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FORMULATION AND EVALUATION OF FLOATING MICROSPHERES CONTAINING RABEPRAZOLE

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ABSTRACT

The aim of the present study was to develop floating microspheres containing rabeprazole. Floating microspheres were prepared by solvent evaporation technique by varying the drug polymer ratio. The floating microspheres formulations were then evaluated for their micromeritic properties such as carr's index, hausner's ratio, density, size and shape, drug incorporation efficiency and buoyancy percentage. *In-vitro* dissolution studies for all the formulations were performed in 0.1M HCl media, which is the ideal media. From the dissolution studies it was evident that all the formulations showed a better drug release pattern. But the formulation F3 was considered as an optimised formulation because of its desired drug release pattern of up to 98%. The release was sustained as the polymer is increased.

KEYWORDS: Rabeprazole; sustained release; floating microspheres; dissolution.

INTRODUCTION

Among the different routes of drug administration, the oral route has achieved the most attention, partly due to the ease of administration and to the important flexibility in dosage form design. Unfortunately, in most cases, the important variability of the gastrointestinal tract physiology and of its transit time leads to unpredictable bioavailability and non-reproducible therapeutic effects. One requisite for the successful performance of oral controlled release drug delivery systems is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion. Most drugs are well absorbed throughout the entire intestinal tract, but some compounds, usually those that are polar in nature, are poorly absorbed from the large intestine. For such drugs, the main area from which absorption occurs is the small intestine. Gastric emptying of dosage forms is

an extremely variable process and the ability to prolong and control emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is associated with time of contact with the small intestinal mucous. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolongation of gastric residence time (GRT) of a rate-controlled oral drug delivery system reduces inter-subject variability and the so-called "peak and valley" effect, leading to increased predictability and bioavailability of the dosage form, especially for molecules with a narrow absorption window. Moreover, the total gastrointestinal transit time is prolonged, thus, the number of dosage regimen can be reduced and solubility can be improved for drugs that are less soluble in a high pH environment. The development of gastro retentive dosage forms capable of staying in the stomach over an extended period of time may be particularly useful for drugs that may act locally in the stomach, e.g., antacids, antibiotics for ulcers of bacterial origin, drugs that are absorbed primarily in the stomach, e.g., albuterol, chlordizepoxide drugs that are absorbed rapidly from the GI tract, e.g., amoxicillin drugs that have a narrow absorption window and are (mainly) absorbed from the upper small intestine, e.g., ofloxacin, levodopa, riboflavin, theophylline drugs having low bioavailability and drugs that degrade in the colon, e.g., ranitidine, metoprolol and drugs that are poorly soluble in intestinal pH, e.g., diazepam, weak bases such as dipyridamol. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Most of the floating systems reported in literature are single-unit systems, which are generally unreliable and non-reproducible in prolonging the GRT, in virtue of their unpredictable all-or-nothing emptying process. On the other hand, multiple-unit dosage forms appear to be better suited, since they claim to reduce inter-subject variability in absorption and have a lower dose-dumping probability. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave way to the development of gastro retentive floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core. These

are free flowing particles. The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. The objective of the present review is to focus on the method of preparation, and the various parameters affecting the performance and characterization of floating microspheres.

MATERIALS AND METHODS

Rabeprazole was received as gift sample from Intas Pharmaceuticals Pvt Ltd, Ahmedabad, India. Hydroxyl propyl methyl cellulose was purchased from Corel Pharmaceutical Chemicals, Ahmedabad, India. Tween 80 was procured from Central Drug House Ltd, Delhi. Dichloromethane and ethanol were purchased from E.Merk Pvt Ltd, Mumbai, India. All the chemicals were used of analytical grade.

Preparation of floating microspheres

Floating microspheres were prepared by solvent evaporation technique as employed by struebel. Rabeprazole and HPMC were dissolved in a mixture of solvent system at room temperature. This was poured into a 250ml of water containing 0.01% tween80 solution maintained at a temperature of 30-40^{0}c and subsequently stirred at speed for 2hrs 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 1hr at room temperature and subsequently stored in desiccators.

Evaluation of floating microspheres

Size and shape of microsphere

The size distributions in terms of average diameter of microsphere were determined by optical microscopy method. A compound microscope fitted with a calibrated ocular micrometer and a stage micrometer slide was used to count at least 100particles. Scanning electron microscope was performed to characterize the surface morphology of the formed microsphere.

Flow property

Flow properties were determined in terms of carr's index and hausner's ratio using the following equations. Carr's index is a measure of potential strength that powder could build up in its arc in hopper and also the case with an arch could be broken. Hausner's ratio is an indirect index of measuring the powder flow.

Carr's index = Tapped density-bulk density /Tapped density

Hausner's ratio = Tapped density/Bulk density

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling of formulation. Bulk density is determined by pouring preseived microspheres into a graduated cylinder via a large funnel and measure the volume and weight.

Bulk density = weight/bulk volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of microspheres and mechanical tapper apparatus, which is operated for a fixed number of taps until the volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density=weight/tapped volume.

Angle of repose

The angle of repose of microspheres which measure the resistance to the particle flow was determined by the fixed funnel method.

Drug incorporation efficiency

Microspheres (100mg) were taken, thoroughly crushed by trituration 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 analysed after suitable dilution by spectrophotometry at 265nm.The amount incorporation in the microspheres was calculated by the following formula.

Incorporation efficiency = (amount of drug actually present /theoretical drug load expected) × 100

Buoyancy percentage

An invitro buoyancy study was carried out using an USP XXIV dissolution apparatus (type II) filled with the 900ml 0.1M acidic solution (HCL) containing 0.02%tween80 as a dispersing medium. The medium was agitated with a paddle rotating at a speed of 100rpm for 12 hours. After each time interval, two fractions of the microspheres were observed, one was floating on the surface of the medium and the other was the settle portion. The settled portion

of the microspheres was collected and recovered separately at a predetermined time interval, dried in vacuum and weighed. The buoyancy was calculated by the following formula.

% buoyancy of microspheres = (weight of floating microspheres /initial weight of floating microspheres) × 100

Invitro drug release

A USP basket apparatus has been used to study drug release from the prepared floating microspheres. In the present study, the drug release was studied using a modified USP XXVII dissolution apparatus type I (basket mesh#120)at 100rpm in 0.1M HCL as the dissolution fluid at 37±0.5^{0}c. The samples were collected from the release medium at regular intervals. After each sample collection, the same amount of fresh release medium at the same temperature was added to the release medium to maintain sink condition. The drug concentration of each sample was determined spectrophotometrically at 233nm.

RESULTS AND DISCUSSION

Size and shape of microspheres

The surface morphology was observed by scanning electron microscopic photographs, which showed that the fabricated microspheres were spherical with a smooth surface.

Table-1: Particle size of microspheres.

Formulation	Mean particle size
F1	326.2 ± 1.62
F2	332.7 ± 2.81
F3	346.8 ± 1.72

Flow properties

The flow properties for F1, F2, F3 formulations were found to be in the following ranges respectively and they were found to possess good flow properties.

Table-2: Flow properties of prepared floating microspheres.

Angle of repose	Carr's index	Hausner's ratio	Type of flow
>20	5-15	-	Excellent
20-30	11-16	<1.2	Good
30-40	16-20	-	Fair

Drug Incorporation Efficiency

The drug incorporation efficiency for F1, F2, F3 formulations were found to be 59.05%, 35.74%, 72.37% respectively.

Table-3: Drug incorporation efficiency of various formulations.

S.no.	Formulation	Practical yield	Theoretical yield	Incorporation efficiency
1.	F1	18.11	32	59.05%
2.	F2	14.44	34	35.74%
3.	F3	16.37	50	72.37%

Table-4: Comparison of various parameters of three formulations.

S.no.	Formulations	Percentage yield	Angle of repose	Drug content	Incorporation efficiency
1	F1	73.5%	48.4	14.4	59.05
2	F2	77%	25.5	16.37	35.74
3	F3	83%	18	18.77	72.37

Buoyancy percentage

The buoyancy percentage of F1, F2, F3 formulations was found to be as.

Table-5: Buoyancy percentage of various formulations.

Formulation	Buoyancy percentage
F1	72.5±1
F2	70.3±7
F3	67.6±5

Invitro dissolution studies

The percentage drug release of formulations F1, F2, F3 was found to be 95.16%, 93.89%, 98.12% respectively.

Table-6: Invitro dissolution studies.

S.no.	Formulation	1hr	2hr	3hr	4hr	5hr	6hr
1	F1	46.6	63.2	82.1	93.2	81.1	73.33
2	F2	24.5	37.2	49.1	65.8	83.9	95.2
3	F3	42.2	60.3	79.9	85.2	93.8	85.4

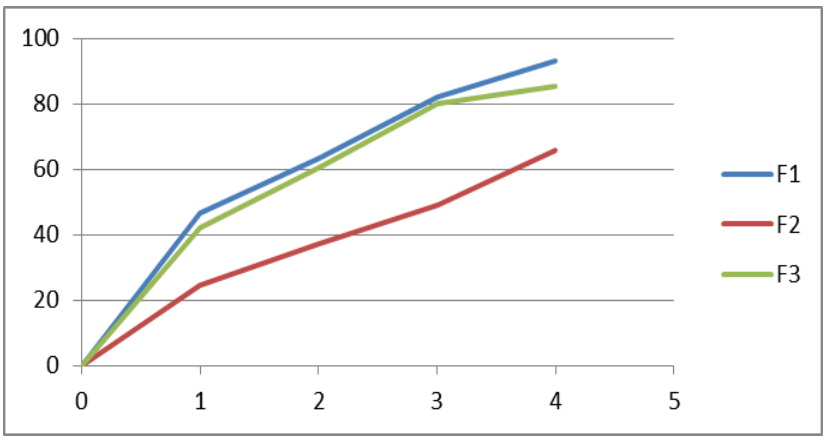

Fig-1: Drug release from F1, F2 and F3 formulations.

Table-7: Zero order release profile of F1 formulation.

Time(hrs)	Amount of drug release
0	0
1	37.50
2	69.37
3	95.43
4	121.68

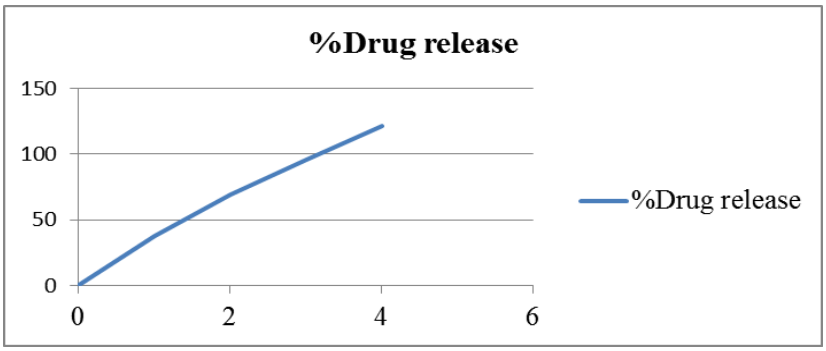

Fig-2: Zero order release profile of F1 formulation.

Table-8: Zero order release profile of F2 formulation.

Time(hrs)	Amount of drug release
0	0
1	24.04
2	41.33
3	57.37
4	74.6

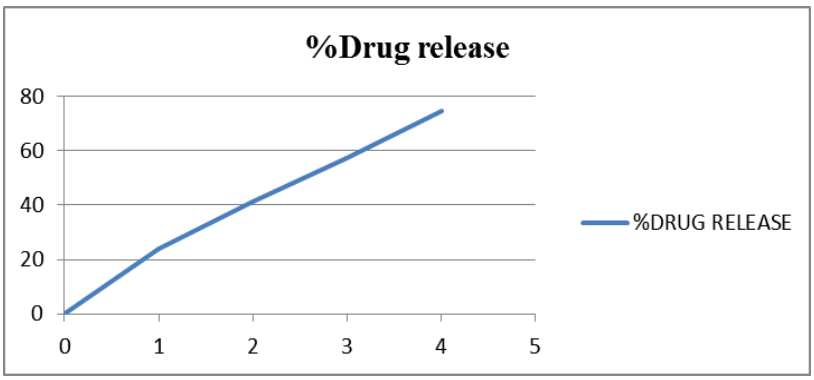

Fig-3: Zero order release profile of F2 formulation.

Table-9: Zero order release profile of F3 formulation.

Time(hrs)	Amount of drug release
0	0
1	31.77
2	63.62
3	95.93
4	116.3

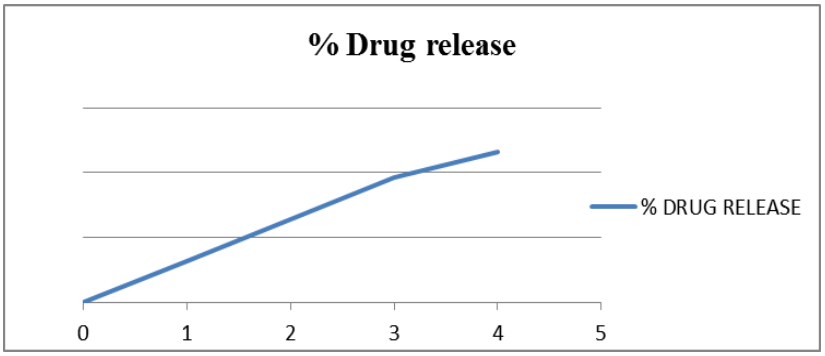

Fig-4: Zero order release profile of F3 formulation.

CONCLUSION

The floating microspheres of rabeprazole were prepared and evaluated. Scanning electron microscope photographs reveal that they are spherical, non-porous, and uniform with smooth surface. The angle of repose was found to be in the range 20-30^{o} and shows good flow property. The drug content was uniform and reproducible in each batch. The incorporation efficiency of the drug depends on solubility of the drug in the solvent. An increase in the polymer concentration in fixed volume of organic solvent resulted in an encapsulation efficiency. The prepared microspheres showed good percentage yield. The microspheres prepared with HPMC showed considerable sustained release characteristics. The release was sustained as concentration of polymer increased. Gastro- retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The control of gastro intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patients.

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