelling and relaxation of polymer. There was no significant change in physico-chemical characteristics of the microspheres stored at different storage condition after 3 months of stability study. The developed system has the dual advantages of being gastroretentive, to increase oral bioavailability and releasing drug in a controlled manner, to reduce the required frequency of administration thereby promoting patient compliance.

INTRODUCTION

Sustained release oral drug delivery systems are the most common and popular dosage forms for drug administration, due to excellent patient compliance and dose reliable properties. However, good drug bioavailability is a major problem in the development of sustained release oral drug delivery systems. The drug bioavailability of pharmaceutical dosage forms is influenced by numerous factors [1]. One of the most important factor is the gastric residence time (GRT) of the dosage forms. A short gastric emptying time results in an incomplete release of the drug from the dosage form leading to decreased efficacy of the administered dose [2].

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Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastricretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [3]. Several approaches are being designed and developed for increasing the residence time of dosage form in the GIT such as: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid [4], mucoadhesive systems, unfoldable, extendible, or swellable systems, superporous hydrogel

systems [5], magnetic systems [6] etc. The other various floating preparations such as microballoons, granules, foam powders [7], capsules, tablets, *in situ* gelling systems [8] and laminated films are also attempted. An excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in stomach is sufficiently high; however, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded [9]. This serious limitation can be overcome by the use of bioadhesive polymers to enable it to adhere to the mucous lining of stomach wall [10]. Therefore, a synergic drug delivery system combining buoyancy and mucoadhesion may overcome these problems and prove more effective in treating gastric disease [11].

Floating and bioadhesive drug delivery systems offer the advantages of increased contact time with stomach mucosa, more effective absorption and bioavailability of drugs with absorption windows near proximal intestine and stomach, and low dosing frequencies[12]. Amongst the various floating and bioadhesive drug delivery approaches, mucoadhesive hollow microspheres is an attractive concept in which the dosage form adhere to the mucus layer, prolonging the drug residence time in the GI tract and release the loaded drug in a sustained manner.

Mucoadhesive hollow microspheres upon contact with the gastric fluid, hydrate to form a colloidal gel barrier that controls the rate of fluid penetration and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres [13]. The intimate contact of the mucoadhesive polymer with the mucus surface results in an increased drug retention time and drug concentration in the GI tract. Medication is released from microspheres by drug leaching from the polymer or by degradation of the polymer matrix [14].

In the present investigation, Nizatidine (NIZ), a H2 receptor antagonist, was used as a model drug. NIZ is a competitive inhibitor of gastric acid secretion and is used for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer and active duodenal ulcers. It is having an oral bioavailability of 70% with a very short biological half life of 1-2 hours [15]. It mainly acts by inhibiting acid production by reversibly competing with histamine. Oral administration of NIZ in the form of fast dissolving films [16] and immediate release tablets [17] has already been reported. With the conventional dosage forms of NIZ, the treatment becomes ineffective in some patients with reflux oesophagitis who are being treated with proton pump inhibitors and may continue to produce acid secretion throughout night (nocturnal acid breakthrough) and could be benefited by taking a sustained release formulation of H2 receptor antagonist.

Sodium alginate (SA) is a hydrophilic, colloidal polysaccharide obtained from brown algae. It is a linear polymer of D-mannosyluronic acid and L-gulusyluronic acid residues and a macromolecular electrolyte that has one carboxyl group per constituent unit. The gelation and cross-linking are due to stacking of the guluronic acid blocks of alginate chain with formation of an egg-box junction and it depends on the inorganic ion/ alginate ratio. Therefore; alginate is used as an immobilization matrix for cells and enzymes as well as pharmaceutical and food adjuvants [18]. Bioadhesive characteristics to the microspheres were imparted by employing mucoadhesive polymers like Carbopol 934P (C 934P) and Hydroxypropyl methylcellulose (HPMC).

The objective of the study was to design mucoadhesive hollow microspheres containing NIZ with gastroretentive properties, with an aim to improve oral bioavailability of the drug, and the ability to provide a sustained release profile.

MATERIALS AND METHODS

Nizatidine was obtained as a gift sample from Hulcin Research Limited, Chennai. Sodium alginate, Hydroxypropyl methylcellulose (50 cps) and calcium chloride were procured from Finar Chemicals Private Limited, Ahmedabad, Colorcon Asia Pvt. Ltd, Goa and Sisco Research Labs Private Limited, Mumbai respectively. Carbopol 934P was purchased from Noveon Chemicals, Mumbai and Liquid Paraffin (light & heavy) was purchased from Qualigens Fine Chemicals. All other reagents used were of analytical grade.

Preparation of mucoadhesive microspheres:

Mucoadhesive microspheres containing NIZ were prepared using emulsification – ionic gelation technique [19]. SA (1.0 g) and the mucoadhesive polymer (1.0 g) were dissolved in 32 ml of distilled water to form a homogeneous solution. NIZ was added to the polymer solution

and mixed homogenously to get a smooth viscous dispersion. The resulting dispersion was then added in a thin stream to about 100 ml light liquid paraffin contained in a 500 ml beaker, stirring with 1000 rpm for 15 min to emulsify the added dispersion as fine droplets. Calcium chloride (10 % w/v) solution (40 ml) was then added slowly while stirring for ionic gelation (or curing) reaction. Stirring was continued for 1 h to complete the curing reaction and to produce spherical microspheres. The mixture was then centrifuged and the microspheres thus separated were washed repeatedly with ethanol. The microspheres were dried at 45^{0}C for 4 h and kept in desiccators for one day. Different formulations were prepared using sodium alginate and the mucoadhesive polymers viz. Carbopol 934P and HPMC 50 cps, in the ratio 1:1, 1:1.5 and 1:2 while keeping the amount of drug (0.5 g) constant. The composition of different formulations is represented in Table 1.

Evaluation of Microspheres

Determination of percentage yield

The practical percentage yield was calculated from the weight of dried microspheres recovered from each batch in relation to the sum of the initial weight of starting materials. The percentage yield [20] was calculated using the following equation:

$$\% \text{ Yield} = \frac{\text{Weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

Drug Entrapment Efficiency

Microspheres equivalent to 100 mg of NIZ were crushed in a glass mortar and pestle and the powdered microspheres were suspended in 100 ml of 0.1N HCl. After 24 h, the solution was filtered, 1 ml of the filtrate was pipetted out and diluted to 25 ml and analyzed for the drug content using Elico SL- 159 UV Visible spectrophotometer at 314 nm [21].

The drug entrapment efficiency [20] was calculated using the following equation:

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Particle Size Analysis

Particle size of the floating microspheres was determined by optical microscopy. The eye piece micrometer was calibrated with the help of a stage micrometer. The particle diameters of more than 300 microspheres were measured randomly. The average particle size of the microspheres [22] was determined by using Edmondson's equation.

$$D_{mean} = \frac{\sum nd}{\sum n}$$

Where, n = Number of microspheres checked; d = Mean size range

Microsphere Surface Morphology:

The shape and surface characteristics [22] of the microspheres were evaluated by means of scanning electron microscopy (JEOL – JSM - 840A, Japan). The samples were prepared by gently sprinkling the microspheres on a double adhesive tape, which is stuck to an aluminium stub. The stubs were then coated with gold using a sputter coater (JEOL Fine coat JFC 1100E, ion sputtering device) under high vacuum and high voltage to achieve a film thickness of 30 nm. The samples were then imaged using a 20 KV electron beam.

In vitro floating ability study

Fifty milligrams of the floating microspheres were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 12 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. The percentage of floating microspheres [23] was determined by the following formula:

$$\% \text{ Buoyancy} = \frac{Wf}{Wf + Ws} \times 100$$

Where Wf and Ws are the weights of the floating and settled microparticles, respectively. The tests were carried out in triplicate.

Swelling measurement

Swelling studies were conducted using a water bath with a shaking speed of 100 rpm at 37±0.5^{0}C. Approximately 300 mg of microspheres were placed in small shallow containers in 0.1N HCl (pH 1.2) allowed to swell over a period of 12 h. After the set time interval, the samples were removed and blotted with filter paper to remove excess moisture.

Table 1: Formulation composition of NIZ mucoadhesive microspheres

Formulation code	Amount of NIZ (g)	Amount of SA (g)	Amount of C 934P (g)	Amount of HPMC (g)
NSC1	0.5	1.0	1.0	-
NSC2	0.5	1.0	1.5	-
NSC3	0.5	1.0	2.0	-
NSH1	0.5	1.0	-	1.0
NSH2	0.5	1.0	-	1.5
NSH3	0.5	1.0	-	2.0

In all the formulations, calcium chloride concentration of 10% w/v and agitation speed of 1000 rpm, was kept constant.

The changes in weight were measured and recorded [24]. The swelling rate was then calculated using the following equation:

$$\% \text{ Swelling Rate} = \frac{W_e - W_o}{W_o} \times 100$$

Where W_o is the initial weight of dry beads and W_e is the weight of the swollen beads at equilibrium.

In Vitro Mucoadhesion Studies:

The *in vitro* mucoadhesion study of microspheres was assessed using Falling liquid film technique [25]. A freshly cut piece, 4 X 2 cm of sheep stomach mucosa obtained from local slaughter house within 1 h of killing the animal was cleaned by washing with isotonic saline solution. The mucosa was then mounted on a glass slide and 50 mg of accurately weighed microspheres were sprinkled on the mucosa. This glass slide was incubated for 15 min in a desiccator at 90% RH to allow the polymer to interact with the membrane and finally placed on the stand at an angle of 45^0. A reservoir containing 0.1N HCl (pH 1.2) warmed at 37 ± 0.5^0C was placed at certain height above the mucosa. The media was allowed to flow over the microspheres and membrane at the rate of 1 ml/min for 5 min with the help of a peristaltic pump. At the end of this process, the detached particles were collected and weighed. The % *in vitro* mucoadhesion was calculated using the following formula:

$$\% \text{ Mucoadhesion} = \frac{\text{Weight of sample} - \text{Weight of detached particles}}{\text{Weight of sample}} \times 100$$

In Vitro Drug Release Studies:

The drug release rate from mucoadhesive microspheres was carried out using USP dissolution apparatus I (Basket). Mucoadhesive microspheres equivalent to 150 mg of NIZ were filled into capsules and placed in the basket. Dissolution media was 900 ml of 0.1N HCl (pH 1.2) maintained at 37±0.5^0C with an agitation speed of 50 rpm. At hourly intervals, 5 ml of the sample was withdrawn and 5 ml fresh dissolution medium was replaced after each withdrawal [21,26]. The samples were diluted suitably and analyzed spectrophotometrically at 314 nm against blank.

In Vitro Drug Release Kinetics:

In order to investigate the drug release mechanism and release rate kinetics[27,28] from the dosage form, the data obtained was analysed with software (PCP - Disso V2.08) equipped with zero order, first order, Higuchi matrix, Hixon Crowell and Korsmeyer – Peppas model kinetics. By analyzing the R values, the best fit model was arrived at.

Stability studies:

Stability studies for the formulations were carried out as per ICH guidelines [29]. Selected formulations were packed in amber coloured glass containers, closed with air tight closures and stored at, room temperature 25^0C ± 2^0C / 60% RH ± 5% RH and accelerated temperature 40^0C ± 2^0C / 75% RH ± 5% RH for three months using Programmable environmental test chambers (REMI Instruments ltd.). The formulations were then analyzed at the end of 30, 60 and 90 days for % drug entrapment efficiency, particle size, % *in vitro* floating and *in vitro* drug release studies [30].

RESULTS AND DISCUSSION

The gastric retention time of the dosage form will decide the activity of the oral controlled release formulations. This has prevented the development of controlled release formulations that release for more than 12 h. On the other hand, there are some drugs that have better bioavailability only in the upper GIT. Thus, there is a need to increase the gastric residence time so that irregular absorption of such drugs can be

avoided. To increase the GRT of the drugs, we developed hollow microspheres with a floating property so that they can be retained in the upper GIT for a longer time and thus help in prolonged drug action exceeding 12 h. In addition, these will increase the bioavailability in the upper GIT [31].

Nizatidine loaded microspheres of Sodium alginate with mucoadhesive polymer Carbopol 934P and Hydroxypropyl methylcellulose were prepared by emulsification – ionic gelation technique employing calcium chloride as cross linking agent. NIZ, a hydrophilic drug, can partition out into the aqueous processing phase during the preparation of microspheres by external gelation technique. In this study attempt was made to encapsulate NIZ with sufficiently high encapsulation efficiency. Liquid paraffin as the harvesting medium was chosen with the expectation that NIZ would find it non-favorable to diffuse out of the microspheres before they harden. The obtained microspheres were discrete, spherical in shape and freely flowing.

It was observed that as the drug to polymer concentration increased, the product yield also increased. The low percentage yield in some formulations may be due to microcapsules lost during the washing process. The percentage yield was found to be in the range of 87.62 to 92.62%.

NIZ in 0.1N HCl exhibited absorption maxima at 314 nm. The drug obeyed Beer-Lamberts law in the concentration range of 2.0 – 24.0 µg/ml. A calibration curve was constructed in 0.1N HCl. The linear relationship had a slope value of 0.0368 and an intercept value of 0.0071. The drug concentration in the sample was arrived at by making use of the relationship, x = y – 0.0071 / 0.0368. As the ratio of drug to polymer ratio was increased, the % drug entrapment efficiency also increased in the range of 77.4 ± 3.02% to 84.5 ± 1.37% for NSC formulations and 79.7 ± 1.18 to 85.2 ± 0.56% for NSH formulations. An aqueous solution of the polymers SA with C 934P and HPMC containing the drug was dispersed in the oily phase to form a w/o type of emulsion. The cross-linking agent, calcium chloride, was merged with the internal aqueous phase of polymer(s)-drug, resulting in instantaneous gelling of sodium alginate - C 934P and sodium alginate - HPMC, leading to the entrapment of the drug in the resultant three-dimensional lattice of the ionically cross-linked polymers. An increase in the concentration of C 934P and HPMC from 1.0 to 2.0% resulted in the formation of larger microspheres thus entrapping more amount of the drug. Also higher viscosity of the polymer solution at the highest polymer concentration is expected to decrease the diffusion of the drug into the external phase and thus resulting in higher entrapment efficiency. The % yield and drug entrapment efficiency of formulations coded NSC1 to NSC3 and NSH1 to NSH3 is displayed in Table 2.

The mean particle size of the microspheres is given in Table 2. It was observed that due to increase in the mucoadhesive polymer concentration the mean particle size of the microspheres significantly increased. This is due to the increase in micro-viscosity, which in turn increase the droplet size during addition of the polymeric dispersion to the harvesting medium. The mean particle size of mucoadhesive microspheres prepared from the combination of Sodium alginate and HPMC was found to be in the range of 451 ± 1.21 µm to 545 ± 1.55 µm, whereas average size of mucoadhesive microspheres prepared from the combination of Sodium alginate and Carbopol 934P was found to be in the range of 498 ± 1.64 to 645 ± 2.24 µm.

The SEM photographs of the optimized formulations coded NSC2 and NSH2 are depicted in the Figure 1(A) and (B). The photographs revealed that the microspheres were discrete and spherical in shape with a rough outer surface morphology which could be because of the surface association of the drug with the polymer. Under the scanning electron microscope, hollow microspheres were characterized by a spherical cavity enclosed within a hard polymer shell, and loaded with drug in the shell (Figure 2(A) and (B)). The microspheres have a rough exterior surface, and a hollow interior. SEM photographs in Figure 3(A) and (B) show porous surface which is indicated by the presence of minute pores on the surface of the hollow microspheres.

All formulations showed a degree of buoyancy immediately when placed in aqueous media of pH 1.2. The good buoyancy behaviour of the microspheres may be attributed to the hollow nature of the microspheres. The % *in vitro* floating of formulations NSC1, NSC2, NSC3, NSH1, NSH2 and NSH3 was found to be 73.6%, 65.2%, 46.5%, 75.2%, 53.1% and 48.2% respectively at the end of 12 h. The swelling rate at pH 1.2 demonstrates a gradual increase in swelling over time beginning as soon as the formulations were in contact with aqueous media.

Table 2: Evaluation parameters of Nizatidine loaded mucoadhesive hollow microspheres

Formulation code	% Yield	% Drug entrapment efficiency*	Particle size* (µm)	Swelling Rate* (%)	% Mucoadhesion*
NSC1	87.62	77.4 ± 3.02	498 ± 1.64	32.5 ± 1.15	75.63 ± 0.018
NSC2	91.37	82.9 ± 1.54	567 ± 1.37	45.7 ± 0.88	81.22 ± 0.123
NSC3	88.44	84.5 ± 1.37	645 ± 2.24	53.9 ± 2.48	85.57 ± 0.208
NSH1	89.26	79.7 ± 1.18	451 ± 1.21	34.6 ± 1.18	77.64 ± 0.077
NSH2	92.62	83.6 ± 2.06	512 ± 1.68	47.2 ± 1.38	81.64 ± 0.110
NSH3	90.55	85.2 ± 0.56	545 ± 1.55	56.5 ± 0.76	88.64 ± 0.198

*Data are expressed as mean ± SD., n = 3

Table 3: *In vitro* release data fitting into various mathematical models

		NSC1	NSC2	NSC3	NSH1	NSH2	NSH3
Zero order	R	0.976	0.981	0.985	0.979	0.983	0.976
	k	1.011	0.598	0.655	0.708	0.603	0.610
First order	R	0.994	0.993	0.994	0.997	0.991	0.990
	k	2.960	1.775	0.601	0.509	0.891	1.025
Matrix	R	0.935	0.926	0.966	0.972	0.92	0.901
	k	1.706	1.578	1.432	1.996	1.606	1.251
Hixon-Crowell	R	0.897	0.845	0.901	0.899	0.942	0.898
	k	0.062	0.002	0.087	0.101	0.097	0.065
Peppas	R	0.885	0.906	0.945	0.913	0.929	0.948
	k	1.784	1.817	1.868	1.739	1.263	1.369
	n	0.615	0.599	0.69	0.701	0.606	0.715

Table 4: Stability data of formulations NSC2 and NSH2 at the end of 3 months

Evaluation parameter	40^{0}C ± 2^{0}C / 75 ± 5% RH		25^0 ± 2^{0}C / 60 ± 5% RH	
	NSC2	NSH2	NSC2	NSH2
% Drug entrapment efficiency*	83.6 ± 1.22	84.5 ± 1.11	83.6 ± 1.22	84.5 ± 1.11
Particle Size*	560 ± 2.48	558 ± 3.15	572 ± 2.15	510 ± 1.19
***In vitro* floating (%)**	68.2	57.2	67.2	56.2
***In vitro* drug release* (%)**	88.57 ± 1.11	93.45 ± 1.02	87.65 ± 0.18	95.55 ± 1.20

*Data are expressed as mean ± SD., n = 3

The swelling rate of formulations at the end of 12 h is presented in Table 2. It can be observed that, with increase in the concentration of the mucoadhesive polymer the swelling rate increased. The % *in vitro* floating can be correlated with the results of the swelling rate study. All formulations swelled appreciably at pH 1.2, which correlates with a decrease in buoyancy. This swelling involves media fluid penetrating into the formulation and would result in an increase in the apparent density of the formulation and subsequent decline in buoyancy. The % *in vitro* floating decreased and swelling rate increased with increase in the concentration of the mucoadhesive polymer which is depicted graphically in Figure 4.

Polymer swelling is known to correlate with mucoadhesion. The *in vitro* mucoadhesion data is presented in Table 2. The microspheres consisting of sodium alginate in combination with HPMC and C 934P exhibited good mucoadhesive properties ranging from 75.63 ± 0.018% to 85.57 ± 0.208% and 77.64 ± 0.077% to 88.64 ± 0.198% respectively.

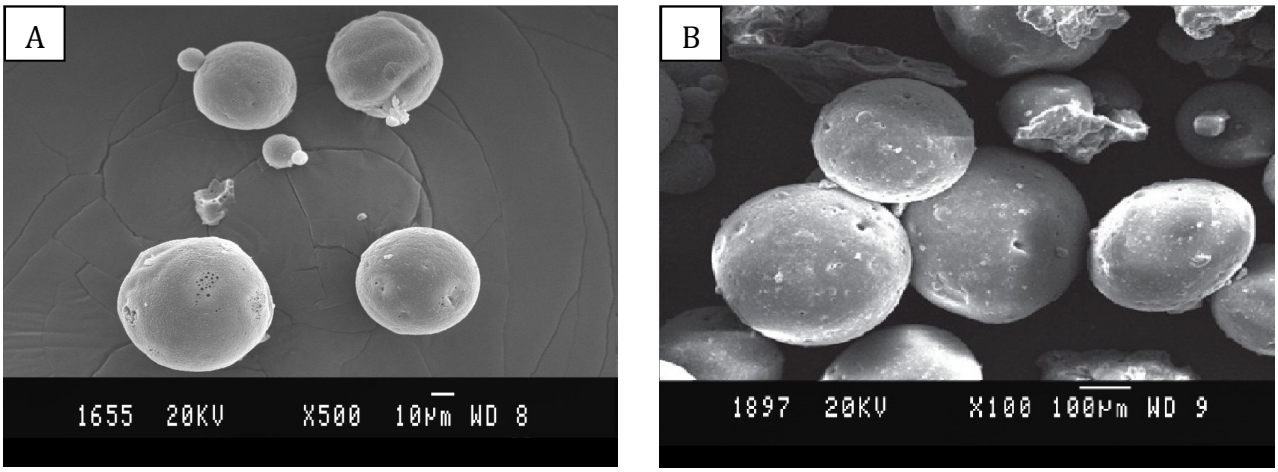

Figure 1: Scanning Electron microphotograph of optimized microsphere formulation (A) NSC2 (B) NSH2

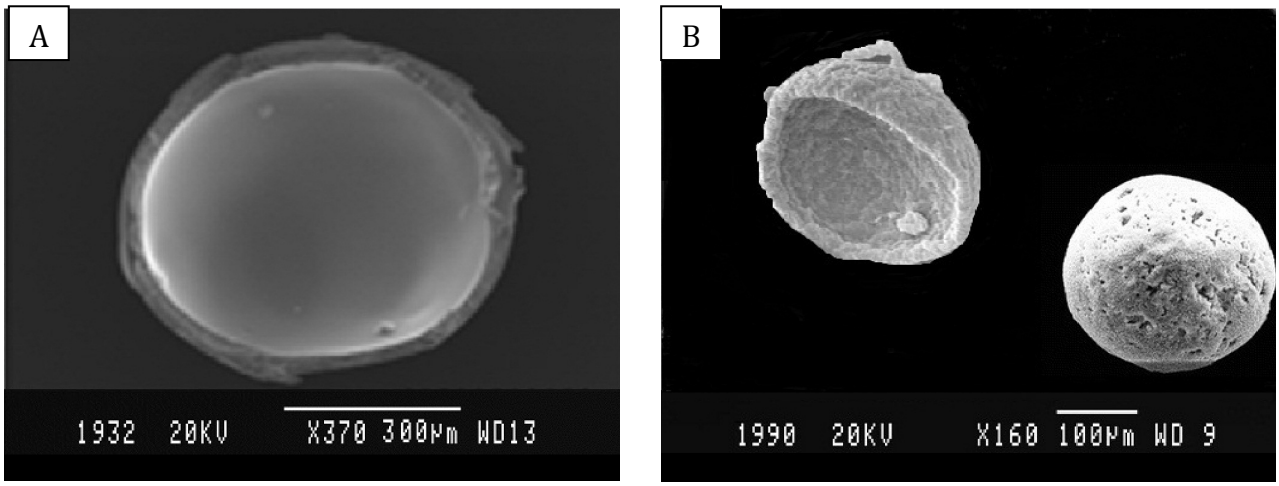

Figure 2: Scanning Electron microphotograph of microsphere hollow structure (A) NSC2 (B) NSH2

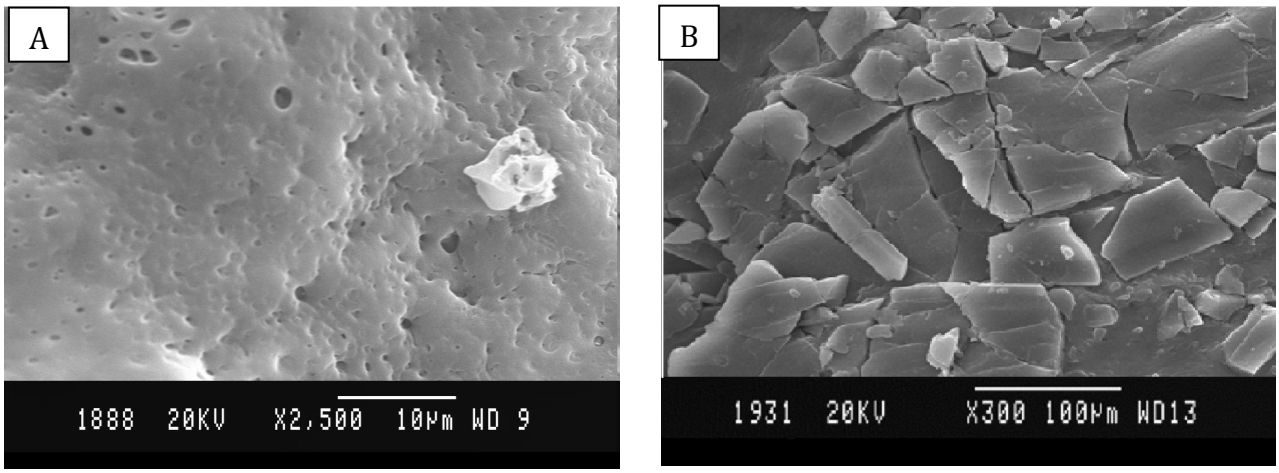

Figure 3: Scanning Electron microphotograph of microsphere surface (A) NSC2 (B) NSH2

The magnitude of mucoadhesion increased with increase in the mucoadhesive polymer concentration. The following stages have been occurred during mucoadhesion. Initially, an intimate contact between the mucus gel and the swelling of mucoadhesive polymer that is (wetting), which makes the polymer strands to relax which is followed by penetration of the mucoadhesive polymer into the mucus gel network and finally the formation of secondary chemical bonds between the mucus and the mucoadhesive polymer[32]. The developed mucoadhesive microspheres would adhere to the GI walls, thus resisting gastric emptying. It would ensure the prolong residence time at the absorption site to facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability.

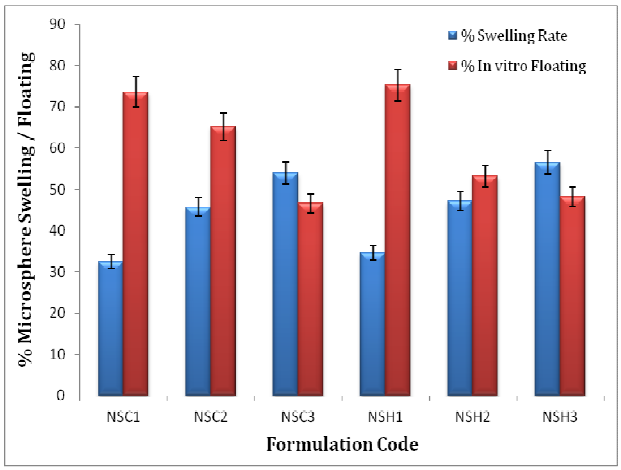

Figure 4: % Swelling ratio and % Floating ability of mucoadhesive microspheres

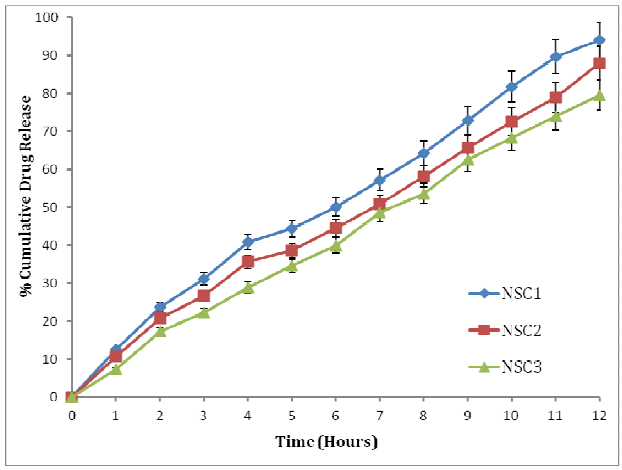

Figure 5: *In vitro* drug release profile from formulations coded NSC1 – NSC3

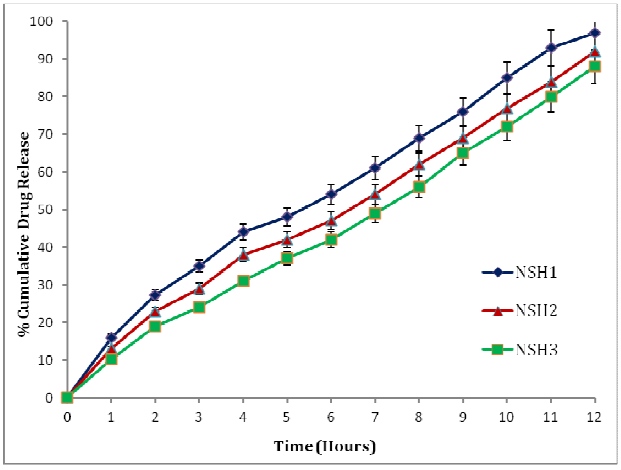

Figure 6: *In vitro* drug release profile from formulations coded NSH1 – NSH3

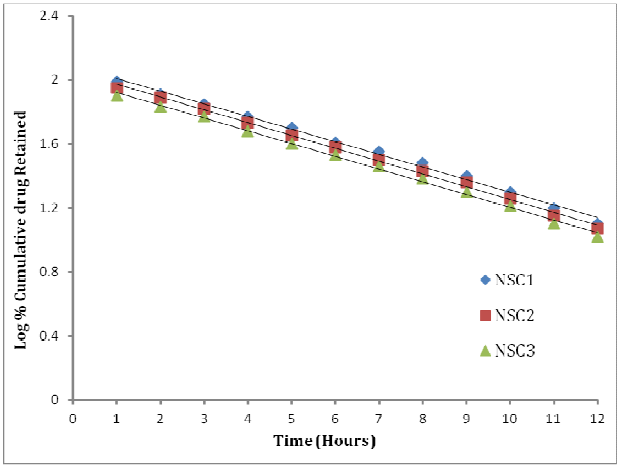

Figure 7: First Order Plot for formulations coded NSC1 – NSC3

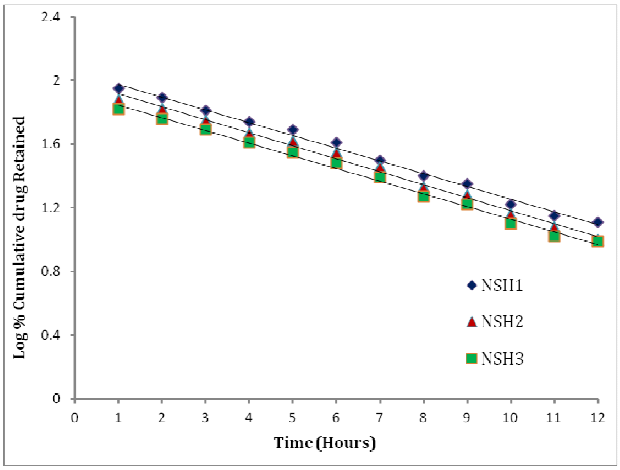

Figure 8: First Order Plot for formulations coded NSH1 – NSH3

In vitro release studies demonstrated 94.08 ± 0.016 %, 87.96 ± 0.172% and 79.55 ± 0.167% drug release from NSC1, NSC2 and NSC3 respectively in 0.1N HCl dissolution medium, where as formulations NSH1, NSH2 and NSH3 showed 97.11 ± 0.148 %, 92.55 ± 0.241% and 88.52 ± 0.167% drug release respectively at the end of 12 h. It was found that there was decrease in drug release with increase in mucoadhesive polymer content. This could be attributed to the greater degree of swelling upon hydration with greater mucoadhesive polymer content in the microspheres which leads to increase in the diffusional path length that slows down drug

release. The *in vitro* drug release profiles for formulations coded NSC1 – NSC3 and NSH1 – NSH3 are shown in Figure 5 and 6 respectively.

The drug release data was subjected to kinetic analysis for zero order, first order, Higuchi matrix, Hixon-Crowell and Korsmeyer-Peppas kinetics. The regression values obtained indicated that the drug release pattern from the formulated microspheres was closer to first order kinetics than zero order. This could probably be due to the fact that mucoadhesive microspheres are adhesive micro matrix systems, which consists of drug and mucoadhesive polymers. In this system, the drug is homogenously dispersed throughout the polymer matrix which acts as rate controlling element and release of drug is thus controlled by its diffusion throughout the rate controlling polymer matrix. Since the R values of First order kinetics are closer to 1, the drug release follows first order kinetics. The regression values (R) for all formulations are given in Table 3. Further, the observed diffusion coefficient values (n) value of microspheres of different formulations were lying between 0.599 and 0.715; indicating a non-Fickian transport mechanism controlled by swelling and relaxation of polymer. First order plots for NSC series and NSH series of formulations are presented in Figure 7 and Figure 8 respectively.

The stability data displayed in Table 4 showed that there was no change in the appearance of the microspheres indicating that the formulations were stable at different conditions of storage. The stability study was performed for the prepared formulation as per the ICH guidelines and it showed that the formulations NSC2 and NSH2 were stable, with no physical change and also there was no significant reduction in drug content when compared to the initial. Thus, we may conclude that, the drug does not undergo degradation on storage.

CONCLUSION

In this study, we successfully designed mucoadhesive floating hollow microspheres of Nizatidine for use as a gastroretentive delivery system. The preparation process was simple, reliable, and inexpensive. The prepared hollow-bioadhesive microspheres were spherical with porous surface and hollow interiors. The *in vitro* drug release test indicated that the hollow microspheres composed of either Carbopol 934P or Hydroxypropyl methylcellulose possessed almost similar drug release profiles and sustained the drug release over a period of 12 h. The microspheres demonstrated good buoyancy and bioadhesion properties. In conclusion, our study demonstrates clearly that the synergic drug delivery system combining hollow structure with bioadhesive properties could increase drug retention time in the gastric chamber to improve the treatment of gastric disease. This novel system could play a potentially important role in pharmaceutical drug delivery for gastric therapeutics.

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