Available online on 15.10.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

FORMULATION, CHARACTERIZATION AND *IN VITRO* EVALUATION OF FLOATING MICROSPHERES OF MEBENDAZOLE AS A GASTRO RETENTIVE DOSAGE FORM

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ABSTRACT

The present study involves preparation and evaluation of floating microspheres using Mebendazole (MBZ) as a model drug for improving the drug bioavailability by prolongation of gastric retention time. Ethyl cellulose, hydroxyl propyl methyl cellulose microspheres loaded with mebendazole were prepared by solvent diffusion evaporation method. The microspheres had smooth surfaces, with free-flowing and good-packing properties. The yield of the microspheres was up to 85.65±0.14% and ethyl cellulose microspheres entrapped the maximum amount of the drug. Scanning electron microscopy confirmed their hollow structures with sizes in the range 215.1 to 251.80 nm. The prepared microspheres exhibited prolonged drug release and Percentage buoyancy was found to70.25±0.15. The formulated batches were evaluated for percentage yield, particle size measurement, flow properties, percent entrapment efficiency, swelling studies. The formulations were subjected to Stability studies and In-vitro release and Release kinetics data was subjected to different dissolution models.

Keywords: solvent diffusion evaporation method, Mebendazole, Ethyl cellulose, Hydroxyl propyl methyl cellulose

Article Info: Received 12 Sep, 2018; Review Completed 07 Oct 2018; Accepted 08 Oct 2018; Available online 15 Oct 2018

Cite this article as:

Parmar L, Gupta M, Parkhe G, Formulation, characterization and in vitro evaluation of floating microspheres of mebendazole as a gastro retentive dosage form, Journal of Drug Delivery and Therapeutics. 2018; 8(5-s):311-314

DOI: http://dx.doi.org/10.22270/jddt.v8i5-s.1980

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INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms. Thus, drug absorption in gastrointestinal (GI) tract may be very short and highly variable in certain circumstances [1, 2]. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. Various attempts have been made to prolong the retention time of the dosage form in the stomach. One such method is the preparation of a device that remains buoyant in the stomach contents due to its lower density than that of the gastric fluids [3,4]. Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit forms has relative merits compared to a single unit preparation. Indeed, the gastric emptying of a multiparticulate floating system would occur in consistent manner with small individual variations. On each subsequent gastric emptying, sunk particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way. Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced [5, 6]. Mebendazole is a highly effective broad spectrum antihelmintic indicated for the treatment of nematode infestations, including roundworm, whipworm, threadworm, and hookworm.

When administered orally, only around 10% of the mebendazole is absorbed with peak plasma concentrations after 1 or 2 hours. [7] It has a short plasma half-life of 2.5 to 5.5 hours[8], but this drug is less absorbed in the stomach and has the extensive hepatic metabolism. Therefore, it requires to be formulated in the improved form to get the improved bioavailability of drug and to reduce the frequency of dosing. The objective of the present work was to develop and characterize floating microspheres of Mebendazole, which after oral administration could prolong the gastric residence time and increase the drug bioavailability.

MATERIAL AND METHODS

Mebendazole was provided as gift sample from Pharmaceutical company. Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Ethyl cellulose, hydroxyl propyl methyl cellulose was purchased from Loba Chemie Pvt ltd, Mumbai All the other chemicals used were of analytical grade.

Preparation of floating microspheres

Floating microspheres loaded with Mebendazole were prepared using solvent diffusion evaporation method [9] using Ethyl cellulose and hydroxyl propyl methyl cellulose. Drug and polymer in proportion of 1:2 were dissolved in 1:1 mixture of solvent system of, dichloromethane and ethanol. 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 desiccator.

Size and shape of microspheres

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°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement. The results of measurement of mean particle size of optimized formulation F4 of floating microsphere was found to be 215.1 nm. From the formulated batches of microspheres, formulations (F4) 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.

Flow properties

The flow properties of microspheres were characterized in terms of angle of repose, carr's index and hausner ratio [10]. For determination of angle of repose (θ), the microspheres were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The microspheres were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the height of the pile / radius of its base gave the angle of repose. Microspheres were poured gently through a glass funnel into a graduated cylinder cut exactly to 10ml mark. Excess microspheres were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and carr index (IC) were calculated according to the two equations given below: HR= ρt /ρb IC = (ρt% ρb)/ρt

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 [2, 11].

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

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. 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.[12, 13]

In-vitro release studies

The 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 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 256 nm to determine the concentration of drug present in the dissolution medium.

Determination of zeta potential

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

RESULTS AND DISCUSSION

The floating microspheres of mebendazole 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 73.25– 85.65%. Result shown in Table I. The prepared floating microspheres were found to be discrete, spherical and free flowing. Surface morphology characteristics were studied using SEM. SEM indicated that the prepared microspheres are spherical with smooth surface; distinct pores are evident on the surface of microspheres, which will be responsible for the release.

Table 1: Percentage Yield for Different Formulation

Formulation	Percentage Yield*
F1	80.25±0.25
F2	83.35±0.32
F3	85.65±0.14
F4	79.98±0.45
F5	73.25±0.58
F6	79.98±0.74

*n=3 Determination

Angle of repose, hausner ratio, and carr index were determined to predict flowability. A higher Hausner ratio indicates greater cohesion between particles while a high Carr index is indicative of the tendency to form bridges. The prepared microspheres exhibited good flow properties and can be arranged as: F4 > F6 > F5 Percentage incorporation efficiency was in the range of 65.89±0.45% to 78.98±0.36%, F4 microspheres entrapped maximum amount of the drug. 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 63.45±0.26to 70.25±0.15 at the end of 10 h. The nature of the polymer influenced the floating behaviour of the microspheres. 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 F4 of floating microsphere was found to be 215.1 nm (Figure 2).

Results of zeta potential of optimized formulation F4 of floating microsphere was found -36mV (Figure 3).

The drug release from floating microspheres was found to be 99.78% at the end of 12 h for F4 (Figure4). The data obtained from in vitro dissolution studies were fitted to zero-order, first-order (Table 2)

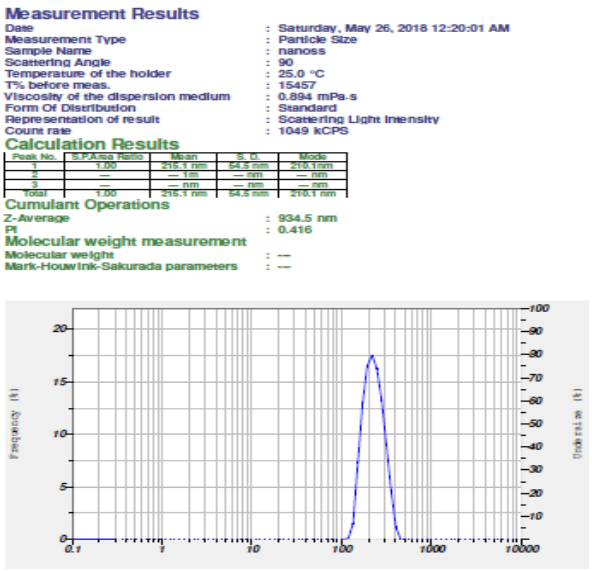
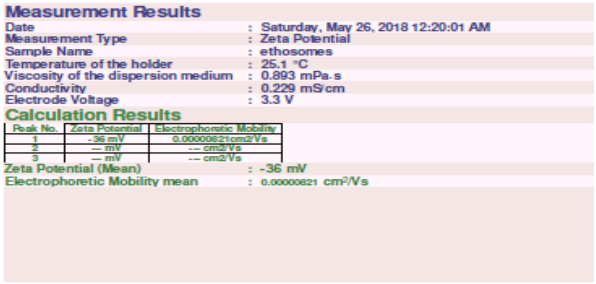


Figure 2: Particle size data of optimized microsphere formulation F4



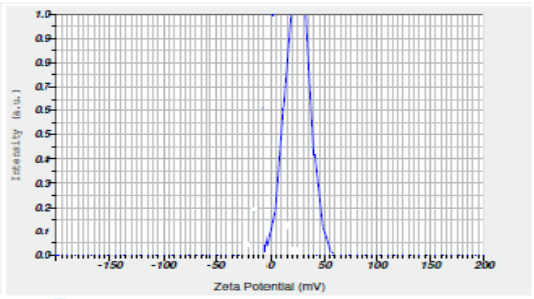


Figure 3: Zeta potential data of floating microsphere

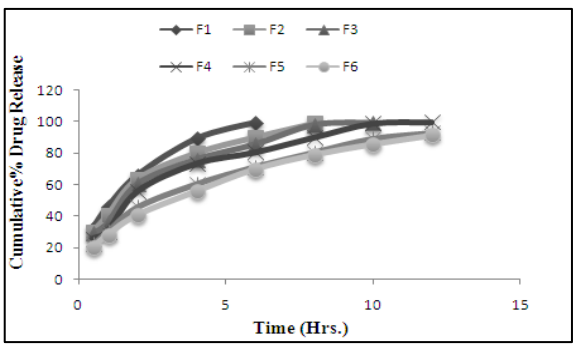


Figure 4: Graph of release study of formulation F1-F6

Table 2: Comparative study of regression coefficient for selection of optimized Formulation F-4

Release Kinetics		Zero order	First order
R^2	Microsphere	0.881	0.904

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 'r' values of microsphere was maximum first order i.e 0.904 hence indicating drug release from formulations was found to follow first order for floating microsphere.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable process. Floating microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres of mebendazole as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

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