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FORMULATION, CHARACTERIZATION AND *IN VITRO* EVALUATION OF FLOATING MICROSPHERES OF ESOMEPRAZOLE

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Abstract: The present study involves preparation and evaluation of floating microsphere using Esomeprazole as a model drug for prolongation of the gastric retention time. The microspheres were prepared by the solvent evaporation method using different polymer like Hydroxy Propyl Methyl Cellulose and Methyl Cellulose. The surface morphology of the prepared microsphere was characterized by Scanning Electron Microscopic. *In vitro* drug release studies were also performed. The objective of the present study was to develop floating microsphere of Esomeprazole in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and there by improved bioavailability. The prepared microspheres were evaluated for particle size, *in vitro* release and incorporation efficiency. The effects of various formulation variables on the size and drug release were also investigated.

Keywords: Esomeprazole, Floating Microsphere, Gastric Retention Time, Bioavailability.

INTRODUCTION

Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms [1, 2]. The multiple unit system has been developed to identify the merit over a single unit dosage form because the single unit floating systems are more popular but have a disadvantage of high variability of the gastrointestinal transit time [3, 4], still the multiple unit dosage forms may be better suited because they are claimed to reduce the inter subject variability in absorption and lower the probability of dose dumping [5]. Such a dosage form can be widely distributed throughout the gastrointestinal tract (GIT), which afforded the possibility of a longer lasting retention and more reliable release of the drug from the dosage form [6]. The synthetic polymers have been used to prepare floating Microsphere of various drugs [7]. These Microspheres exhibited good *in vitro* floatability but showed drastically decreased drug release with increasing polymer concentration. Many researchers reported work on floating microsphere using different polymer [8, 9]. Esomeprazole magnesium trihydrate is a classical example of proton pump inhibitor. Esomeprazole is approved by FDA for the treatment of symptomatic gastroesophageal reflux disease, short-term treatment and maintenance of erosive esophagitis [10]. Its half life is 1.5 h [11]. The stability of esomeprazole decreases with a corresponding decrease in the pH of the media. Hence, the exposure of esomeprazole to the acidic contents of the stomach would lead to significant degradation of the drug and would result in reduced bioavailability. Few attempts have been made to enhance bioavailability of this drug [12-14]. Thus the present study involves preparation and evaluation of floating microsphere of esomeprazole as a model drug for prolongation of the gastric retention time, thus increasing its bioavailability.

MATERIAL AND METHODS

Esomeprazole was procured from Torrent Pharmaceutical Ltd., Baddi, India. Hydroxy Propyl Methyl Cellulose and Methyl Cellulose were procured from Corel Pharmaceutical Ahmedabad, India. Chitosan and Tween 80 were procured from Central Drug House Ltd, Delhi. All other chemicals were used of analytical grade.

Preparation of floating microspheres: Microspheres were prepared by the solvent evaporation technique. Esomeprazole and HPMC/Chitosan were dissolved in a mixture of the solvent system at room temperature. this was poured in to a 250 ml of water containing 0.01% Tween 80 solution maintained at a temperature of 30-40°C and subsequently stirred for 2 h to allow the volatile solvent to evaporate completely. The microspheres formed were collected by filtration using a nylon cloth, washed repeatedly with distilled water and dried in vacuum for 1 hour at room temperature and subsequently stored in desiccators. Different Esomeprazole formulations are shown in Table.1.

Table.1: Various formulations of Esomeprazole floating microspheres

Formulations Code	Drug: Polymer ratio	Organic solvent system	Tween 80 (%w/v)
E1	1:1	Dichloromethane :Ethanol	0.01
E2	1:1.5	Dichloromethane :Ethanol	0.01
E3	1:2	Dichloromethane :Ethanol	0.01
E4	1:2.5	Dichloromethane :Ethanol	0.01
E5	1:3	Dichloromethane :Ethanol	0.01

Size and Shape of the Microsphere: The size distributions in terms of average diameter of the microsphere were determined by an Optical Microscope method. A compound microscope fitted with a calibrated ocular micrometer and a stage micrometer slide was used to count at least 100 particles. Scanning Electron Microscope was performed to characterize the surface morphology of the formed microspheres.

Flow properties: Flow properties were determined in terms of Carr's index, angle of repose (θ) of the microspheres, which measures the resistance to particle flow, determined by the fixed funnel method. The flow properties of the prepared floating microspheres are shown in the **Table.2**.

Incorporation efficiency (IE): To determine the IE, microspheres (100 mg) were taken, thoroughly crushed by triturating and suspended in a minimal amount of dichloromethane for dissolving the coat shell of the microspheres. The suspension was suitably diluted with water and filtered to separate the shell fragments. Drug content was analyzed after suitable dilution by spectrophotometer at 315 nm.
The amount of drug incorporation in the microspheres was calculated by the following formula:

IE (Incorporation efficiency) =
(Amount of drug actually present/theoretical drug load expected) x 100

***In vitro* release:** A USP basket apparatus has been used to study drug release from the prepared floating microspheres. In the present study, drug release was studied using a modified USP XXVII dissolution apparatus type I at 100 rpm in 0.1 mol/l hydrochloric acid (pH 1.2) as the dissolution fluid (900 ml) maintained at 37 ± 0.5°C. The withdrawn samples (5 ml) were analyzed spectrophotometrically as stated above. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate.

RESULTS AND DISCUSSION

Floating microsphere were prepared by the solvent evaporation method using various proportions of drug and polymer, such as Hydroxy Propyl Methyl Cellulose and Methyl Cellulose by varying stirring rate for qualitative and quantitative determination of the microspheric characteristics. It was found that HPMC-containing microsphere showed a desirable high drug content, good flow properties and adequate release characteristics; hence, formulations prepared by such a polymer are suitable for the development of gastric retention dosage forms. The surface morphology was observed by Scanning Electron Microscopic photographs, which showed that the fabricated microspheres were spherical with a smooth surface (Figure.1). Microspheres were prepared using a gradually increasing polymer concentration in combination with a fixed concentration of the drug to assess the effect of polymer concentration on the size of the microspheres. The mean particle size or average diameter of the microspheres significantly increased with increasing HPMC concentration and was in the range 325.2±1.214 - 383.9±1.848µm (Table.2). Larger particles developed due to increased viscosity of the medium with an increasing higher polymeric concentration. This is because at higher viscosities there is enhanced interfacial tension and diminished shearing efficiency. Thus, as expected, the higher polymeric concentrated microspheres influence particle size, drug IE and drug release of the microspheres. Microspheres also showed good flow properties (Table.2). All formulations showed good floating time also, the microspheres showing lower densities, helped in improving the bioavailability of the drugs used for gastric ulcerative treatment. *In vitro* drug release studies were also performed in 0.1 mol/l hydrochloric acid. The cumulative release of drug decreased with increasing polymer concentration (Figure.2). The increased density of the polymer matrix at higher concentrations results in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres formed at a lower polymer concentration and having a larger surface area when exposed to the dissolution medium showed a faster drug release (Figure.2). Thus the prepared floating microsphere of Esomeprazole showed good flow properties and characteristics.

Table.2: Characterization of prepared floating microspheres

Formulations code	Mean particle size	Angle of repose (Ø)	Carr's Index (%)	Incorporation Efficiency (%)
E1	325.2±1.214	20.210+0.557	12.445+0.534	87.88±0.038
E2	331.9±2.726	21.440+0.015	14.546+0.356	84.97±0.032
E3	347.1±1.844	22.480+0.411	13.686+0.383	84.35±0.031
E4	373.1±2.067	20.210+0.414	12.245+0.431	83.11±0.021
E5	383.9±1.848	22.570+0.442	11.257+0.578	82.56±0.021

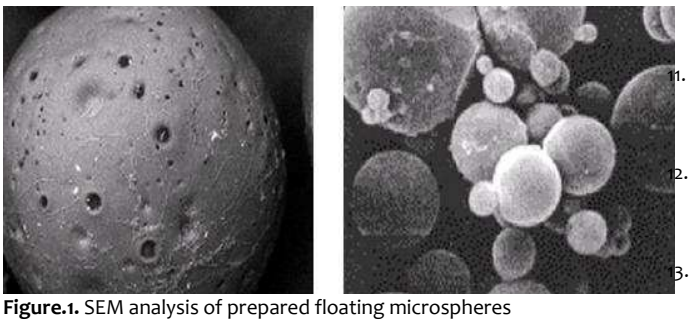

Figure.1. SEM analysis of prepared floating microspheres

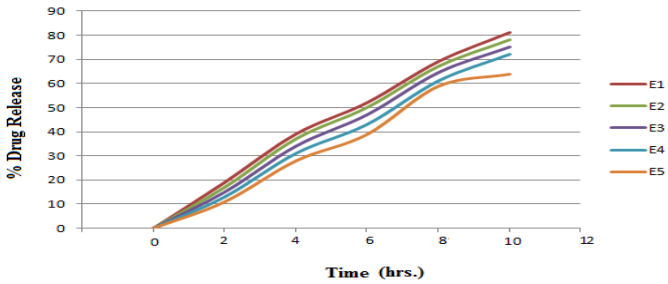

Figure.2. % Drug release of prepared floating microspheres

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