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Preparation and Evaluation of Microspheres of Antiulcer Drugs (Nizatidine)

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ABSTRACT

Peptic ulcers are wounds in the mucous lining of the stomach or proximal duodenum. Usually, a peptic ulcer is a problem characterized by duodenal mucosa that extends into the submucosa. The mucoadhesive microspheres were developed using polymers like Chitosan using the emulsification cross-linking method. A total of 9 batch formulations were prepared. The prepared microspheres were evaluated various parameters such as % yield, entrapment efficiency, drug release study, in vitro wash-off test, optimization was done and characterization by FTIR. Each batch's average microsphere particle size varied from 10.09 to 29.98 µm, ensuring that every batch had appropriate handling qualities. It was discovered that the range of drug encapsulation efficiency for all formulations was 81.75% to 94.66%. It was discovered that the medication yield percentage for each formulation ranged from 86.11 to 96.11. Mucoadhesion percentages were observed to range from 59.4% to 82.56%. When all of the formulations were tested for drug release in vitro using phosphate buffer pH 7.4, microspheres showed regulated drug release for up to six hours. The result indicated that the prepared mucoadhesive microspheres can release the nizatidine in sustained manner and helps in the management of peptic ulcers.

KEYWORDS: Peptic Ulcer, Microspheres, Nizatidine, Chitosan

INTRODUCTION

Peptic ulcers are wounds in the mucous lining of the stomach or proximal duodenum. Usually, a peptic ulcer is a problem characterized by duodenal mucosa that extends into the submucosa [1]. This disease is one of the bacterial diseases which are mainly caused by Helicobacter pylori. (H. pylori) infections. Various antibacterial drugs are used to treat bacterial infections like-ciprofloxacin, nalidixic acid, norfloxacin acid, rosoxacin, etc., but these drugs are effective or work on some particular bacteria [2, 3]. Nizatidine, a competitive H2 receptor antagonist, acts specifically on the gastric parietal cells and is widely used in the treatment of peptic ulcers, reflux esophagitis and other conditions where inhibition of gastric acid secretion is beneficial. At present, nizatidine is the drug of choice for the long-term treatment of hyperacidity and for the management of recently healed active duodenal ulcers. [4, 5] Nizatidine is well absorbed (>70%) from the upper gastrointestinal tract following oral administration, and peak plasma concentration is reached within 0.5-3 h. A short half-life of 1-2 h, rapid clearance, susceptibility to metabolism by colonic bacteria, chemical and enzymatic stability, sparingly soluble nature and better absorption profile in the stomach make nizatidine an ideal candidate for the formulation of modified release gastroretentive dosage forms. Overall reduction in dosage and frequency of administration can be achieved, which enhance patient compliance and treatment efficacy. [6, 7]

The novel oral mucoadhesive drug delivery system has the ability of retaining in the stomach for longer times and can release the drug content slowly so that an effective level of drug can be provided to its site of absorption (stomach) to heal the ulcer. Moreover, these systems can channel the local drug action in the upper region of the small intestine, which can be suitable for the treatment of duodenal ulcer as. [8, 9] It is utmost important in drug delivery system to meet the current demand of drug therapy by maintaining drug concentration in blood circulation for prolonged times. [10-14] Mucoadhesive microspheres are tiny spherical units (~1000 µm), have the ability to form bioadhesion to the gastric mucosa which restricts gastric emptying of formulation through the pyloric sphincter. These carrier systems can be spread out homogeneously over the entire region of the stomach and upper small intestine, which can facilitate improved absorption and localized action of drug. [15, 16, 17] The bioadhesion of these carriers are generally facilitated by muco-polymers, having the ability to adhere to the surface of epithelial tissues of the stomach by intimate contact. This results in delaying gastric emptying time, thus the time of retention of the product in the gastric region is enhanced. [18] In this work, mucoadhesive microspheres were prepared using polymers Chitosan as a polymer with different concentrations of polymers by using the emulsification cross-linking technique.

MATERIALS AND METHODS

Materials: Nizatidine was procured by Yarrow Chem Pvt. Ltd. (Mumbai, India). Chitosan (assay 95%) was obtained by the Central Institute of Fisheries Technology (Cochin, India) as a gift sample. Glacial acetic acid, DOSS and glutaraldehyde was procured from Merck, Mumbai, India. Distilled water was used in all the preparations. All other reagents were used for analytical grade and purchased from Merck, Mumbai, India.

Determination of Analytical Wavelength(λ_{max}): A standard stock solution of Nizatidine was prepared by dissolving accurately weighed 5 mg of Nizatidine in water in a 50 ml volumetric flask and the volume was made up to 50 ml with water to obtain a stock solution of 100 µg/ml. From the standard stock solution, 10 ml was pipetted into 100 ml volumetric flask. The volume was made up to 100 ml with water. The resulting solution containing 10 µg/ml was scanned between 200 and 400 nm. [19]

Chemical compatibility studies by FT-IR: FTIR spectra of drug, polymer and all superdisintegrants alone and along with drug were taken by using KBr pellet method and scanned at a moderate scanning speed between 4000-400 cm^{-1} using FT-IR. The peak values and the possibility of functional groups shown in spectra were compared with standard values. [20]

Method of Preparation:

- Step-1: Taken a 10 of 2% aqueous acetic acid solution (2 ml acetic acid dissolved in 100 ml distilled water).
- Step-2: Now taken a given quantity of (0.1/0.2/0.3 gm) of chitosan was dissolved in a 10 ml of 2% aqueous acetic acid solution by continuously stirring until a homogenous solution was obtained.
- Step-3: Then added the drug (0.1 gm) slowly with stirring in prepared chitosan solution. Dispersed phase was prepared.
- Step-4: Now we prepared stabilizing agent with DOSS. Given quantity about 50 mg of DOSS was dissolved in 25 ml glycerine continuously stirring by glass road.
- Step-5: Then 50 ml heavy and 50 ml light liquid paraffin was taken in 500ml beaker, place under electronic stirring machine for 15 mins at 1200 rpm.
- Step-6: Added DOSS (stabilizing solution) as per the given quantity (2 ml or 3 ml) constant stirring at 1200 rpm for 15 minutes. External Phase was prepared.
- Step-7: The dispersed phase (drug + chitosan + acetic acid) was added slowly to the above prepared external phase under constant stirring at 1200 rpm for 15 minutes.
- Step-8: Added Glutaraldehyde was added to above solution using continuously stirring for next 2 or more hours at 1200 rpm.
- Step-9: Microspheres was prepared and filtered using vacuum filtration.
- Step-10: Firstly, washed with the n-hexane and then washed with the water. Kept for air drying about 24 hours and then stored in desiccator until next use. [21, 22]

Optimization of Process and Formulation Variables

Emulsification Cross Linking Method: In the present study, microspheres were prepared by emulsification cross linking method. For preparation of w/o type of emulsion, polar organic solvent was employed as aqueous phase.

Selection of Internal Phase:

Selection of dispersing agent: The present study showed that liquid paraffin was external phase; DOSS was used which is soluble in liquid paraffin and conc. Of 0.2% w/v was found to be satisfactory for preparation of microspheres. DOSS seems to have provided a protective sheath around organic polymer droplets and also prevented the droplets form coalescing. [23, 24]

Selection of Washing Solvent: Microsphere were washed to remove the residual traces of liquid paraffin. A washing solvent had to be selected in which only liquid paraffin was soluble, but it had to be non-solvent for polymer, hexane was tried in which liquid paraffin is soluble, but polymers are not. The microspheres obtained so were discrete in nature.

Table 1: Different variables of microspheres

Formulation and process variables				Constant parameters		
For. Code	**Drug: Polymer**	**Vol. of stabilizing agent (DOSS)**	**Vol. of cross linking agent (Glutaraldehyde)**	**Constant parameter aqs to oil phase**	**Stirring rate**	**Cross linking**
NM1	1:1	2 ml	2 ml	1:10	1100-1200	2 hrs
NM2	1:2	2 ml	2 ml			
NM3	1:3	2 ml	2 ml			
NM4	1:1	2 ml	3 ml			
NM5	1:2	2 ml	3 ml			
NM6	1:3	2 ml	3 ml			
NM7	1:1	2 ml	4 ml			
NM8	1:2	2 ml	4 ml			
NM9	1:3	2 ml	4 ml			

Characterization and Evaluation

Determination of Percentage Yield of Microspheres: The percentage yield of prepared microspheres was determined by the using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for the preparation of microspheres. Then dried microspheres were collected and weighed accurately. The percentage yield was then calculated. [25]

Determination of Drug Content and Entrapment Efficiency: Accurately weighed 100 mg microspheres, crushed in glass mortar and pestle and the powdered microspheres was dissolved in 100 ml methanol with the help of ultrasonic stirrer. After 12 hours the solution was filtered through Whatmann filter paper no. 41 and the filtrate was analyzed for the drug content using UV –Visible spectrophotometer at 265 nm. Encapsulation efficiency was calculated using the following formula:

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content\%}}{\text{Theoretical drug content\%}} \times 100$$

Where,

Wo = initial weight of the dry microspheres,

We = weight of the swollen microspheres at equilibrium swelling in the media.

Particle size analysis: All the microspheres were evaluated with respect to their size and shape. The prepared slide of microspheres was examined by an optical microscope and size of the microsphere was measured using the microscope with modified software magnus pro 3.0 and Olympus master through a camera. A quantity of dried microspheres suspended in glycerine average particle size was determined. [26]

Degree of Swelling: Accurately weight 50 mg microspheres (W) were weighed and placed in phosphate buffer saline (pH 7.4) for 24 hours. After 24 hours the swollen microspheres were separated using Whatman filter paper. The microspheres were collected and blotted to remove excess of water and their weight (Wt) was noted. The swelling index was also found to be dependent on the surface area of particle. As the particle surface area increased, the swelling index was also found to be increased. [27]

Mucoadhesive Property by Wash-Off Test: The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised piece of intestinal mucosa (2 x 2 cm) from goat were mounted on to glass slides (3 x 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support, about 25 microspheres were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given slow, regular up-and-down moment in the test fluid (phosphate buffer pH 7.4) at 37 ± 0.5°C. At the end of 30 min, 60 min at the hourly intervals up

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to 6 hours, the machine was stopped and number of microspheres still adhering to tissue was calculated. [28] The adhering percentage was presented by following formula:

Mucoadhesion = No. of microspheres adhered / No. of microspheres applied x 100

In-Vitro Drug Release or Dissolution Studies: Dissolution studies were carried out for all the formulations, employing USP XXIV apparatus (Basket method) at 37 ± 0.5°C rotated at constant speed of 50 rpm using 900 ml of Phosphate buffer (pH 7.4) as the dissolution medium. A sample of microspheres equivalent to 10 mg of nizatidine drug were used in each test. An aliquot of the sample was periodically with drawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The percentage of drug dissolved at different time intervals was calculated at 265 nm. [29]

Stability Study: From the prepared microspheres the formulation (NM1-NM9) for stability studies. The formulation was divided into 3 sample sets and store at 4 ±1, 25±2 & 60±5%RH and 37±2 & 65±5%RH. The samples were assayed for drug release after 30 days. Entrapment efficiency also checked for the same formulation. [30]

RESULTS AND DISCUSSION

Determination of analytical wavelength (λ_{max}) of Nizatidine: By using UV-Spectrophotometer Nizatidine drug solution in water was scanned between the range of 200-400 nm using water as the blank and a sharp peak was observed at 265 nm which reports that the analytical wavelength is 265 nm.

Calibration Curve of Nizatidine: The absorbances of solution of Nizatidine in 0.1N HCl and in pH 6.8 buffer solution at 265 nm have been taken and it was found that the solutions show linearity in absorbance at a concentration of 0-50 µg/ml and obey beer-lamberts law.

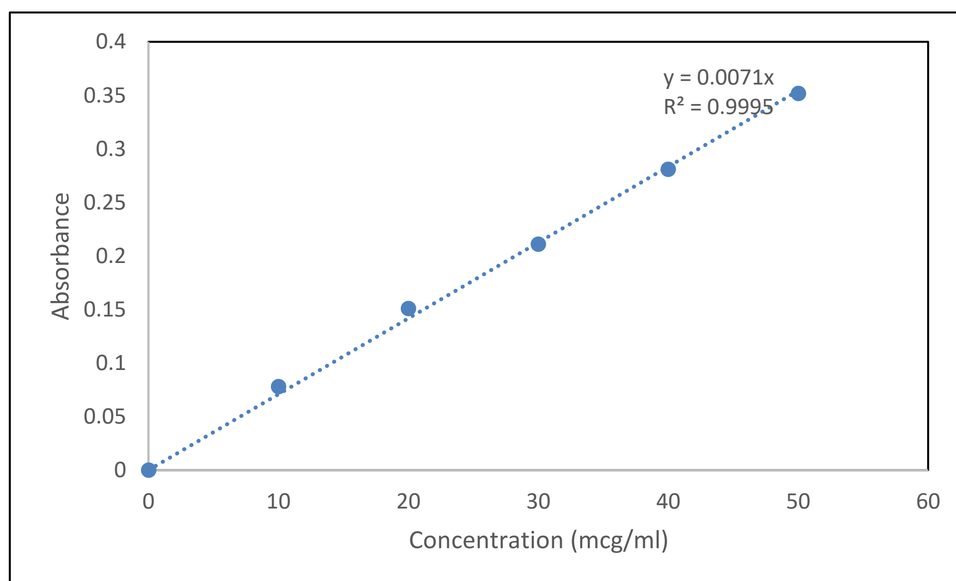

Figure 1: Calibration Curve of drug in 0.1 N HCl

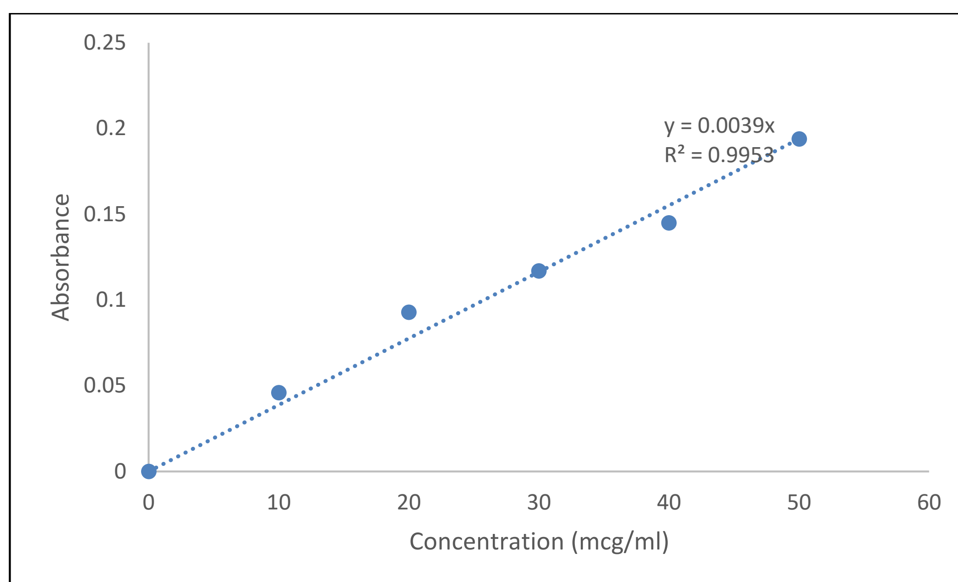

Figure 2: Calibration curve of drug in phosphate buffer pH 6.8

Physical Compatibility Studies of Drug and Excipients: Physical compatibility study of drug and excipients is necessary for the stable and effective solid dosage form which is performed on visual basis. The study reveals that the drug, polymer and other excipients were physically compatible with one another as there was no change in physical description. The results have been illustrated in Table 2.

Table 2: Physical compatibility studies of drug and excipients

S. No	Drug + Excipients	Description at initial day	RT, 35 ± °C/ 65±5% RH in days		
			10th	20th	30th
1	NZ	Off white to brown crystalline powder	NC	NC	NC
2	Chitosan	White to yellowish white	NC	NC	NC
3	DOSS	White amorphous powder	NC	NC	NC
4	NZ + Chitosan	Off white to brown crystalline powder	NC	NC	NC
5	NZ+DOSS	Off white to brown crystalline powder	NC	NC	NC

NZ – Nizatidine, DOSS- Dioctyl sulfosuccinate, NC – No change.

Chemical compatibility studies by FTIR: The IR spectral analysis of the Nizatidine, polymer and other excipients was carried out by using KBr pellet method. All the characteristic peaks appear for the pure Nizatidine and its physical mixture indicating no interaction between Nizatidine and excipients.

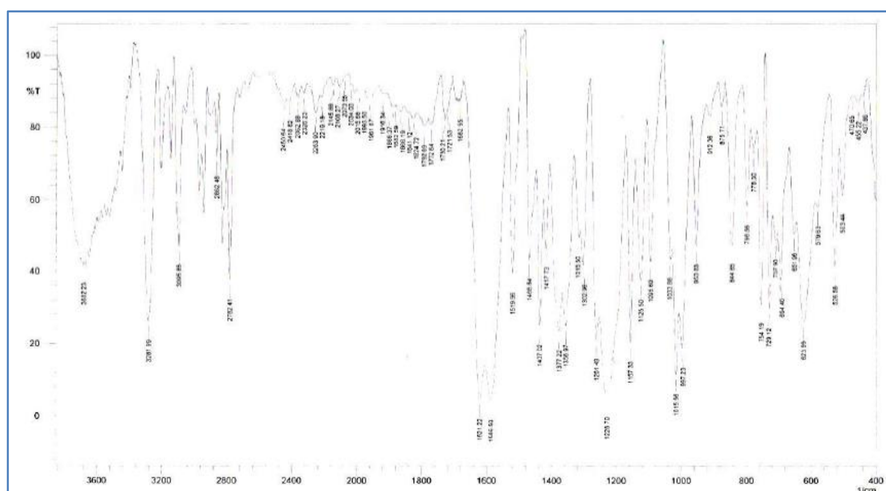

Figure 3: FTIR Spectra of Nizatidine and excipients

The peaks observed in the FTIR spectrum of chitosan and nizatidine + chitosan showed no shift and no disappearance of characteristic peaks of drug as well as polymer. This suggests that there is no interaction between the drug and polymer. Hence it can be concluded that the drug maintains its identity without undergoing any chemical interaction with chitosan.

Characterization And Evaluation

Production Yield: After the preparation of microspheres practical yield and percentage yield were calculated. The percentage yield of different formulations is shown in Table 3. The percentage yield of NM7 was found out to be maximum, followed by NM1, NM2, NM3, NM4, NM5, NM6, NM8 and NM9. The percentage yield was found to be in the range of 86.11% - 93.87%. Formulation NM7 showed best yield of 96.11. It was observed that an optimum concentration of polymer and crosslinking agent is required, below or above this concentration microspheres are not formed. The loss of material during preparation of microspheres was due to process parameters. Another region for that may be agglomeration and sticking of polymer to blades of stirrer and to the wall of the beaker during microsphere formulation.

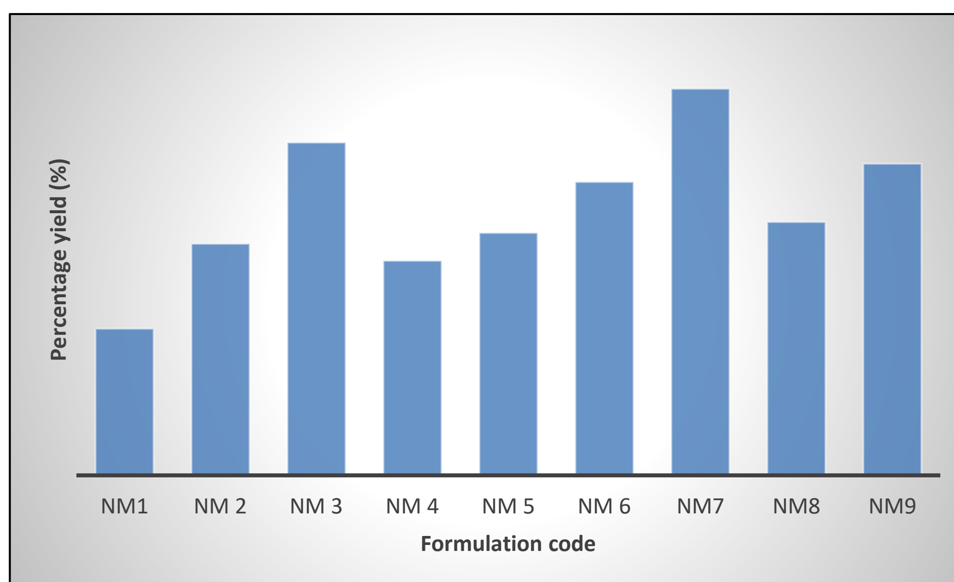

Figure 4: Data For Percentage Yield of Microsphere

Drug Content and Entrapment Efficiency: The drug content determination showed that even if the polymer composition was changed the process was highly efficient to give microspheres having maximum drug content. The drug content percentage was found in the range of 80.76 to 90.34% w/w. The drug content percentage of NM7 was found out to be maximum, followed by NM1,

NM2, NM3, NM4, NM5, NM6, NM8 and NM9. The drug content percentage was found to be in the range of 80.76 to 90.34% w/w. Formulation NM7 showed best drug content percentage of 95.65% w/w.

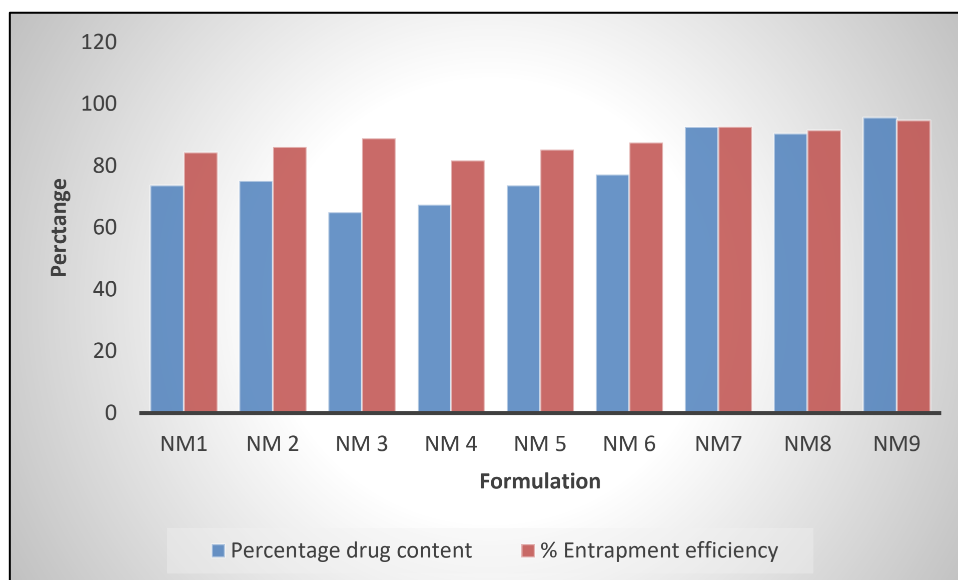

Figure 5: Percentage drug content of prepared microspheres

The results of entrapment efficiency of the microspheres are given in Figure 5. The percentage entrapment efficiency calculated for all microspheres ranged from 82.09 to 95.65%. The highest entrapment efficiency is found for formulation NM9. It may be roughly concluded that the entrapment efficiency is affected by polymer concentration. Entrapment efficiency of the formulations containing 3 %w/v of chitosan (i.e., NM3, NM6 and NM9) were higher than that of the formulations having 1%w/v and 2% w/v of chitosan (i.e., NM1, NM4 and NM7) (NM2, NM5 and NM8). It was observed that with the increase in polymer concentration the entrapment efficiency.

Particle Size Analysis of Microspheres: The particle size analysis of all prepared microspheres was done by using OLYMPUS INEA. The mean particle size of the formulated microspheres is shown in Figure 6. The microspheres were in the size range of 10.09±1.12 to 29.98±2.23 µm. The particle size was found to be more dependent on the crosslinking agent concentration than on polymer concentration. Higher chitosan conc. leads to the formation of small size particles upto a certain limit which may be due to high anionic concentration.

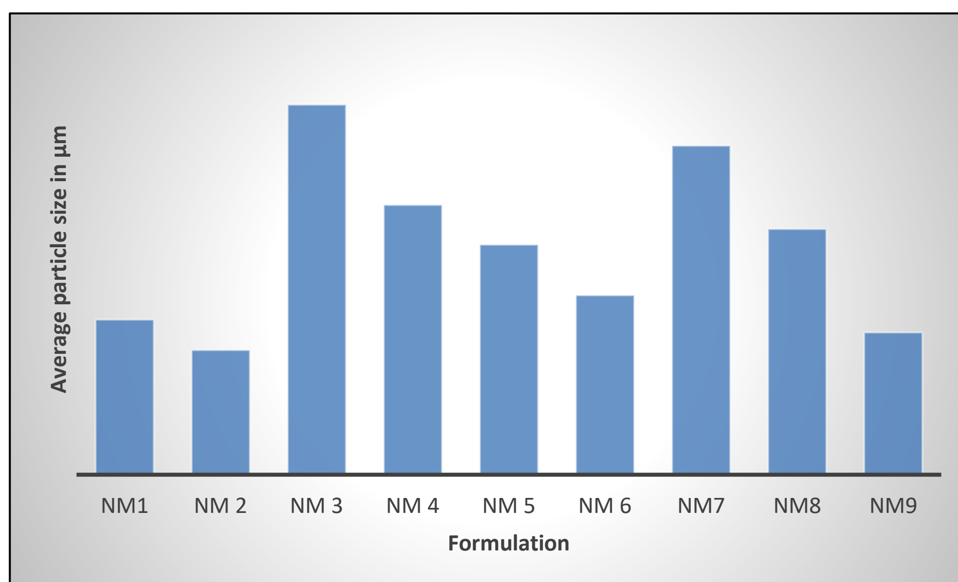

Figure 6: Mean Particle Size Analysis of Microspheres

Swelling Property: Swelling Index of the formulations are given in Figure 7. It was noticed that with respect to time, formulations NM3, NM6 and NM9 with higher polymer concentration (3 %w/v) showed higher swelling and maintained their integrity till 4 hrs unlike formulations NM1, NM4 & TF7 with 1% w/v and NM2, NM5 & NM8 with 2% w/v polymer concentration which lost their integrity after 3 hrs. This may be because the density of former was greater and so the rate of solvent penetration was less in it but for longer duration as compared to the later. The swelling index was also found to be dependent on the surface area of particle. As the particle surface area increased, the swelling index was also found to be increased.

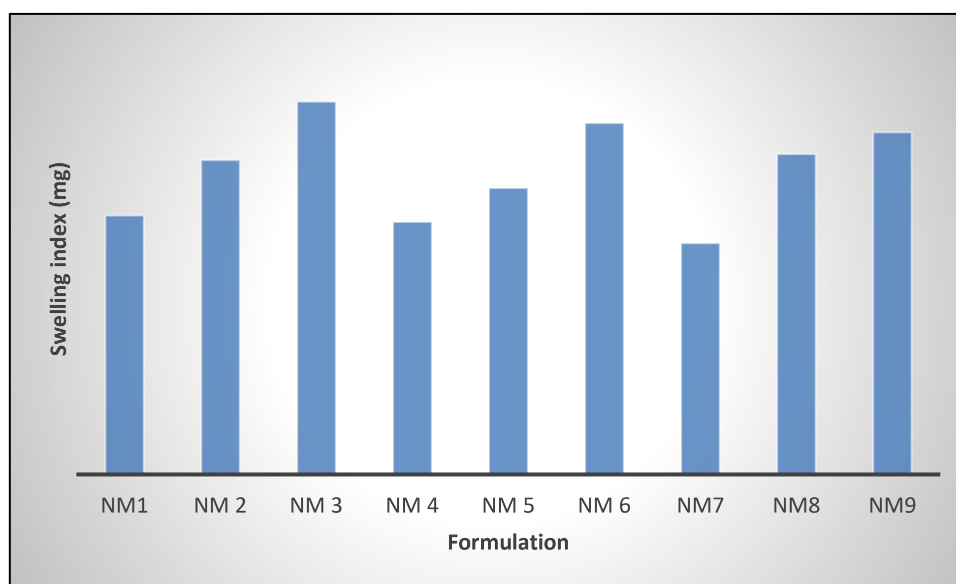

Figure 7: Swelling index of Microspheres

In-vitro mucoadhesion Test for Microspheres: The result of mucoadhesion test is shown in Table no. 3. The result observed indicate that the mucoadhesive strength increases with increase in the polymer concentration. Mucoadhesive strength was more in formulations containing 3 % w/v polymer concentration (i.e. NM3, NM6 and NM9) than in formulations with 1% w/v polymer concentration (i.e. NM1, NM4 and NM7). The mucoadhesion was also found to be dependent on the surface area of particle. As the particle surface area increased, the mucoadhesion was also found to be increased.

Table 3: In-Vitro Wash Off Test For Mucoadhesion in Phosphate buffer pH 7.4

Formula code	Mean percentage of microspheres adhering to tissue (n=3)					
	0.5 hr	**1 hr**	**2hrs**	**3 hrs**	**4 hrs**	**5 hrs**
NM1	75.56	71.76	68.36	65.23	61.87	53.23
NM 2	80.56	74.64	70.11	67.87	62.98	54.45
NM 3	85.87	79.34	73.42	68.12	59.23	56.38
NM 4	74.87	70.56	67.45	65.34	60.98	52.23
NM 5	78.98	75.34	72.23	67.98	65.34	53.23
NM 6	80.45	77.23	73.23	69.45	63.28	56.34
NM7	69.87	70.56	69.45	67.11	60.98	51.23
NM8	76.98	74.65	73.23	69.45	68.34	58.23
NM9	82.56	78.37	75.86	73.65	72.28	59.34

In-vitro Release Studies: The in-vitro release data of all the formulations were tabulated in table 4. The cumulative percentage drug release after 6 hours was to be 73. Respectively for the formulation TF1 to TF6. The release studies of nizatidine microspheres were in Table 4, it was clear that both the variables (stirring rate & concentration of polymer) had significant impact on the drug release. As the concentration of mucoadhesive polymer increased, the drug release than concentration of mucoadhesive polymer. Drug release increased steeply as the stirring rate was increased from lower to higher level. The presumably is due to the smaller particle size of microsphere at higher stirring rate which leads to much larger surface area available for release and shorter pathlength for drug to diffuse through microspheres. The greater drug release from chitosan which forms hydrophilic passage inside the microspheres who help drug diffuse out. The increase hydrophilic pores formed by chitosan facilitated the water penetrating into

microspheres, accelerated the erosion of swelling matrix and resulted in a combination of the diffusion and erosion mechanism of drug release from microspheres.

Table 4: In-vitro drug release of prepared microspheres formulations

Time in hrs	Cumulative % drug release ± SD								
	NM1	**NM2**	**NM3**	**NM4**	**NM5**	**NM6**	**NM7**	**NM8**	**NM9**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	5.09	7.11	8.87	5.25	7.23	8.02	4.05	7.23	8.87
1	14.98	17.28	20.87	15.34	18.45	19.03	12.97	24.45	20.87
2	23.45	27.76	38.87	24.98	28.26	33.91	20.65	34.26	36.87
3	34.76	38.29	49.09	35.82	40.87	47.11	29.54	46.87	49.09
4	45.09	50.98	60.98	46.99	47.93	57.09	38.98	62.93	59.98
5	60.59	68.87	75.76	62.09	69.45	72.76	59.97	73.45	74.76
6	74.49	77.76	82.98	78.87	80.98	84.98	67.98	79.98	86.98

Stability Study: Stability study was carried out for the NM9 formulation by exposing it to a temperature 4 ±1 °C, 25± 2°C/ 60 ± 5% RH and 37 ± 2 °C/ 65±5% RH for 1 months. The sample was analyzed for % drug content and percentage entrapment efficiency at the time. It was found that no remarkable change in the drug content of NM9 formulation. This indicates that NM9 was stable for following temperature. These results may be attributed to erosion of polymer matrix to some extent during storage.

Table 5: Stability studies of formulation NM9

S. No.	Storage condition	% Drug content	Entrapment efficiency
1	4 ±1 °C	95.65	94.66
2	25± 2°C/ 60±5 RH	95.43	.94.45
3	37 ± 2 °C/ 65±5% RH	95.06	94.08

CONCLUSION

Peptic ulcer illness is still a common clinical concern in our society, affecting people of all ages. Peptic ulcer disease is predicted to continue to have a large global influence on health-care delivery, health economics, and patient quality of life as the prevalence of the illness rises with age. The concept of formulating microspheres containing nizatidine offers a suitable, practical approach to achieve a prolonged therapeutic effect by controlling the release of the medication over extended period of time. In present work, controlled microspheres of nizatidine were prepared in order to minimize the side effects by controlling the release of the drug in the gastric environment. This was achieved successfully by emulsification cross-linking method using the different concentration of natural polymer chitosan. As the drug to polymer ratio was increased, the mean particle size of nizatidine microspheres also increased with the range of 20µm to 100µm. The microspheres exhibited good mucoadhesive retention properties. Therefore it can be concluded that microspheres of nizatidine using chitosan polymer would be an excellent approach for gastric retention along with a controlled drug release.

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