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DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERE FOR EFFECTIVE TREATMENT OF GASTRIC ULCER

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ABSTRACT

The present study was to prepare and evaluate the floating microspheres of Esomeprazole as a model drug for prolongation of the gastric retention time for oral delivery. Esomeprazole is a proton pump inhibitor which acts by irreversibly blocking the (H+K+)-ATPase enzyme system of the gastric parietal cell. Its half-life is 1-1.5 hrs. Esomeprazole poor absorption may be because of degradation in gastric acid which can be prevented by incorporation of sodium bi carbonate which is a systemic antacid and act as buffer. The Esomeprazole floating microspheres were prepared by double emulsion solvent diffusion method by using Ethyl cellulose and different grades of Eudragit RLPO and RSPO, using Dichloromethane and alcohol solvent systems. The drug entrapment efficacies of different formulations were in range of 63.21±0.36- 75.45±0.14% w/w. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. The optimized formulation of both batches subjected to further studies.

Keywords: Esomeprazole, Floating microspheres, Evaluation, RLPO, RSPO.

INTRODUCTION

Medication activity can be enhanced by growing new medication conveyance framework, for example, the microsphere sedate conveyance framework. These frameworks stay in close contact with the ingestion tissue, the mucous layer, discharging the medication at the activity site prompting a bioavailability increment and both nearby and foundational impacts [1]. The oral course of medication organization constitutes the most helpful and favoured methods for sedate conveyance to foundational dissemination of body. However oral organization of the greater part of the medications in traditional

measurements frames has here and now restrictions because of their failure to limit and confine the framework at gastro-intestinal tract.

Microspheres constitute an essential piece of these particulate medication conveyance frameworks by uprightness of their little size and productive bearer limit. Microspheres are the bearer connected medication conveyance framework in which molecule estimate is ranges from 1-1000 µm extend in distance across having a centre of medication and completely external layers of polymer as covering material. Be that as it may, the accomplishment of these microspheres is restricted because of their short habitation time at site of assimilation. It would, in this way be worthwhile to have implies for giving a private contact of the medication conveyance framework with the engrossing layer. Microspheres have focal points like proficient retention and upgraded bioavailability of the medications because of a high surface to volume proportion, a substantially more cozy contact with the bodily fluid layer and particular focusing of medications to the ingestion site [2].

Microspheres incorporate microparticles and microcapsules (having a center of medication) of 1-1000µm in distance across and comprising either totally of a floating polymer or having an external covering of it, individually. Microspheres, as a rule, can possibly be utilized for focused and controlled discharge sedate conveyance; however, coupling of floating properties to microspheres has extra preferences e.g. effective assimilation and bioavailability of the medications because of high surface to volume proportion, a considerably more personal contact with the mucous layer, particular focusing of medications to the ingestion site.

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. Floating or hydrodynamically controlled drug delivery systems are useful in such applications. Various gastroretentive dosage forms are available, including tablets, capsules, pills, laminated films, floating microspheres, granules and powders. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. Such systems have more advantages over the single-unit dosage forms.So our aim of the study is formulation, development and evaluation of Floating microspheres of esomeprazole.

MATERIAL AND METHOD

Esomeprazolewas obtained as a gift sample from Torrent Pharma Ltd., Ahmedabad, India. Hydroxypropylmethylcellulose (HPMC) was purchased from Himedia labs, Mumbai. Eudragit RLPO and Eudragit RSPO were obtained from Sigma Aldrich, Mumbai. All other chemicals and solvents were of analytical grade and used as received. Distilled water was prepared in laboratory using all glass distillation apparatus.

Preparation of floating microsphere of Esomeprazole

Floating microspheres loaded with Esomeprazole were prepared using solvent-evaporation method using HPMC and Eudragit RLPO 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±2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desicator[3-4].

Table 1: Formulations of the floating microspheres prepared

S. No.	Formulation Code	Esomeprazole (mg)	HPMC (mg)	Eudragit RLPO (mg)	Eudragit RSPO (mg)
1.	F1	15	50	50	-
2.	F2	15	50	75	-
3.	F3	15	50	100	-
4.	F4	15	50	-	50
5.	F5	15	50	-	75
6.	F6	15	50	-	100

Evaluation of microspheres

Percentage Yield

The prepared microspheres with a size range of 1μm to 1000μmwere 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.

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

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[5].The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than 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[6]. 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.

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

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[7].

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[8].

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[9,10]. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37±0.5°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 282 nm to determine the concentration of drug present in the dissolution medium.

RESULTS AND DISCUSSION

Results and Discussion

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±0.41 – 78.58±0.14%. The maximum percentage yield was found in formulation F3, 78.58±0.14 as compare to all formulation table 2.The drug entrapment efficacies of different formulations were in range of 63.21±0.36- 75.45±0.14% w/w. Results demonstrated that increase in concentration of polymer increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulations. The maximum drug entrapment was found in formulation F-3 (75.45±0.14) table 2.The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. The optimized formulation of both batches subjected to further studies table 2.The results of measurement of mean particle size of optimized formulation F3 of floating microsphere was found to be 189.3 nm figure 1.Results of zeta potential of optimized formulation F3 of floating microsphere was found -26.3 mV figure 2**.**

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield	Drug entrapment (% w/w) of prepared microsphere	Percentage Buoyancy
1.	F1	75.35±0.45	69.98±0.45	65.47±0.45
2.	F2	69.98±0.23	65.45±0.32	69.98±0.32
3.	F3	78.58±0.14	75.45±0.14	75.45±0.41
4.	F4	70.23±0.36	69.98±0.25	65.45±0.25
5.	F5	65.58±0.41	63.21±0.36	63.32±0.36
6.	F6	71.14±0.32	69.74±0.47	69.74±0.45

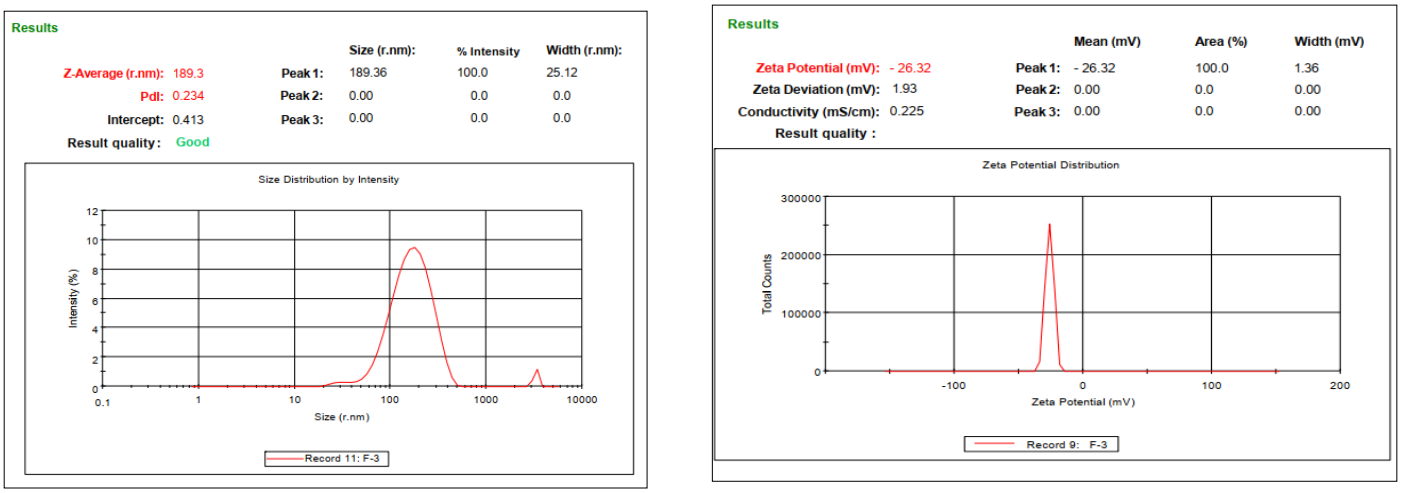

Figure 1: Particle size and Zeta potential of optimized microsphereformulation F3

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, 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 0.979 hence indicating drug releases from formulations was found to followzero order for floating microsphere.

Table 3: Release Kinetics of optimized formulation of microsphere F3

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	23.32	1.368	76.68	1.885
1	1	0	36.65	1.564	63.35	1.802
2	1.414	0.301	45.58	1.659	54.42	1.736
4	2	0.602	52.23	1.718	47.77	1.679
6	2.449	0.778	63.32	1.802	36.68	1.564
8	2.828	0.903	75.56	1.878	24.44	1.388
10	3.162	1	89.98	1.954	10.02	1.001
12	3.464	1.079	99.42	1.997	0.58	-0.237

Table 4: Comparative study of regression coefficient for selection of optimized Formulation F3

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.979	0.752	0.972	0.972

Conclusion

Floating microspheres of esomeprazole were prepared using solvent-evaporation method using HPMC and Eudragit RLPO. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. The optimized formulation of both batches subjected to further studies. Based on the entrapment efficiency, in vitro release F3 was found to be best formulation.

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