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Omeprazole – Floating drug delivery system

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ABSTRACT

The present work was carried out to prepare and evaluate floating drug delivery system of Omeprazole using various grades of low-density polymers such as HPMC and ethyl cellulose alone or in combination in various proportions. The microspheres were prepared by emulsionsolvent diffusion method. The drug retained in the floating microspheres decreased with increase in HPMC content. The floating microspheres were found to be spherical by SEM. FT-IR study confirmed the drug-polymer compatibility. All floating microspheres formulations showed good flow properties. Floating ability was tested in 0.1 N HCl containing 0.02% Tween 20. The formulation BP6 exhibited balance between floating ability and release. The prepared formulation will minimize the irritant effect of Omeprazole on the stomach by avoiding direct contact with the mucosa and providing a mean of low dosage for prolonged period.

Keywords : Omeprazole, floating microspheres, Ethyl cellulose, HPMC K4M, emulsion solvent Diffusion.

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INTRODUCTION

The objective of any drug delivery system is to offer a therapeutic amount of drug to the proper site in the body to attain promptly and then maintain the desired drug concentration. Oral route is most convenient and commonly employed route of drug delivery historically. Oral controlled release dosage forms have been formulated over the past three decades due to their significant therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, the development process is prohibited by several physiological difficulties, such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Further incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract (prominent site for absorption of many drugs) will lead to lower bioavailability. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to twelve hours. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels. Gastro retentive dosage forms (GRDFs) is one of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract. Gastro retentive dosage form can stay in the gastric region for several hours. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time[1- 2]. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms of these drugs. The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems[3-8].

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floatation system[9-10], bioadhesive systems, which adhere to mucosal surface[11-12], density controlled system, which either float or sink in gastric fluid[13], swellable delivery system, which increase in size after swelling and retard the passage through the pylorus[14], modified shape systems[15], magnetic systems[16], superporous hydrogel system[17] and other delayed gastric emptying devices. In fact, the buoyant dosage unit enhances GRT without affecting the intrinsic rate of emptying[18]. Unfortunately, floating devices administered in a single-unit form such as hydrodyanamically balanced system (HBS)[19] are unreliable in prolonging the GRT owing to their 'all-or-nothing' empty process[20] and, thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of the GIT. While multiple unit particulate dosage form (e.g. microspheres) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release,

thereby reducing the intersubject variability in absorption and risk of local irritation[21]. The concept of floating microspheres can also be utilized to minimize the irritant effect of weakly acidic drugs on the stomach by avoiding direct contact with the mucosa and providing a mean of getting low dosage for prolonged periods. The object of the present investigation is to develop floating drug delivery system of omeprazole to minimize the irritant effect of drug on the stomach by avoiding direct contact with the mucosa and providing a mean of low dosage for prolonged period. Omeprazole is a novel PPIs indicated for the symptomic treatment of pain in epigastric region. The mean plasma elimination half life is 4 h[22].

MATERIALS AND METHODS

Materials

Omeprazole was received as a gift sample from Aristo Pharmaceutical Pvt Ltd (Mandideep, India). Ethyl cellulose was purchased from. Loba chemie Pvt. Ltd, Mumbai. Ethanol was obtained from Sakthi Sugar Pvt Ltd (Erode, India) Dichloromethan and sodium lauryl sulphate was purchased from S.D. Fine Chem. Ltd (Mumbai, India). All other chemicals were of analytical grade.

Preparation of floating microspheres of aceclofenac

Floating microspheres containing omeprazole were prepared using emulsion- solvent diffusion technique[23-24]. The drug to polymer ratio used to prepare the different formulations was as shown in table 1. The drug polymer mixture dissolved in a mixture of ethanol (8 mL) and dichloromethane (8 mL) was dropped in to 0.2% sodium lauryl sulfate solution (400 ml). The solution was stirred with a propeller-type agitator at room temperature for 1 h at 500 rpm. The formed floating microspheres were filtered, washed with water and dried at room temperature in a desicator.

Scanning electron microscopy

The external and internal morphology of the microspheres were studied using scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The stub containing the coated samples was placed in the scanning electron microscope (JSM- 6360A; JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 20 kV. Microphotographs were taken on different magnification and higher magnification was used for surface morphology.

Drug entrapment and yield of floating microspheres

The floating microspheres containing drug were dissolved in a mixture of dichloromethane and ethanol (1:1 v/v) by ultrasonication. The dissolved drug amount was measured by UVspectrophotometer (UV-1601 Shimadzu, Japan) at 274 nm after suitable dilution. No interference was found due to the other components at 274 nm. Drug entrapment and yield were calculated as follows.

% Drug entrapment = Calculated drug concentration / Theoretical drug concentration x100

% Yield = [Total weight of floating microspheres / Total weight of drug and polymer] x 100

In vitro evaluation of floating ability

Fifty milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL) containing 0.02% Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 8 hours. The collected microspheres were dried in a desiccator over night[23-25].

The percentage of floating microspheres was calculated by the following equation :

%Floating microspheres = (Weight of floating microspheres / Initial weight of floating microspheres) x100

In vitro release studies

The drug release rate from floating microspheres was carried out using the USP dissolution paddle assembly (Elico Lab, Mumbai). 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 ..0.5.C and stirred at 100 rpm. At preselected time intervals sample was withdrawn. The collected samples were suitably diluted with 0.1 N HCl and analysed spectrophotometrically at 274 nm. The initial volume of the dissolution fluid was maintained by adding same volume of fresh dissolution fluid after each withdrawal. The dissolution studies were repeated using phosphate buffer pH 6.8 as dissolution medium.

All the previous experiment were done in triplicate Kinetic modeling of drug release In order to understand the kinetics and mechanism of drug release, the result of the in vitro dissolution study of floating microspheres were fitted with various kinetic equations like zero order as cumulative percentage released Vs. time, First order as log percentage of drug remaining to be released Vs. time, and Higuchi's model[25-27] cumulative percentage drug released Vs. square root of time. r2 and k values were calculated for the linear curves obtained by regression analysis of the above plots.

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RESULTS AND DISCUSSION

Micromeritic properties the particle size was determined by optical microscopy. The particle size of floating microspheres plays important role in floating ability and release character of drug from microspheres. Smaller the microspheres floating ability will be less and faster will be the release rate of the drug form the microspheres, while larger the size, floating ability will be more and sustained will be the release of drug. The mean particle size of microspheres was increased with the increasing ethyl cellulose concentration. The viscosity of the medium increase at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities, result in the formation of larger particles. The tapped density values ranged from 0.406 ± 0.012 to 0.443 ± 0.023 g/cm3, while their true density ranged between 0.707 ± 0.043 to 0.786 ± 0.064 g/cm3 of all the formulations obviously, the density values of the floating microspheres were less than that of the gastric fluid (.1.004 g/cm3) thereby, employing that these floating microspheres will have the propensity to exhibit an good buoyancy effect in vivo. The porosity of all the formulations was found to be in the range of 38.76± 1.76 – 43.43 ±1.54%. All formulation showed excellent flowability as represented in terms of angle of repose. Percentage compressibility value ranged between 13.68 ± 1.76 to 18.4± 2.46% suggested excellent flowability of floating microspheres (table 1).

Morphology

Scanning electron microscopic photographs of floating microsphere of ethyl cellulose are shown in Fig. 1 A to D. Fig 1 A and B illustrates the microphotographs of formulation at lower magnification. Fig. 1 C and D illustrate the microphotographs of formulations at some higher magnification. The view of the microspheres showed exhibited a range of sizes within each batch. The outer surface of the microspheres was smooth and dense, whereas the internal surface was porous. The SEM photographs reveal the absence of crystals of the drugs on the surface of the hollow microspheres, indicating uniform distribution of the drugs in the walls of the hollow microspheres. SEM photographs also indicated the presence of minute pores on the surface of the hollow microspheres. Some of the microspheres showed a dented surface structure due to the collapse of the wall of the microspheres during the in situ drying process, but they showed good floating ability on the surface of the medium indicating intact surface. Figure 1. Scanning electron microphotographs of ethyl cellulose floating microspheres. (A and B) lower magnification (C and D) higher magnification

In vitro evaluation of floating ability

The purpose of preparing floating microspheres was to extend the GRT of the drug. The floating ability test was carried out to investigate the floatability of the prepared microspheres. The floating test was carried out to investigate the floatability of the prepared microspheres in 0.1 N HCl (pH 1.2) containing 0.02% Tween 20. Tween 20 was added to counteract the downward pulling at the liquid surface by lowering surface tension.

Table 1: Formulation code size* (µm) True density* Tapped density*(g/cm3) Compressibility index*Pvalue Mean particle

BP1	264.13±13.94	0.744± 0.018	0.406 ± 0.012	13.68 ± 1.76	0.85'
BP2	302.31± 16.73	0.765 ± 0.087	0.417 ± 0.018	16.87 ± 1.65	0.85'
BP3	354.61± 18.14	0.771 ± 0.054	0.434 ± 0.016	17.62 ± 1.98	0.85'
BP4	381.39± 10.03	0.786 ± 0.064	0.443 ± 0.023	17.82 ± 1.57	1.82'
BP5	345.45± 10.28	0.765 ± 0.024	0.423 ± 0.017	17.48 ± 2.45	0.89'
BP6	318.19 ±6.05	0.718 ± 0.016	0.418 ± 0.014	18.4 ± 2.46	0.98'
BP7	306.22 ±12.66	0.707 ± 0.043	0.410 ± 0.015	17.67± 1.87	0.53'

The microspheres containing ethyl cellulose also showed good floating ability due to the insolubility of ethyl cellulose polymer in the SGF (pH 1.2). The results also showed a tendency that the larger the particle size, the longer the floating time and formulation BP4 showed the best floating ability (Table 14). It should be noted, however, that the situation in vivo can be quite different and the residence time may vary widely depending on the phase of gastric motility. The floating ability of floating microspheres decreased on increasing the HPMC ratio. These results were attributable to conversion of less spherical form of floating microspheres on adding HPMC. In addition 0.1 N HCl (pH 1.2) can readily penetrate floating microspheres due to the dissolution of HPMC in solution.

In vitro drug release study

In vitro dissolution studies of omeprazole from ethyl cellulose floating microspheres were performed in 0.1 N HCl (pH 1.2) and Ph 6.8 using USP dissolution test apparatus I. Formulations BP1 gave 80.41 ± 2.16 BP2, BP3 and BP4 showed 68.75 ± 1.04, 55.93 ± 1.64 and 44.14 ± 1.77 to drug release respectively in 12 hours. As drug was not released completely, the HPMC concentration was increased to achieve further drug release. For formulations BP5, BP6, and BP7, the drug release was 56.19 ±1.80 to 82.37 ± 1.26 in 12 hrs. In pH 6.8, formulation BP1 showed 98.11 ± 3.22 % and BP4 59.52 ± 1.93 % drug release while from BP5 to BP6 73.19 ± 2.32 to 97.83 ± 0.87 release in 12 hrs.

CONCLUSION

The designed system BP6 combining high buoyant ability and suitable drug release rate, could possibility be advantageous in terms of increased bioavailability of aceclofenac. The designed system BP6 might be able to float in the stomach. This phenomenon could prolong the gastric residence time (GRT) and delay drug arrival at the absorption site; consequently, the sustained action provided, in addition, floating microspheres enabled increased drug

absorption rate of drug as the floating microspheres in the stomach gradually sank and arrived at the absorption site. Same time the prepared formulation will minimize the irritant effect of aceclofenac on the stomach by avoiding direct contact with the mucosa and providing a mean of low dosage for prolonged period. Therefore, multiple unit floating system, i.e, floating microspheres should be possibility beneficial with subject to sustain action. The developed formulation overcomes and alleviates the drawbacks and limitations of sustained release preparations. Major advantages of the prepared formulations include. Easy of Preparation, Good Buoyancy, Sustained Release over Several Hours.

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