

Formulation and Evaluation of Floating Microspheres of Esomeprazole

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Abstract: Oral controlled release systems are designed to release the drug in-vivo with prediction so as to increase efficacy, minimize adverse effects and increase bioavailability of drugs. Floating drug delivery systems (FDDSs) are expected to remain buoyant in a lasting way upon the gastric contents. The various buoyant preparations include hollow microspheres, granules, powders, tablets, capsules, pills and laminated films. Floating microspheres are especially gaining attention due to their wide applicability in the targeting of drugs to the stomach. Floating microspheres (Hollow Microspheres) are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micrometer. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better the therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilize only in stomach, Gastric retention time is increased because of buoyancy. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core.

Keywords: Esomeprazole magnesium trihydrate, Hydroxy methyl Propyl Cellulose K4M and K15M(HPMC), Ethyl Cellulose.

1. Introduction

Floating drug delivery systems or hydro dynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate⁽¹⁾. The drug is released slowly at a desired rate from the system and drug residual systems are emptied from the stomach. This results in increase in the gastric residence time and a better control of qualification in plasma drug concentration. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μ m to 1000 μ m). Microspheres are sometimes referred to as microparticles⁽²⁾. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Hollow microspheres, microballoons or floating microparticles are terms used synonymously for floating microspheres⁽³⁾.

Floating microspheres are, in a strict sense, spherical empty particles without a core. These are free-flowing particles, with size ranging from 1 to 1000 μ m. Kawashima have developed non-effervescent hollow polycarbonate microspheres by using an emulsion solvent evaporation method. This gastrointestinal method. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than one. This property results in delayed transit through the stomach.

The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time.

Mechanism of Flotation of Microspheres -

When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, 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 exterior 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 lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy Mechanism of Drug Release from the Microspheres⁽⁴⁾.

The mechanism of drug release from multiparticulates can occur in the following ways:

Diffusion: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating⁽⁵⁻⁶⁾.

2. Materials and Method

Esomeprazole magnesium trihydrate was obtained as a Gift sample from Lantex Pharma, Hyderabad, HPMCK4M and K15M purchased from Colorcon Ltd. Goa.072 Goudanavar et al. / Journal of Applied Pharmaceutical Science 3 (03);

2013: 071-077 Ethyl Cellulose 20cps was Gift sample from ColorconLtd, Goa. All other chemicals and reagents were of analytical grade and were used as obtained.

Preparation of Floating Microspear

The floating microspheres loaded with Esomeprazole magnesium trihydrate were prepared by double emulsion solvent diffusion technique. The polymer Ethyl cellulose in different ratios, HPMC different grades (K4M, K15M), magnesium Stearate and drug were dissolved in mixture of alcohol and Dichloromethane (1:1) and then the drug polymer solution was constantly stirred with magnetic stirrer to get a uniform solution. By adding tabulated amount of

distilled water in which sodium bicarbonate was dissolved, drug-polymer solution w/o emulsion was formed. The w/o primary emulsion prepared was poured in to 70ml of light liquid paraffin containing Span 80 as a surfactant with vigorous stirring at 800 rpm by a mechanical stirrer using four bladed propeller type stirrer for 2 hr. Magnesium Stearate was added to avoid the flocculation. Then the formulated microspheres were separated through vacuum filtration equipment and washed with n-hexane followed by petroleum ether till oil free microspheres achieved. Then collected microspheres were dried for 1 hr at room temperature and subsequently stored in desiccators for 24 hr.

Table 1: Formulation of Esomeprazole Floating Microspheres

Code	Drug (mg)	EC (mg)	HPMC K4M (mg)	NaHco3 (mg)	Mg. Stearate (mg)	Water(ml)	Alcohol: DCMC (1:1) (ml)	Liquid paraffin (ml)	Span 80
F1	200	100	100	400	300	4	12	70	0.5%
F2	200	300	100	400	300	4	12	70	0.5%
F3	200	500	100	400	300	4	12	70	0.5%

3. Evaluation of Floating Microsphere

Characterization of floating microspheres is an important phenomenon which helps in the evaluation of suitable drug delivery systems. Floating microspheres are characterized by following parameters:

1) Particle size analysis

Particle size of floating microspheres is determined by using an optical microscopy and size distribution is carried out by sieving method. This is useful in the determination of mean particle size with the help of calibrated ocular micrometer.

2) Percentage yield

Percentage yield of floating microspheres is calculated by dividing actual weight of product to total amount of all nonvolatile components that are used in the preparation of floating microspheres and is represented by following formula:

$$\% \text{ Yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100 \dots \dots (1)$$

3) Drug entrapment efficiency

Estimation of drug content in floating microspheres can be carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl and analysed spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in a triplicate manner. The entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of Microspheres.

4) Surface morphology

Surface characteristics of floating microspheres are analysed using a scanning electron microscopy. Samples are coated with gold dust under vacuum prior to observation. Cross sections should be made in order to observe the core and

internal structure of the microspheres. These studies are useful in the examination of internal and external morphology of floating microspheres.

5) Swelling ratio

Swelling property of floating microspheres is studied by soaking the known weight of microspheres at $37 \pm 0.5^\circ\text{C}$ in 0.1 N HCl or phosphate buffer pH 6.8 in a glass beaker for the required period of time. The microspheres are allowed to swell and removed at different time intervals.

6) In vitro drug release studies

Release rate of drug from hollow floating microspheres is determined using USP dissolution apparatus type I or type II at $37 \pm 0.5^\circ\text{C}$. The dissolution test is carried out using 900 ml of 0.1 N HCl dissolution medium at 100 rpm for the required period of time. At an appropriate interval, specific volume of aliquots are withdrawn and replaced with an equivalent volume of fresh dissolution medium to maintain the constant volume of dissolution medium. The sample solutions are filtered through Whatman filter paper and solutions are analysed using UV spectrophotometer.

7) Hausner's ratio

Hausner's ratio of floating microspheres is determined by comparing the tapped density to the fluff density using the equation.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{fluffy density}}$$

4. Result and Discussion

The floating microspheres loaded with Esomeprazole magnesium trihydrate were prepared by double emulsion solvent diffusion technique. This method produces good yield, which indicates minimum loss of microspheres during the preparation. The results suggest that all the values are within the range, which indicates good flow properties. The results showed that, the entrapment efficiency was increases with increase in polymer concentration.

Formulation Code	Practical yield (%)	Hausner's Ratio	Entrapment of efficiency (%)	Swelling Ratio	Mean Particle size (μm)
F1	70.20	1.121	84.2	5.54 \pm 1.02	67.21 \pm 4.5
F2	73.65	1.251	88.22	5.78 \pm 1.07	70.18 \pm 2.06
F3	77.09	1.072	90.3	5.80 \pm 1.1	75.17 \pm 3.05

5. Conclusion

Floating microspheres of Esomeprazole were prepared by double emulsion solvent diffusion technique using Ethyl Cellulose, HPMC K4M and HPMC K15M. The entrapment efficiency, percentage of yield as well as particle size improved with combination of Ethyl Cellulose +HPMCK15M than Ethyl Cellulose +HPMC k4M. The FTIR and DSC studies revealed that no interaction between drug and polymer. Based on the entrapment efficiency, *in vitro* release F5 was found to be best formulation.

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