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Nizatidine Based Floating Microspheres by Ionotropic Gelation Technique - Morphology and Release Characteristics

A. Shylaja Rani, U. Ashok Kumar, D.V. R. N. Bhikshapathi*

Mewar University, NH-79, Gangrar, Chhitorgarh-312901, Rajasthan, India

ABSTRACT

Nizatidine is a histamine H_2-receptor antagonist that inhibits stomach acid production and used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. The main aim of the present investigation was to develop gastro retentive floating microspheres for Nizatidine. These are prepared by ionotropic gelation method with an aim of increasing the gastric residence time and for controlled release. The polymeric mixture of Sodium alginate and HPMCK4, HPMC K15M and HPMC K 100M, was used as polymers. Calcium carbonate was used as the gas forming gent. Prepared Microspheres were characterized for the Micromeretic properties, incorporation efficiency, buoyancy test, SEM analysis, FTIR, and in vitro dissolution studies. The dissolution studies were carried out in 0.1N HCl and the results were applied to various kinetic models. Among the total 18 formulations F17 was optimized. The % yield of F17 formulation was found to be 95.47 ± 0.36%. Based on optical microscopy, the particle size was 50.67 ± 0.13µm. The % buoyancy, % entrapment efficiency and swelling index of F17 formulation was 94.23%, 93.62 ± 0.29% and 92.13 ± 0.17%, respectively. The Cumulative % drug release of F17 formulation was 98.23 ± 5.49% in 12 h when compared with marketed product 95.87 ± 0.31 in 12 h. SEM studies showed the particles were in spherical shape. Based on obtained results, Floating alginate Nizatidine microspheres were of good candidate for targeting to GIT.

Keywords: Nizatidine, Floating microspheres, Peptic ulcer, SEM, HPMC.

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***Corresponding author**: Dr. D.V. R. N. Bhikshapathi
Address: Mewar University, NH-79, Gangrar, Chhitorgarh-312901, Rajasthan, India
Tel.: +91-9848514228
E-mail ✉: dbpathi71@gmail.com

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INTRODUCTION

The floating drug delivery system was first described by Davis (1968). Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems. FDDS are known as Hydro dynamically balanced systems or low-density system that has been made developed to increase the gastric transit time of drug. [1] Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented

keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. [2] These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200µm. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. [3]

Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability and to target drug to specific sites. Floating microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance. [4]

Nizatidine is a histamine H_2-receptor antagonist that inhibits stomach acid production and used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. Nizatidine absorption and stability is found from the upper gastric mucosa, short half-life (1–2 h) and rapid clearance of it suggested as rationale drug for gastroretentive drug delivery as microspheres. [5] The present works aims to design gastroretentive drug delivery system for floating Nizatidine using microspheres as the carrier system that could give site specific and controlled drug release. The prepared microspheres were evaluated for particle size, micromeritics, entrapment efficiency, % yield, % drug release, % buoyancy, in vitro drug release studies and characterized by FTIR and SEM analysis.

MATERIALS AND METHODS

Formulation of Nizatidine Floating microspheres

Nizatidine Microspheres were prepared by using various excipients includes sodium alginate as microsphere core forming agent, HPMC K4M, HPMC K15M and HPMC K100M as rate controlling agent, calcium carbonate as gas generating agent, and calcium chloride as cross-linking agent.

Floating microspheres Preparation

Nizatidine Microspheres were formulated by ionotropic gelation technique mentioned in **Table 1**. Initially, 2% sodium alginate solution was prepared by dissolving in distilled water and stirred thoroughly by magnetically. On complete solution, accurately weighed quantity of drug followed by HPMC K4M, HPMC K15M, HPMC K100M and calcium carbonate of different weights were added to the above dispersion. Then the above dispersion was stirred at 500 rpm, maintained room temperature. The mixture was sonicated for 30 min to eliminate air bubbles that may have been formed during the stirring process. The homogenous dispersion was extruded using a 20G needle fitted with a 10 ml syringe into 100 ml of 1% of calcium chloride solution, being stirred at 100 rpm for 10 min into the gelation medium. Then microspheres were collected, washed with distilled water and oven dried at 60°C. [6]

Evaluation Parameters

Micromeritic properties

The characterization of prepared microspheres was carried out by particle size, angle of repose, bulk density, tapped density, Carr's index and %buoyancy. [7]

Determination of swelling index

For determining the swelling index, the accurately weighed quantities of Nizatidine microspheres were suspended in 0.1 N HCl with pH 1.2 (simulated gastro intestinal fluids). Liquid droplets adhered to the surface of microspheres was removed by using blotting paper and then weighed it with the help of a microbalance. The swollen microspheres were dried in oven at 60°C for 5 h or until showed the constant weight. [8] The variation in swelling of microspheres before and after drying was used to calculate the % of swelling index. The following equation was used.

Swelling index= (Mass of swollen microspheres - Mass of dry microspheres/mass of dried microspheres) 100.

% yield of microspheres

The prepared Nizatidine microspheres were collected and weighed. The actual weight of obtained microspheres divided by total weight of added drug and polymer was used for the calculation of % yield and mentioned below [9]

% yield = [Total weight of microspheres / Total weight of drug and polymer] × 100

Entrapment efficiency

Nizatidine incorporation efficiency was analyzed by weighing 10 mg of floating microspheres then dissolved in methanol. The above solution was agitated to solubilize the drug and polymers and to extract the drug. Then solution was filtered using membrane filter (0.45µm) to separate shell fragments. The drug was determined using spectrophotometer (Shimadzu, UV-1800) at the λ_{max} of 224 nm. [9] The encapsulation efficiency was determined using the following equation.

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

Test for buoyancy

Buoyancy test was carried out by weighing 100 mg of the microspheres and transferred to a USP type II dissolution test apparatus containing 900 ml of simulated gastric fluid (0.1N HCl) at 37°C. The content of the beakers was stirred at 100 rpm. Then microspheres were separated at different time intervals and dried until a constant weight obtained. [10] The % of buoyancy is calculated by using following equation.

$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

In vitro drug release

Nizatidine floating microspheres release studies of were conducted in 900 ml of simulated gastric fluid (0.1N HCl pH 1.2) at 37 ± 0.5°C by using USP

dissolution apparatus II. Accurately weighed quantity of 100 mg floating microspheres 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 224 nm using double beam spectrophotometer. The samples withdrawn were replaced with same dissolution medium and all the samples were analyzed in triplicate. [11]

Release order kinetics

Drug release data of optimized floating microspheres formulation were fitted to various kinetic models to reveal the drug release mechanism from the microspheres. Those consist of Zero order, first order, Higuchi model and Korsmeyer-Peppas exponential equation and r^2 values were determined.

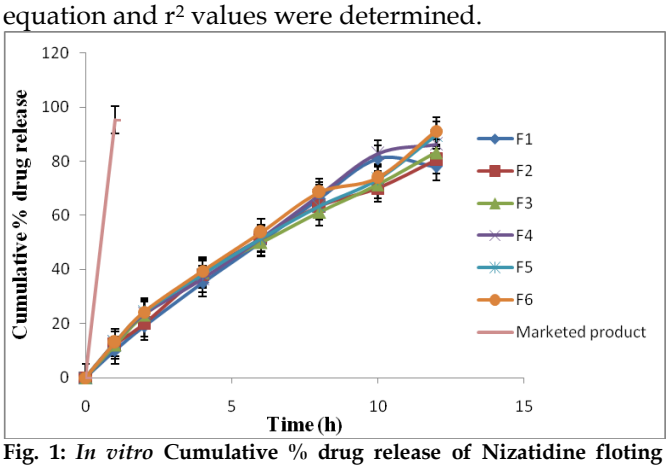

Fig. 1: *In vitro* Cumulative % drug release of Nizatidine floting microspheres F1 to F6 and marketed product

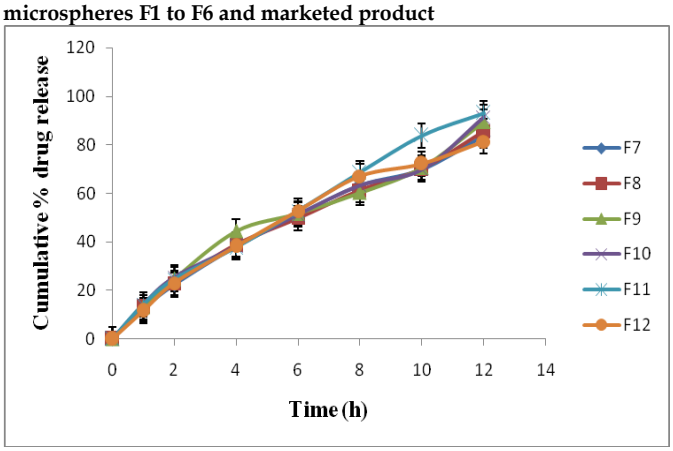

Fig. 2: *In vitro* Cumulative % drug release of Nizatidine floating microspheres from F7 to F12

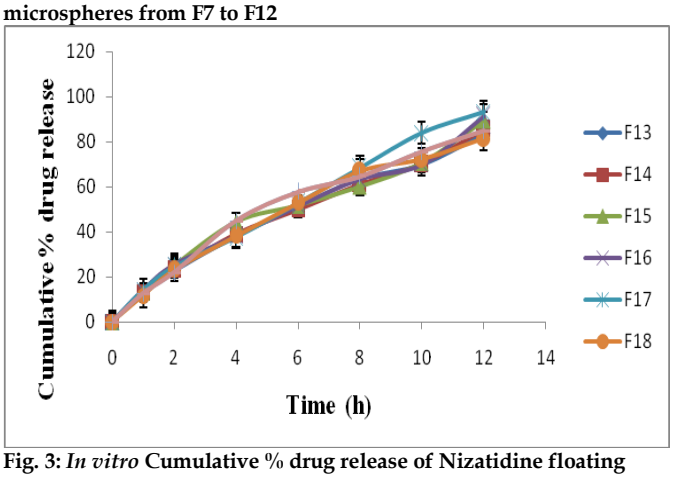

Fig. 3: *In vitro* Cumulative % drug release of Nizatidine floating microspheres from F13 to F18

Mathematical modeling of optimized formulation (F17)

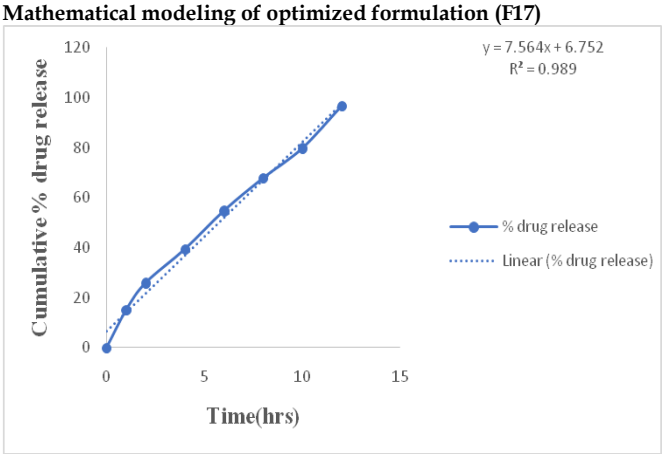

Fig. 4: Zero order plots for the optimized formulation of floating microspheres (F17)

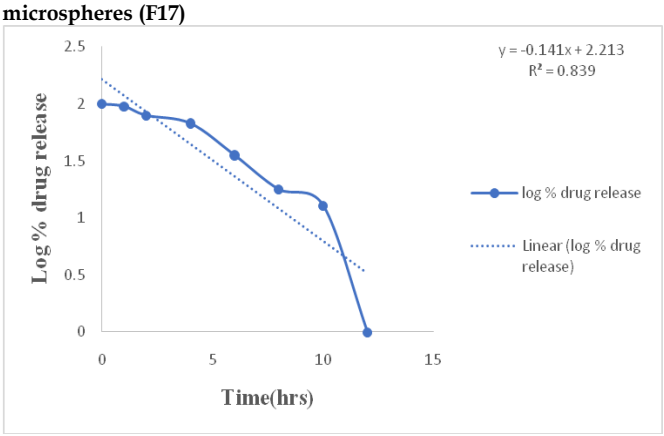

Fig. 5: First order plot for the optimized formulation of floating microspheres (F17)

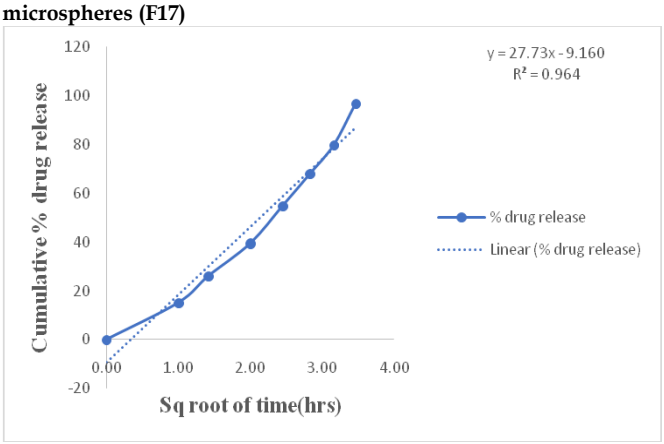

Fig. 6: Higuchi model for the optimized formulation of floating microspheres (F17)

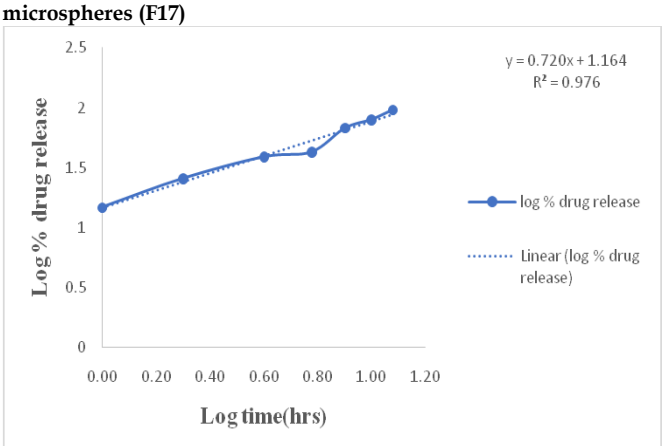

Fig. 7: Korsmeyer Peppas model for the optimized formulation of floating microspheres (F17)

Table 1: Formulation trials of Nizatidine Floating microspheres

Formulation code	Nizatidine (mg)	Sodium alginate (%)	HPMCK 4M (mg)	Calcium Carbonate (mg)	Calcium Chloride (%)
F1	150	2	300	50	1
F2	150	2	250	100	1
F3	150	2	200	150	1
F4	150	2	150	200	1
F5	150	2	100	250	1
F6	150	2	50	300	1
Formulation Code	**Nizatidine (mg)**	**Sodium alginate (%)**	**HPMC K15M (mg)**	**Calcium carbonate (mg)**	**Calcium chloride (%)**
F7	150	2	300	50	1
F8	150	2	250	100	1
F9	150	2	200	150	1
F10	150	2	150	200	1
F11	150	2	100	250	1
F12	150	2	50	300	**1**
Formulation Code	**Nizatidine (mg)**	**Sodium alginate (%)**	**HPMC K100M (mg)**	**Calcium carbonate (mg)**	**Calcium chloride (%)**
F13	150	2	300	50	1
F14	150	2	250	100	1
F15	150	2	200	150	1
F16	150	2	150	200	1
F17	150	2	100	250	1
F18	150	2	50	300	1

Table 2: Micromeretic properties of Nizatidine floating microspheres

Formulation Code	Particle Size (µm)	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's Index (%)	Buoyancy%
F1	55.45 ± 0.04	0.59	0.58	27°.93	14.56	50.13
F2	60.12 ± 0.08	0.66	0.59	23°.91	9.34	64.42
F3	65.29 ± 0.13	0.74	0.62	29°.67	8.34	78.86
F4	73.43 ± 0.04	0.76	0.73	30°.54	13.36	69.53
F5	62.35 ± 0.04	0.59	0.57	27.94	8.12	91.24
F6	79.67 ± 0.09	0.89	0.83	30°.15	9.23	67.12
F8	75.45 ± 0.09	0.67	0.72	25°.54	13.95	90.17
F9	55.23 ± 0.14	0.51	0.63	22°.91	10.32	65.08
F10	63.22 ± 0.11	0.79	0.75	23.70	11.04	52.05
F11	83.34 ± 0.10	0.68	0.65	30°.24	12.34	66.74
F12	78.45 ± 0.21	0.67	0.55	22°.91	10.98	87.29
F13	65.32 ± 0.09	0.82	0.82	25°.54	13.95	70.18
F14	55.23 ± 0.14	0.56	0.63	22°.91	10.32	75.30
F15	73.22 ± 0.11	0.72	0.77	21.70	8.08	75.64
F16	81.34 ± 0.10	0.68	0.65	30°.24	12.34	80.47
F17	50.67 ± 0.13	0.47	0.51	20°.74	7.67	94.23
F18	74.35 ± 0.32	0.80	0.72	29°.67	11.43	85.16

Table 3: % yield, % swelling index, and entrapment efficiency of Nizatidine Floating microspheres formulations

Formulation Code	Percentage Yield (%)	Swelling index (%)	Entrapment Efficiency (%)
F1	90.35 ± 0.12	82.24 ± 0.24	70.23 ± 0.31
F2	84.35 ± 0.35	78.24 ± 0.16	89.14 ± 0.22
F3	77.95 ± 0.27	80.15 ± 0.31	87.63 ± 0.17
F4	92.45 ± 0.21	70.51 ± 0.28	83.45 ± 0.34
F5	68.75 ± 0.32	87.31 ± 0.25	78.29 ± 0.12
F6	83.92 ± 0.28	80.19 ± 0.17	67.83 ± 0.35
F7	65.45 ± 0.19	76.17 ± 0.23	73.16 ± 0.30
F8	74.35 ± 0.17	82.93 ± 0.36	65.27 ± 0.21
F9	88.65 ± 0.36	85.31 ± 0.24	78.13 ± 0.15
F10	78.35 ± 0.33	69.27 ± 0.19	75.52 ± 0.28
F11	86.98 ± 0.29	89.11 ± 0.33	82.94 ± 0.11
F12	91.23 ± 0.12	83.34 ± 0.27	71.11 ± 0.32
F13	62.75 ± 0.25	73.92 ± 0.12	78.25 ± 0.33
F14	82.34 ± 0.31	88.92 ± 0.26	75.16 ± 0.14
F15	76.95 ± 0.11	81.62 ± 0.31	70.19 ± 0.26
F16	85.45 ± 0.24	77.24 ± 0.32	68.10 ± 0.15
F17	95.47 ± 0.36	92.13 ± 0.17	93.62 ± 0.29
F18	80.42 ± 0.29	79. 19 ± 0.30	84.73 ± 0.13

Drug-excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

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

SEM studies

Surface nature of microspheres includes size and shape was examined with the help of Scanning Electron Microscope (HITACHI, S-3700N). The microspheres were dried completely prior to analysis and SEM was carried out at various magnifications. [12]

Stability studies

Optimized formulation was subjected to stability testing at 40°C ± 2°C/75% RH ± 5% RH for 6 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0,

30, 60, 120 and 180 days period according to ICH guidelines. Various *in vitro* parameters like % yield, entrapment efficiency and *in vitro* release studies were determined. [13]

Table 4: Release order kinetics of optimized formulation Reference Standard

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	Peppas n value
F1	0.905	0.668	0.911	0.922	0.555
F2	0.911	0.711	0.914	0.933	0.636
F3	0.965	0.815	0.922	0.944	0.587
F4	0.925	0.718	0.922	0.924	0.688
F5	0.954	0.804	0.931	0.941	0.647
F6	0.907	0.709	0.918	0.933	0.599
F7	0.913	0.804	0.949	0.916	0.596
F8	0.939	0.721	0.922	0.951	0.666
F9	0.957	0.807	0.949	0.55	0.647
F10	0.981	0.819	0.933	0.922	0.720
F11	0.977	0.824	0.952	0.970	0.567
F12	0.984	0.785	0.944	0.958	0.679
F13	0.957	0.824	0.919	0.949	0.622
F14	0.944	0.829	0.958	0.971	0.597
F15	0.954	0.819	0.911	0.947	0.711
F16	0.980	0.824	0.957	0.967	0.714
F17	0.989	0.839	0.964	0.976	0.720
F18	0.944	0.816	0.954	0.967	0.711
Marketed product	0.77	0.936	0.921	0.948	0.393

Table 5: Staility studies of optimized floating microspheres

Retest Time for Optimized formulation	% yield	Entrapment efficiency (%)	*In vitro* drug release profile (%)
0 day	95.47 ± 0.36	92.13 ± 0.17	96.54 ± 0.72
30 days	94.75 ± 0.242	91.91 ± 0.186	96.25 ± 0.293
60 days	94.28 ± 0.173	91.26 ± 0.153	95.33 ± 0.184
120 days	93.61 ± 0.265	90.87 ± 0.291	94.19 ± 0.253
180 days	93.12 ± 0.321	90.33 ± 0.172	93.65 ± 0.341

RESULTS AND DISCUSSION

The particle size, % buoyancy and micromeritic properties of the microspheres were determined in the form of bulk density, tapped density, angle of repose and carr's index results mentioned in Table 2. The size of prepared microspheres ranged in from 50.67 ± 0.13 to 83.34 ± 0.10µm, comparatively, lower particle size was observed in HPMC K100M as rate retarding polymer. The bulk density and tapped density of were ranged from 0.47 to 0.89 g/ml and 0.51 to 0.83 g/ml, respectively. The angle of repose values was in the range of 20˚.74 - 30˚.54, which shows excellent to good flow properties, while the carr's index for all formulations was in the range of 7.67% - 14.56%, which indicated excellent to good flow properties. This suggests that the microspheres can be easily handled during processing. The % buoyancies of the microspheres were found highest (94.23) in F17 this may be due to slow penetration of the dissolution medium in the microspheres, as HPMC K100M is better water swellable polymer than HPMC K4M and HPMC K15M.

Entrapment efficiency, % yield and swelling index

The % yields ranged from 62.75% to 95.47% with the % entrapment efficiency being between 65.27% to 93.62%. The swelling index results from 69.27% to 92.13%. The better results were observed in F17 formulation prepared with HPMC K100M as rate retarding polymer and the results are shown in Table 3.

Mathematical modeling of Marketed product

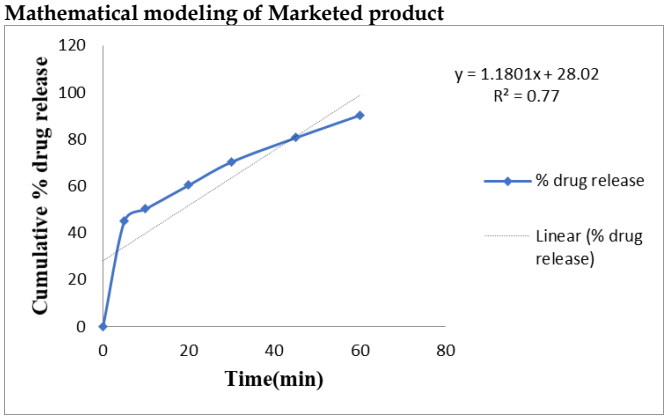

Fig. 8: Zero order plot for Marketed product

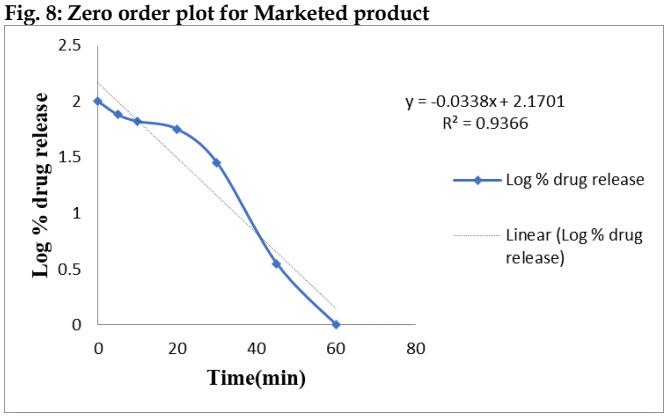

Fig. 9: First order plot for Marketed product

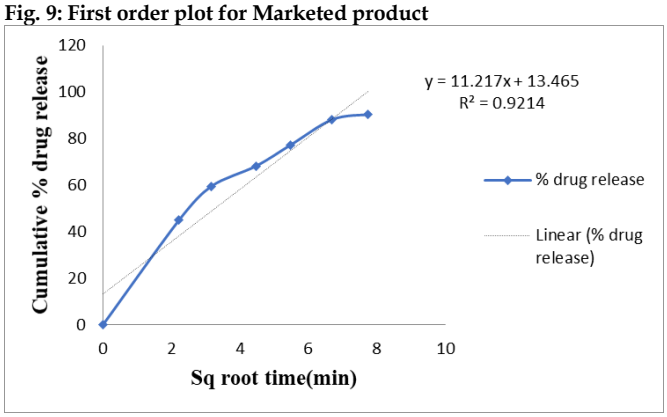

Fig. 10: Higuchi model for Marketed product

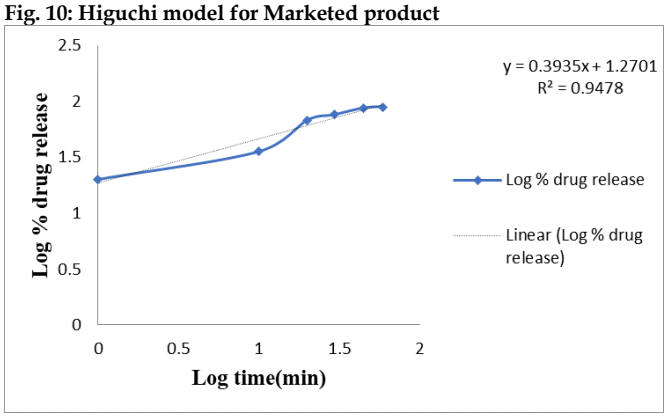

Fig. 11: Korsmeyer Peppas model for Marketed product

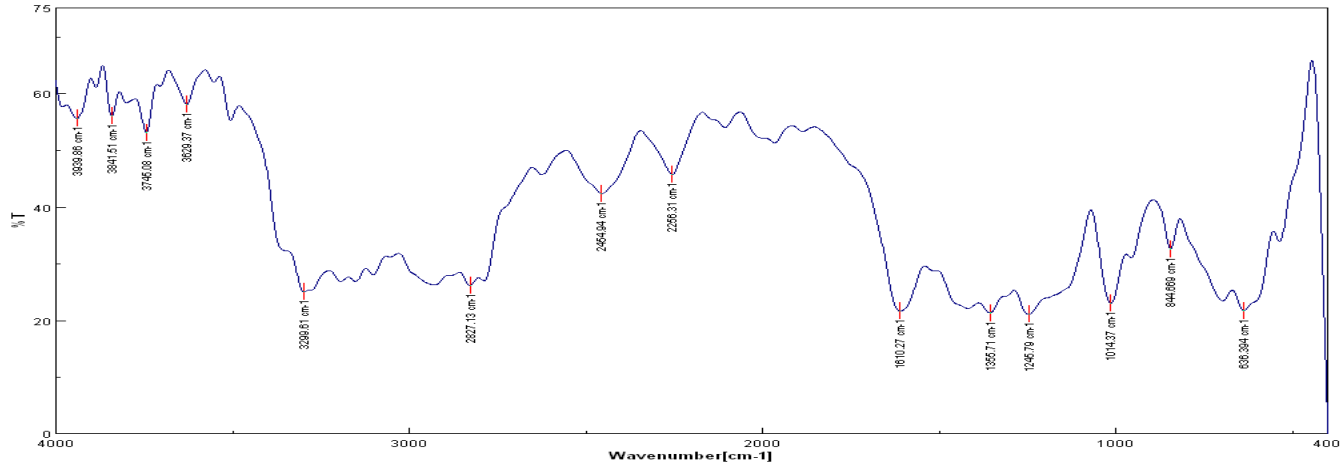

Fig. 12: FTIR spectrum of pure drug Nizatidine

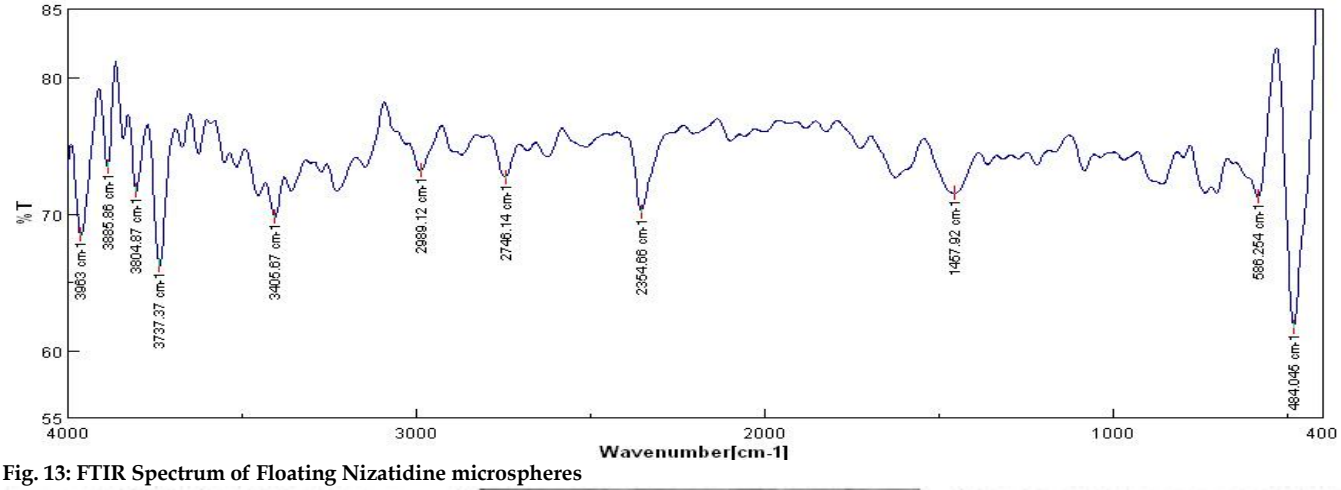

Fig. 13: FTIR Spectrum of Floating Nizatidine microspheres

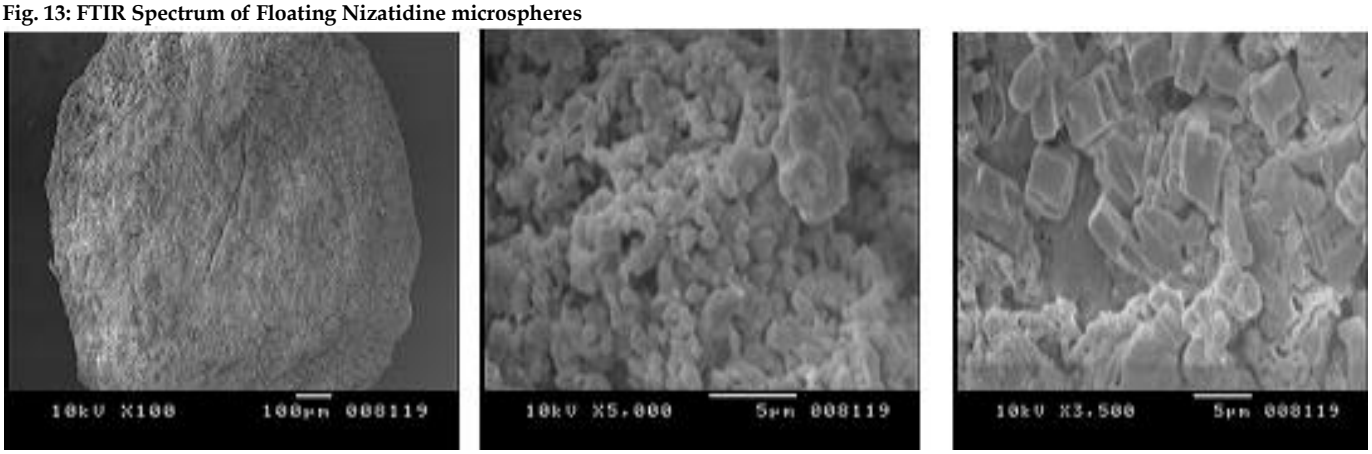

Fig. 14: Scanning electron micrographs of optimized floating microspheres

In vitro drug release studies

The drug release from the floating microspheres of Nizatidine was controlled over a period of 12h and graphical representation of all the formulations were shown in Figures 1, 2 & 3. The Cumulative % drug release of optimized formulation F17 was found to be 96.54 ± 0.72% at the end of 12 h where as marketed product noted 94.53 ± 0.26% within 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 R^2 and n values shown in Table 4. The optimized formulation was best fitted in Zero Order and Korsmeyer-Peppas (Figure 4-7). The optimized formulation n value was 0.720 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion. The marketed conventional formulation followed the first order kinetics indicating drug release is directly proportional to the concentration of drug (Figure 8-11).

Drug excipient compatibility studies

FTIR spectroscopy of Nizatidine microspheres

The FTIR spectrum of pure drug (Figure 13) showed characteristic sharp peaks at 3421 cm^{-1} (C-N stretch), 2951 cm^{-1} (C-H stretch), 1436 cm^{-1} (C=H deformation in NCH, CH), 1500 cm^{-1} (CH & OCH groups), 1587 cm^{-1} (Conjugated with NO), 1419 cm^{-1} for CH_2 bond. There were no new significant bonds observed in the pure

drug (Figure 12) and optimized formulation (Figure 13), which indicates that no interaction observed between the drug and excipients.

SEM studies of Nizatidine microspheres

The microspheres surface was rough and spherical in shape as seen in Figure 14. The surface of the Nizatidine microspheres was rough due to higher concentration of drug consistently discreted at the molecular level in the matrices.

Stability studies

Stability studies of optimized Nizatidine microspheres as per ICH guidelines was carried out for 6months at 40°C ± 2°C/75% RH ± 5% RH showed in the Table 5. At predetermined time intervals samples were withdrawn and subjected to % yield, entrapment efficiency and *in vitro* drug release analysis. Significant change was not observed in results before and after stability studies. Indicating the optimized formulation (F17) was stable.

Nizatidine loaded floating microspheres were prepared by ionotropic gelation method. From the results it concluded that formulation F17 was found to be satisfactory results in terms of excellent Micromeretic properties, particle size (50.67 ± 0.13µm), yield of microsphere (95.47 ± 0.36%), Entrapment efficiency (93.67 ± 0.29%), % buoyancy (94.23%), swelling index (92.13 ± 0.17%) and highest *in vitro* drug release of 98.23 ± 5.49% in a sustained manner with constant fashion over extended period for 12 h compared with marketed product 95.87 ± 0.31 in 12 h. The drug and excipients were compatible studied by using FTIR. Drug release from Nizatidine microspheres followed Zero order and Higuchi model. It was suggested that mechanism of drug release from microspheres was diffusion controlled. The prepared microspheres were spherical in shape studied by SEM studies. The optimized formulation F17 was stable. Hence the formulated and prepared floating Nizatidine microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability.

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