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Formulation and Evaluation of Floating Beads of Nizatidine

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ABSTRACT:
The main intention of the present study is to develop the ideal floating beads of nizatidine for prolongation of the gastric retention time in the stomach and enhance patient compliance in the treatment of peptic ulcers. Nizatidine is a histamine type-2 receptor antagonist (H2 blocker) and it is a selective H2 antagonist which inhibits gastric acid secretion to treat gastric ulcer and gastroesophageal reflux disease. The half-life of nizatidine is 1-2hrs.Nizatidine floating beads was prepared by using sodium alginate, HPMC (K4M, K15M, K100M) as a polymer and calcium carbonate used as gas forming agent. The ionotropic gelation method is carried out for preparation of floating beads. The compatibility of drug and polymers were study FTIR technique. The particle size and surface morphology are characterized by SEM analysis. The prepared beads were evaluated for physical characterization floating lag time, swelling index, entrapment efficiency, buoyancy studies, invitro drug release studies.
The formulation remains buoyant for more than 12hrs and all the nine formulation shows the mark increases in drug release. SEM analysis studies shows the particles are in spherical shape. Formulation F8 containing HPMC K100 M shown the better result. The percentage yield of F8 formulation found to be 96.6%, swelling index 92.3%, percentage entrapment efficiency 75.7%.
KEYWORDS: Nizatidine, peptic ulcer, ionotropic gelation, floating beads, Gastric residence time, Buoyancy.

I. INTRODUCTION

Peptic ulcer is chronic, frequently develop lesions that happen in any part of the gastrointestinal tract due to the more amount of secretion of acid peptic juices. Peptic ulcer develops in a number of parts of the gastrointestinal tract (GIT) which is exposed to gastric acid and pepsin, for example the stomach and duodenum. Peptic ulcers usually induced in rodents by physiological, pharmacological or other surgical medicines which have etiological significance for stimulation of peptic ulcers. A few models are referenced in following which utilized tentatively for testing or assessing against peptic ulcer action of medications.

There are atleast two main targets which could be used for anchoring of delivery system through mucoadhesive in the GIT, the mucosal tissue and mucosal gel layer. The mucos layer is the first surface encountered by particulate system and its complex structure offers many opportunities for the development of adhesive interaction with small polymeric particles either through non-specific or specific interaction between complimentary structures. Due to all above advantages Microsphere delivery is a better choice for drug delivery in colon.

Microballoons are low-density systems that have sufficient buoyancy to float over gastric fluid and remain in stomach for prolonged period of time. As the system floats over gastric fluid, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. When microballoons come in contact with gastric fluid, the gel forms and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the outer 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 makes the density lower than the gastric fluid and confers buoyancy to the microspheres.

Nizatidine is a histamine type-2 receptor antagonist (H2 blocker) and it is a selective H2 antagonist which inhibits the gastric acid secretion to treat gastric ulcer and gastroesophageal reflux disease. The half-life of nizatidine is 1-2hrs. The aim of the research work is preparing nizatidine floating beads by using sodium alginate, HPMC (K4M, K15M, K100M) as a polymer and calcium

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carbonate used as gas forming agent. Nizatidine inhibits the histamine H2-receptors located on the basolateral membrane of the gastric parietal cell, thereby reducing basal and nocturnal gastric acid secretion, resulting in a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli.

II. MATERIALS AND METHODS

MATERIALS

Nizatidine drug got as a gift sample from GMFC Labs Pvt. Ltd. Visakhapatnam, Hyderabad, Sodium Alginate is a chelating agent received from Himedia Laboratories, Mumbai, polymers such as HPMC K 4M, K 15M, K 100M from Yarrow chem products, Mumbai, Calcium carbonate from Karnataka fine chem, Karnataka Calcium chloride from Karnataka fine chem, Karnataka.

Table No 01: Formulation of Nizatidine Floating Beads

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nizatidine	150	150	150	150	150	150	150	150	150
Sodium Alginate	2	2	2	2	2	2	2	2	2
HPMC K4M	50	100	150	----	----	----	----	----	----
HPMC K15M	---	---	---	50	100	150	----	----	----
HPMC K100M	---	---	---	----	----	----	50	100	150
Calcium Carbonate	300	250	200	300	250	200	300	250	2001
Calcium Chloride	1	1	1	1	1	1	1	1	1

PREPARATION OFFLOATING BEADS OF NIZATIDINE

Nizatidine was prepared by Ionotropic gelation method has been widely used for floating beads. The required quantity of nizatidine was dissolved in 15ml of deionized water in a beaker. In another beaker sodium alginate (Bead core forming agent) was soaked for 3hr, in measured amount of distilled water. Weight quantity of HPMC, CaCo3, CaCl2 were dissolved in the separate beaker with distilled water. This solution was slowly to the beaker containing sodium alginate with continuous stirring by using magnetic stirrer at 500rpm. The stirring was continued to obtain uniform dispersion of nizatidine and polymers. The mixture was sonicated for 30 min to eliminate air bubbles which may have been formed during the stirring process. This prepared slurry dispersion dropped through a 21G syringe into 100ml of calcium chloride solutionwhich was kept under stirring to improve the mechanical strength of the beads and to prevent aggregation of them. It is being stirred at 100 rpm for 10-15 min into the gelation medium. After 15min, beads are collected by filtration and washed with distilled water and dried at 40℃ for overnight. The dried, free flowing beads were doubly wrapped in an aluminum foil and kept in a desiccator for further studies.

EVALUATION PARAMETERS

COMPATIBILITY STUDIES

The compatibility of the drug and polymer under experimental condition is an important prerequisite before formulation. It is necessary to confirm that the drug does not react with the polymer or excipients and affects the shelf life of the product. This can be confirmed by carrying out Infrared spectroscopic studies.

Procedure: The drug and polymers were subjected to IR studies by potassium bromide disc (pellet) method. IR spectra were compared with the standard FTIR spectrum of the pure drug.

FOURIER TRANSFORM INFRARED (FTIR)

FT-IR spectroscopic study was performed to monitor the compatibility between drug, polymer and other excipients in formulation. The FT-IR spectra of a drug alone and drug with polymers were obtained by KBr method and compared with the standard FT-IR spectrum of the pure drug.

KBr pellet methodexploits the property that alkali halides become plastic when subjected to pressure and form a sheet that is transparent in the infrared region. Take ⅛of the solid sample on a microspatula and about 0.25-0.50 teaspoons of KBr. Mix thoroughly in mortar while grinding with the pestle. If the sample is in large crystals, grind the samples separately before adding KBr. Place just enough sample to cover bottom in pellet die. Place in a press and press at 5000-10000 psi. check pellet press brochure for details. Carefully removed the pressed sample from die and place in the FTIR sample holder. The pressed die should be nearly clear if properly made. If it is translucent, regrind and repress.

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MICROMERITICS PROPERTIES

The characterization of prepared beads was carried out by particle size, angle of repose, bulk density, tapped density and Carr's index.

BULK DENSITY:

It is also called as the poured density. It is the ratio of total mass of beads to the bulk volume of beads. It was measured by pouring the beads into a 100 ml measuring cylinder and initial volume was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of bead

Vb is the bulk volume of the beads

TAPPED DENSITY:

It is the ratio of total mass of the beads to the tapped volume of the beads. Volume was measured by tapping the beads for 100 times. and tapped volume was noted. It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of beads

Vt is the tapped volume of the beads

ANGLE OF REPOSE:

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane and it can be calculated by the following formula.

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

Where, θ is the angle of repose,

h is the height in cm,

r is the radius in cm.

The beads were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of beads formed. Care was taken to see that the beads slip and roll over each other through the sides of the funnel. Relationship between angle of repose and beads flow property is given as follows.

CARR'S INDEX:

It indicates beads flow properties. It is expressed in percentage and is give

$$I = Dt–Db/Dt \times 100$$

Where, Dt is the tapped density of the beads and

Db is the bulk density of the beads.

HAUSNER'S RATIO:

Hausner's ratio is an indirect index of ease of beads flow. It is calculated by the following formula.

$$Hausner's ratio = Dt / Db$$

Where, Dt is the tapped density.

Db is the bulk density.

CHARACTERIZATION OF FLOATING BEADS:

SCANNING ELECTRON MICROSCOPY (SEM):

Morphological examination of the surface and internal structure of the dried beads of formulation F8 was performed using a scanning electron microscope (SEM). The samples are gold coated prior to the scanning. For examination of the internal structure of the beads, they were cut in half with a steel blade.

DETERMINATION OF SWELLING INDEX:

For determining the swelling index, the accurately weighed quantities of Nizatidine beads were suspended in 0.1 N HCl with pH 1.2 (simulated gastro intestinal fluids). Liquid droplets adhered to the surface of beads was removed by using blotting paper and then weighed it with the help of a microbalance.

The swollen beads were dried in oven at 60°C for 5 h or until showed the constant weight. The variation in swelling of Beads before and after drying was used to calculate the % of swelling index. The following equation was used. Swelling index= (Mass of swollen Beads - Mass of dry Beads /Mass of dried Beads) x 100.

ENTRAPMENT EFFICIENCY:

Nizatidine incorporation efficiency was analyzed by weighing 10 mg of floating Beads then dissolved in methanol. The above solution was agitated to solubilize the drug and polymers and to extract the drug. Then solution was filtered. The drug was determined using spectrophotometer at the λmax of 314 nm. The encapsulation efficiency was determined using the following equation.

% Drug entrapment = Calculated drug concentration / Theoretical drug concentration × 100.

DRUG CONTENT:

Drug content of prepared Nizatidine floating beads estimated in UVSpectrophotometry. An accurately weight quantity of floating beads (equivalent to 10 mg of Nizatidine) was taken and dissolved in 100 ml of 0.1N HCl, from the solution 1ml of solution was diluted to 10 ml and estimated the drug content by using UV at 314nm.

% Drug content = (Actual amount of drug in floating beads /Theoretical amount of drug in floating beads) X100

PERCENT PRACTICAL YIELD (PY):

Practical yield (%) was calculated to know about percent yield or efficiency. Floating Beads were collected and weighed to determine practical yield (PY) from the following equation.

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PY (%) = [Practical Mass / Theoretical Mass (Drug + Carrier)] × 100

BUOYANCY STUDIES:

Buoyancy test was carried out by weighing 100 mg of the Beads and transferred to a USP type II dissolutionfrom Lab India test apparatus containing 900 ml of simulated gastric fluid (0.1N HCl) at 37°C. Then Beads were separated at different time intervals and dried until a constant weight obtained. The % of buoyancy is calculated by using following equation.

$$Buoyancy\ \% = weightoffloatingbeadsinitial \times 100 / weightoffloatingbeads$$

IN VITRO DRUG RELEASE STUDIES:

Dissolution studies of Nizatidine floating Bead was estimated by using USP dissolution apparatus II from Lab India. Accurately weighed quantity of 100 mg floating Beads was transferred into 900 ml of 0.1N HCl medium and stirring at 100 rpm. Aliquots of samples were withdrawn at prespecified time intervals, filtered and diluted with similar medium finally assayed at 314nm using double beam spectrophotometer. The samples withdrawn were replaced with same dissolution medium and all the samples were analyzed in triplicate.

RELEASE ORDER KINETICS:

Drug release data of optimized floating Bead formulation were fitted to various kinetic models to reveal the drug release mechanism from the Beads. Those consist of Zero order, first order, Higuchi model and Korsmeyer-Peppas exponential equation and r2 values were determined.

1) Zero Order Kinetics Model – Cumulative % drug release versus Time T.
2) First Order Kinetics Model - Log cumulative percent drug remaining versus Time T.
3) Higuchi's model – cumulative percent drug released versus square root of Time T.
4) Korsmeyer equation / Peppa's model - Log cumulative percent Drug released versus log time.

III. RESULT AND DISCUSSION

Standard calibration plot of Nizatidine:

The λmax of Nizatidine in 0.1 N HCl buffer was found to be 314 nm. The absorbance values are tabulated in the table. Nizatidine obeyed Beer Lamberts law in the concentration range of 1-10 µg/ml with regression co-efficient 0.999.

Concentration (µg/ml)	Absorbance
o	00
2	0.09
4	0.18
6	0.26
8	0.35
10	0.44

Table 2: Absorbance of nizatidine in 0.1 N HCl buffer at 314 nm

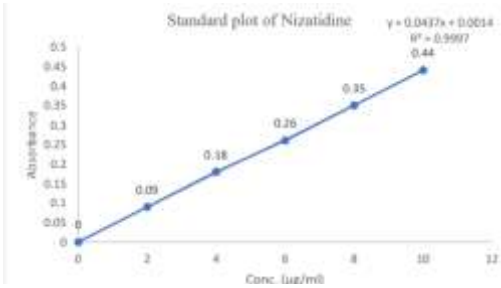

Figure 1: Standard curve of Nizatidine in 0.1N HCl

Drug and polymers used to prepare solid dispersions and inclusion complexes were checked for compatibility by carrying out FTIR spectroscopy. FTIR spectra obtained for pure drug and drug-polymer mixtures from 4000 to 400 cm-1 are given as follows:

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Drug and polymer compatibility studies
FTIR Analysis:

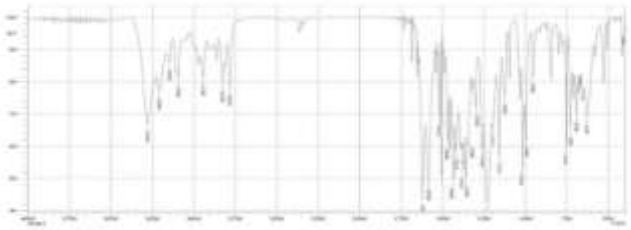

Figure 2: FTIR Analysis of Pure Drug (Nizatidine)

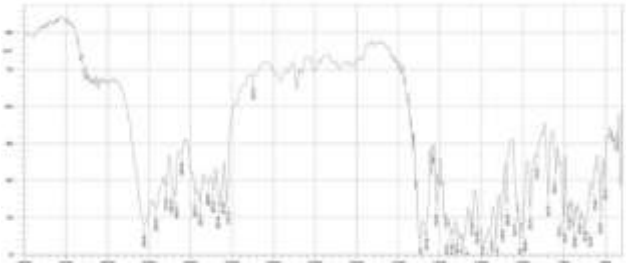

Figure 3: FTIR Analysis of Drug + HPMC K4M

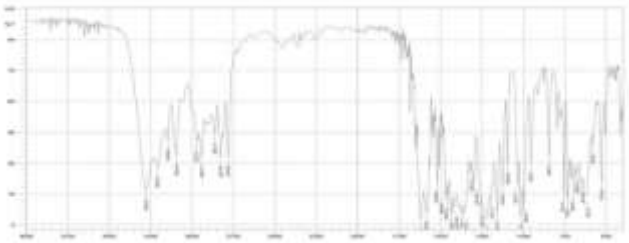

Figure 4: FTIR analysis of Drug + HPMC K 15M

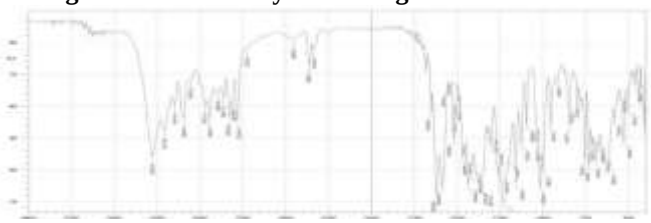

Figure 5: FTIR Analysis of Drug + HPMC K 100M

Table 3: FTIR characteristic peak along with polymer

Sl. no.	Functional group	Pure drug	Drug + HPMC K4M	Drug + HPMC K15M	Drug + HPMC K100M
1.	NH	1613.67	1615.87	1618.97	1613.64
2.	N=O	1516.19	1515.17	1518.22	1516.10
3.	C=N	1219.21	1216.23	1212.24	1219.18
4.	C-H	685.99	685.95	685.48	685.95
5.	C=C	1580.76	1579.27	1582.27	1580.73

EVALUATION OF FLOATING BEADS
Particle size:

The mean particle diameter of the floating beads was between 870 ± 0.005 to 998 ± 0.005µm. as the polymer concentration increases, the particle size also increases. An increase in particle size diameter was also due to an increase in the concentration of calcium carbonating as a gas generating agents. As the amount of calcium chloride was increased, the more cross-linking

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structure was observed that lead to decrease in particle size. The results are shown in Table no.4

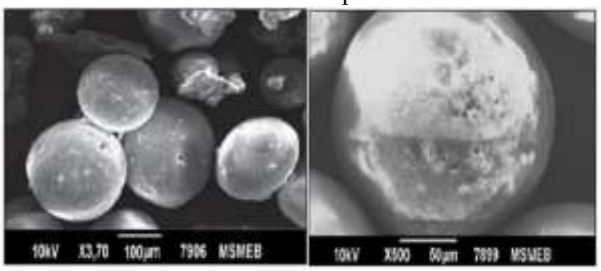

Figure 6: Cross-linking structure by SEM

Bulk density:
The bulk density of the formulation mixture of drug with different polymers was measured by graduated cylinder. The results are illustrated in Table No.4.

Tapped density:
The tapped density of the formulation mixture of drug with different polymers was measured by measuring cylinder. The results are shown in Table No.4.

Compressibility index:
Compressibility index (Carr's index) indicates the flow property of the beads. Flow property plays a major role in the dosage forms. Values of compressibility index below 15% indicate good flow whereas the values above 15% indicate poor flow property. The compressibility index of prepared formulation was calculated by using bulk density and tapped density results. The results are shown in the Table No.4.

Hausner's ratio:
It is an indirect index of ease of beads flow. Lower Hausner's ratio i.e., 1.25. The Hausner's ratio of prepared formulation was calculated by using bulk density and tapped density data. The results are shown in Table No.4.

Angle of repose (θ):
Angle of repose is direct index of the flow property. The angle of repose of various formulation blends of drug with different polymers was measured by using funnel method. The results are illustrated in Table No.4.

Table 4: Micrometrics evaluation of prepared Nizatidine floating Beads

Formulation	Particle size (µm)	Bulk density g/ml	Tapped density g/ cm3	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	950	0.59	0.63	6.61	1.07	27.8
F2	943	0.70	0.75	6.6	1.07	29.7
F3	989	0.72	0.76	4	1.05	31.9
F4	870	0.82	0.87	5.70	1.06	31.9
F5	897	0.54	0.57	5.12	1.05	34.8
F6	910	0.87	0.93	6.4	1.06	31.4
F7	922	0.75	0.80	6.11	1.03	28.7
F8	998	0.85	0.89	4.49	1.04	32.3
F9	940	0.75	0.78	3.84	1.04	30.2

Percentage (%) yield
The percentage yield of the different formulation was determined by weighing the beads after drying. The percentage yield of the various formulations was found to be in the range of 76.6%- 96.6% (Table 5). It was high, and it may be achieved due to optimum viscosity of the drugpolymer solution and ultimately increases the production yield of beads. Further, the yield of the beads is also increasing with the increase in the concentration of the polymer solution during formulation development.

Drug entrapment
The percentage drug entrapment efficiency of various formulations was found to be in the range of 71.1% - 76.44% w/w (Table5). In the present investigation, the encapsulation efficiency was found to be maximum (76.44% w/w) for the formulation.

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Percentage Buoyancy

The formulation F8 has shown the highest percentage buoyancy with minimum floating lag time (Table5). Buoyancy in percentage was found to be in the range of 51.72 % to 93.7%.

Swelling index

The swelling index results from 69.3% to 92.3%. The better results were observed in F8 formulation prepared with HPMC K100M as rate retarding polymer and the results are shown in Table5.

Floating time

The floating ability to prepare beads was evaluated along with dissolution studies. The time required for the beads to rise to the surface and float was determined as floating lag time.

In vitro drug release studies

The drug release from the floating beads of Nizatidine was controlled over a period of 12h and graphical representation of all the formulations were shown in figures. The Cumulative % drug release of formulation F8 was found to be 96.54 ± 0.72% at the end of 12 h.

Release order kinetics

The in vitro drug release profiles of all the formulations were fitted to several kinetic models and release data followed by their R2. The formulation was best fitted in Zero Order and Korsmeyer-Peppas. The formulation n value was 0.720 indicating non-Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion

Table5: Evaluation parameter for prepared Nizatidine Floating beads

Sl.no	Formulation	Buoyancy %	Entrapment efficiency %	Percent yield (%)	Swelling index %	Drug content (%)	Floating lag time (sec.)	Floating time (hrs)
1.	F1	52.44	75.1	82	80.1	75.11	49	≤12
2.	F2	51.72	71.1	80.0	87.3	71.11	43	≤12
3.	F3	75	71.5	84.04%	70.5	71.55	40	≤12
4.	F4	71.4	71.7	92.2%	83.4	71.77	51	≤12
5.	F5	61.2	72.8	78.0%	89.1	72.88	40	≤12
6.	F6	60	73.1	80.2%	69.3	73.11	47	≤12
7.	F7	81.0	74.8	76.7%	79.2	74.88	50	≤12
8.	F8	93.7	74.8	96.6%	92.3	75.77	33	≤12
9.	F9	66.6	74.4	86.4%	77.2	74.44	41	≤12

IV. CONCLUSION

Nizatidine is a histamine H_2 - receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastro esophageal reflux disease. Floating beads were prepared by ionotropic gelation method by using different ratio of drug and carrier. It is concluded that FTIR spectra showed that there was no interaction between drug and polymers; hence they are compatible. The beads were spherical in nature and evaluation of the beads are carried out to know the performance of the beads. The drug is combined with different grades of HPMC K4M, K15M, K100M in various ratios. The beads showed instantaneous and excellent buoyancy and remained a float on dissolution medium throughout the study period. The percentage yield of different formulations was found to be in the range of 76 % to 96%. The In-vitro release study showed that all the formulations gave better drug release. The entrapment efficiency of drug and HPMC K100M gave higher release than other formulations. In formulation F8 showed highest drug release i.e., 99.77% in 12 hr. as compared to other formulations.Thus, the objective of the present work of formulating a dosage form for Nizatidine using sodium alginate, HPMC K4M, K15M, K100M as rate controlling polymer, calcium carbonate as gas generating agent, calcium chloride has been achieved with the success.

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