

FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERES OF NIZATIDINE FOR GASTRORETENTIVE DRUG DELIVERY**Biru Kumar Thakur*, Dr. Nilesh Jain, Dr. R.B. Goswami****Sagar Institute of Research Technology & Science–Pharmacy Ayodhya Bypass Road, Bhopal***Corresponding Author's E mail: Kumarbiru323@gmail.com

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ABSTRACT

Nizatidine is a histamine H₂-receptor antagonist that inhibits stomach acid production and used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. The present study involves preparation and evaluation of floating microspheres using nizatidine as a model drug for improving the drug bioavailability by prolongation of gastric retention time. HPMC, Eudragit RL 100, Eudragit RSPO microspheres loaded with nizatidine were prepared by solvent diffusion evaporation method. The microspheres had smooth surfaces with free-flowing and good-packing properties. The formulated batches were evaluated for percentage yield, particle size measurement, flow properties, percent entrapment efficiency, swelling studies, zeta potential and In-vitro release. The yield of the microspheres (F1-F6) was range from 65.58±0.25 to 78.85±0.36% and F5 microspheres entrapped the maximum amount of the drug. Particle size and zeta potential of optimized microsphere formulation F5 was found to be 210.25 nm and -38.58 mV. The prepared microspheres (F5) exhibited prolonged drug release and percentage buoyancy was found to 79.92±0.36. The formulations were subjected to stability studies and release kinetics data was subjected to different dissolution models. It was concluded that developed floating microspheres of nizatidine offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

Keywords: Nizatidine, Solvent diffusion evaporation method, Hydroxyl propyl methyl cellulose, Eudragit

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 medications². These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200 μ m. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug³. 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 compliance⁴. Nizatidine is a histamine H₂-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 microspheres⁵. The present work 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, entrapment efficiency, % yield, % drug release, % buoyancy, in vitro drug release studies and stability study.

MATERIAL AND METHODS

Material

Nizatidine was obtained as a gift sample from Macleods Pharmaceuticals, Mumbai. Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Eudragit RL 100, Eudragit RSPO, hydroxyl propyl methyl cellulose was purchased from Loba Chem. Pvt. Ltd, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Preparation of floating microsphere of Nizatidine

Floating microspheres loaded with nizatidine were prepared using solvent-evaporation method using HPMC, Eudragit RL 100, Eudragit RSPO in different ratio table 1. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at 27 $\pm$ 2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40 $\pm$ 2°C and stored in desiccator⁶.

Table 1 Formulations of the floating microspheres prepared

S. No.	Formulation Code	Nizatidine (mg)	HPMC (mg)	Eudragit RL 100 (mg)	Eudragit RSPO (mg)
1.	F1	75	100	25	-
2.	F2	75	100	50	-
3.	F3	75	100	75	-
4.	F4	75	150	25	10
5.	F5	75	150	50	20
6.	F6	75	150	75	30

Evaluation of microspheres

Microscopic Observation of prepared Microsphere

An optical microscope (cippon, Japan) with a camera attachment (Minolta) was used to observe the shape of the prepared microsphere formulation.

Percentage Yield

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

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

Drug Entrapment

The various formulations of the Floating microspheres were subjected for drug content. 10 mg of Floating microspheres from all batches were accurately weighed and crushed. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior

Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. 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.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement.

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate.

Shape and surface characterization of microspheres by scanning electron microscopy (SEM)

From the formulated batches of microspheres, formulations (F5) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

***In-vitro* release studies**

The *in vitro* drug release rate from Floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl (pH=1.2) maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 316nm to determine the concentration of drug present in the dissolution medium^{7,8}.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time)⁹⁻¹¹.

Stability studies for optimized formulation

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature,

humidity and light and to establish a re-test period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. long term, Accelerated and where appropriate, Intermediate.

RESULTS AND DISCUSSION

The floating microspheres of nizatidine were prepared by solvent diffusion-evaporation method. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 65.58 ± 0.25 to $78.85 \pm 0.36\%$ Table 2. The maximum percentage yield was found in formulation F5, 78.85 ± 0.36 as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 63.25 ± 0.21 to $76.62 \pm 0.15\%$ w/w. The maximum percentage drug entrapment was found in formulation F3 ($76.62 \pm 0.15\%$ w/w) Table 3. To assess the floating properties, the microspheres were placed in 0.1N hydrochloric acid. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range of 69.95 ± 0.42 to 79.92 ± 0.36 . The nature of the polymer influenced the floating behaviour of the microspheres Table 4. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F5 in floating microsphere. The optimized formulation of F5 was subjected to further studies. The mean size of the microspheres was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a scattering angle of 90° . The results of measurement of mean particle size of optimized formulation F5 of floating microsphere was found to be 210.25nm Figure 1. Results of zeta potential of optimized formulation F5 of floating microsphere was found to be -38.58mV Figure 2. The drug release from floating microspheres was found to be 99.74% at the end of 12 h for F5 Table 5. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microsphere was maximum zero order i.e 0.997 hence indicating drug releases from formulations was found to follow Higuchi for floating microsphere Table 6 & 7. According to ICH guidelines, 3 months accelerated stability study at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH optimized formulations (F3) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference observed in the drug content between initial and formulations stored at $40 \pm 2^\circ\text{C}$ & $75 \pm 5\%$ RH for 3 months.

Table 2 Percentage yield for different formulation

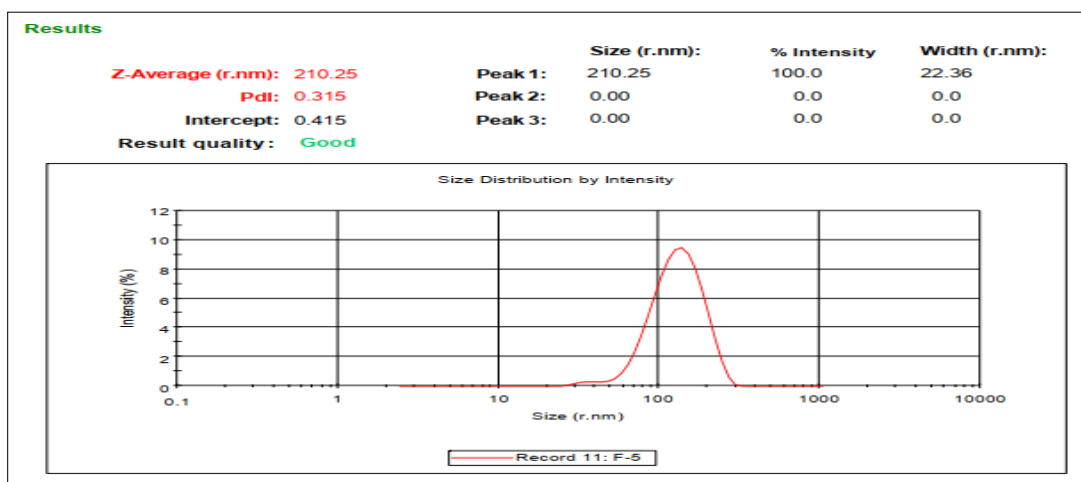
S. No.	Formulation	Percentage Yield
1.	F1	65.58±0.25
2.	F2	69.95±0.36
3.	F3	67.74±0.21
4.	F4	73.32±0.40
5.	F5	78.85±0.36
6.	F6	70.14±0.32

Table 3 Drug entrapment for different formulations

S. No.	Formulation	Drug entrapment (% w/w) of prepared microsphere
1.	F1	63.25±0.21
2.	F2	65.45±0.25
3.	F3	68.85±0.36
4.	F4	72.25±0.21
5.	F5	76.62±0.15
6.	F6	71.25±0.35

Table 4 Percentage Buoyancy and floating lag time of floating microsphere

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	73±4	72.25±0.32
F2	69±3	69.95±0.42
F3	78±5	73.32±0.25
F4	76±3	73.25±0.42
F5	52±6	79.92±0.36
F6	69±2	71.15±0.41

**Figure 1 Particle size data of optimized microsphere formulation F5**

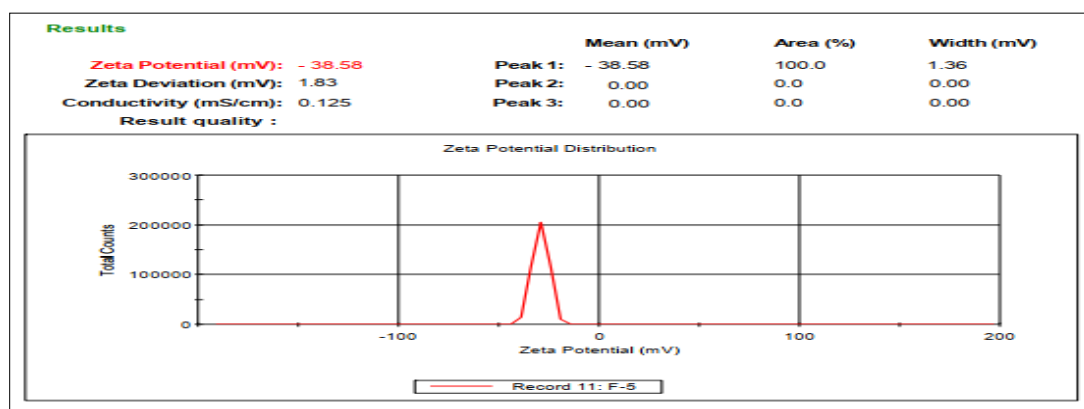


Figure 2 Zeta potential data of floating microsphere F5

Table 5 Release Study data of formulation F1-F6

Time (Hrs)	% of Drug Release						Marketed Formulation (Nizatidine 150mg Tablet)
	F1	F2	F3	F4	F5	F6	
0.5	37.85	34.45	31.15	26.65	25.56	22.25	36.65
1	49.98	45.58	35.65	39.98	33.32	31.14	63.32
2	63.32	60.23	43.32	45.58	42.25	40.56	95.56
4	78.85	70.23	68.85	63.32	58.85	50.14	99.12
6	86.65	76.65	71.14	75.65	69.98	63.32	-
8	98.12	93.32	89.98	83.32	78.85	75.65	-
10	99.45	99.45	99.85	98.85	89.98	82.23	-
12	99.65	99.95	99.96	99.85	99.74	89.98	-

Table 6 Release Kinetics of optimized formulation of microsphere F5

Time (h)	Square Root of Time(h) ^{1/2}	Log Time	Cumulative% Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	25.56	1.408	74.44	1.872
1	1.000	0.000	33.32	1.523	66.68	1.824
2	1.414	0.301	42.25	1.626	57.75	1.762
4	2.000	0.602	58.85	1.770	41.15	1.614
6	2.449	0.778	69.98	1.845	30.02	1.477
8	2.828	0.903	78.85	1.897	21.15	1.325
10	3.162	1.000	89.98	1.954	10.02	1.001
12	3.464	1.079	99.74	1.999	0.26	-0.585

Table 7 Comparative study of regression coefficient for selection of optimized Formulation F5

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.980	0.729	0.997	0.995

CONCLUSION

Floating microspheres of Nizatidine as a gastro retentive drug delivery system specifically control the release rate of drugs to a particular site and facilitate an enormous effect on health care. Microspheres of different size and drug content could be obtained by varying the formulation variables. On the basis of drug release, percentage yield, drug entrapment, percentage buoyancy and floating lag time F5 could be considered as promising formulations. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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