ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation Design and Evaluation of Floating Microspheres of Rabeprazole Sodium

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ABSTRACT

The objective of this study is to formulate and evaluate floating microspheres of Rabeprazole sodium. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation method by using of acetonitrile and dichlormethane solvent system and polymers are hydroxyl propyl methylcellulose (HPMC) such as HPMC K100M and ethyl cellulose (EC). The prepared microspheres were characterized by percentage yield, buoyancy , drug entrapment efficiency and *in-vitro* drug release. An optimized formulation was investigated for morphology and particle size analysis by scanning electron microscopy. Rabeprazole sodium is antacid (proton pump inhibitor) type drug so long time retention required in stomach. Floating microspheres has been accepted as a process to achieve controlled drug delivery by prolonging the residence time of the dosage form at the site of absorption, thereby improving and enhancing the bioavailability of drug.

Keywords Rabeprazole sodium, floating microspheres, hydroxyl propyl methylcellulose , gastroretentive drug delivery, non-aqueous emulsification solvent evaporation.

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ISSN: 0975-8585

INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention time (GRT) improves bioavailability, reduce drug waste and enhance solubility for drugs that are less soluble in high pH environment. [1]

Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [2, 3]

A minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. [4]

Rabeprazole is a selective and irreversible proton pump inhibitor. Rabeprazole suppresses gastric acid secretion. The bioavailability of the drug is about 52%. Protein binding approximately 96%. [5, 6]

MATERIALS AND METHODS

MATERIALS

Rabeprazole sodium, ethyl cellulose, HPMC K100M was purchased from Balaji drug supplier surat, Gujarat, India. All other ingredients were used analytical grade from my college's laboratory.

METHODS

Preparation of Floating Microspheres of Rabeprazole sodium

The microspheres were prepared by non-aqueous emulsification solvent evaporation method. drug and polymer (table 1) i.e. Rabeprazole sodium and ethyl cellulose & HPMC (Hydroxy propyl methyl cellulose) K100 M were mixed in acetonitrile & dichloromethane solvent system stirred for 1 hour. The dissolved solution of drug was introduced in to 100 ml of Liquid paraffin which containing 2.0% span 80 while being stirred at 1000 rpm by Remi mechanical stirrer equipped with a three bladed propeller at room temperature for 2 hour. Allow the solvent to evaporate completely and the microspheres were collected by filtration. The microspheres were washed repeatedly with petroleum ether 40–60^{o}C until free from oil. The collected microspheres were dried for 1hr at room temperature and subsequently stored in desiccator.

ISSN: 0975-8585

Table 1: Formulation Pattern of Floating Microspheres of Rabeprazole Sodium

Formulation Code	Drug-Polymer Ratio And Drug-polymer quantity (mg)	Organic Solvent Ratio (Acetonitrile:Dichloromethane)
F1	1:2 (200:400)	1:1
F2	1:1 (200:200)	1:1
F3	1:0.75 (200:150)	1:1
F4	1:0.50 (200:100)	1:1

EVALUATION OF FLOATING MICROSPHERES [7-9]

Bulk density

The bulk density was obtained by dividing the mass of microspheres by the bulk volume in cm^3. The sample of about 10 cm^3 of microspheres was carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below

$$\text{Bulk density (g/mL)} = \frac{\text{Bulk density (g/mL)}}{\text{Unsettled apparent volume (mL)}}$$

Tapped Density

The tapped density was obtained by dividing the mass of microspheres by the tapped volume in cm3. The sample of about 10 cm^3 of microspheres is carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2- second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm3 of the sample contained in the cylinder. It was calculated by using equation given below

$$\text{Tapped density (g/mL)} = \frac{\text{weight (g)}}{\text{Final tapped volume(mL)}}$$

Carr's Index

The percentage compressibility of microspheres was calculated according to equation given below.

$$\text{Compressibility Index (CI) (\%)} = \frac{100 \text{ X (Tapped density} - \text{Bulk density}}{\text{(Tapped density)}}$$

Buoyancy

Micro particles were spread over the surface of 0.1 mol HCl medium then note lag time of microshere in which microsphere float on medium.

Production yield

The yield was calculated by dividing the weight of the collected microspheres by the weight of all the non-volatile components used for the preparation of microspheres and expressed in the terms of percentage.

$$\text{Production Yield} = \frac{\text{The amount of microspheres obtained}}{\text{The theoretical amount}} \times 100$$

Particle size distribution analysis

Formulations of the microspheres were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1 unit of eyepiece micrometer was equal to 13.33 µm. 100 microspheres sizes were calculated under 10x magnification .

Drug entrapment efficiency (DEE)

About 10 mg equivalent Rabeprazole Sodium loaded microspheres were dissolved in 100 ml of PBS (pH 7.2) by shaking on bottle shaker for 10 h. The solution was filtered through Whatman no.41 filter paper. An aliquot was assayed spectrophotometrically for Rabeprazole Sodium at 284 nm. Drug entrapment efficiency was determined by using the following relationship.

Percentage drug entrapment efficiency = (Amount of drug actually present/ Theoretically expected drug loaded) x100

In vitro drug release study

The dissolution rate of Rabeprazole Sodium from the microspheres was studied at pH 1.2 for 2 h followed by pH 7.2 for 10 h using the basket method. Accurately required weighed microspheres were taken for dissolution studies. The dissolution medium was kept at 37 ± 0.5°C. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 284 nm. The volume withdrawn at each time intervals was replaced with the same amount of fresh dissolution medium.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to examine the surface morphology of microspheres. Dried microspheres were mounted on to stubs by using double-sided adhesive

tape. The microspheres were coated with gold and observed under a scanning electron microscope for surface characteristics.

RESULT & DISCUSSION

Micromeritic properties of floating microspheres of Rabeprazole sodium

Table 2: Micromeritic Properties of floating microspheres of Rabeprazole sodium

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Comppresibility Index (Carr's Index) (%)
F1	0.705	0.625	11.34
F2	0.690	0.615	10.86
F3	0.682	0.609	10.70
F4	0.670	0.601	10.29

Carr's index values shows fair property of microspheres (table 2)

Production yield

Table 3: Practical yield of Rabeprazole sodium floating microspheres

Formulation code	Theoretical weight (mg)	Practical yield (mg)	Percentage yield (%)
F1	600	409	68.30
F2	400	266	66.50
F3	350	227	65.00
F4	300	192	63.70

The Practical yield of floating microsphere formulation F1 to F4 containing ethylcellulose and HPMC was in the range of 68.30 to 63.70. Observe the effect of polymer concentration on the Practical yield of the floating microspheres formulations were prepared at varying concentration of HPMC and ethylcellulose. (table 3)

Particle size distribution analysis

Table 4: Particle size of Rabeprazole sodium floating microspheres

Formulation code	Particle size (µm)
F1	287.18
F2	260.87
F3	250.66
F4	247.34

Floating microspheres of Rabeprazole sodium prepared in this study were well rounded spheres with the size range from 247.34 to 287.18 µm (table 4)

ISSN: 0975-8585

Drug entrapment efficiency

Table 5:- Drug entrapment efficiency of Rabeprazole sodium floating microspheres

Formulation code	Drug entrapment efficiency (%)
F1	65.62
F2	64.45
F3	62.56
F4	60.22

The percentage entrapment efficiency of various formulation parameter of the prepared microspheres. The entrapment efficiency varied from 60.22% to 65.62%. The formulation F1 is having high encapsulation efficiency of 65.62% and F4 is having low encapsulation efficiency of 60.22% (table 5)

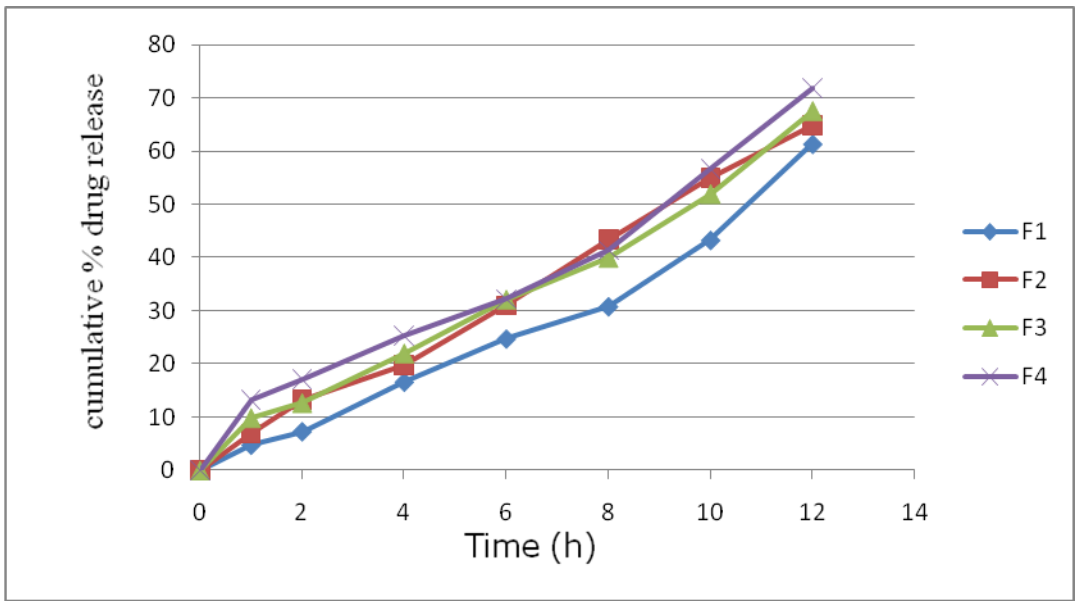
Buoyancy of floating microspheres

Table 6: Buoyancy of floating microspheres of Rabeprazole sodium

Formulation Code	Lag Time (Sec.)
F1	75
F2	70
F3	63
F4	56

The buoyancy test shows that increase in concentration of polymers then lag time increased so F1 formulation shows greater lag time than others. (table 6)

In-vitro drug release study



ISSN: 0975-8585

Fig 1: Drug release pattern of batches F1 to F4 floating microspheres

Table 7: *In-vitro* cumulative percentage drug release of floating microspheres of Rabeprazole sodium

Time (hr)	F1	F2	F3	F4
0	0	0	0	0
1	4.77	6.91	9.85	13.28
2	7.31	13.34	12.64	17.12
4	16.62	19.71	21.95	25.3
6	24.74	30.96	32.05	32.25
8	30.81	43.35	39.87	41.4
10	43.3	54.9	51.87	56.73
12	61.37	64.81	67.41	71.91

In-vitro drug release of floating microspheres of Rabeprazole sodium shows that when increase polymer(Ethyl cellulose and HPMC K100M) concentration drug release increase with respect increased time. Release of batches F1-F4 was 61.37%, 64.81, 67.41, 71.91 % respectively. The batch F1 shows highest release of drug among the all batches. So drug release of F1 over 12 hr (table 7).

Scanning electron microscopy (SEM) of Rabeprazole sodium floating microspheres

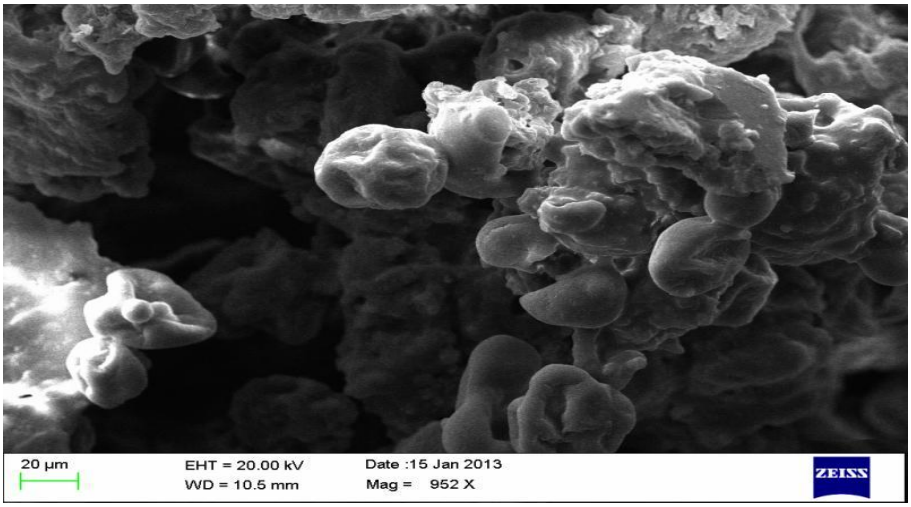


Fig. 2: SEM of optimized batch F1

ISSN: 0975-8585

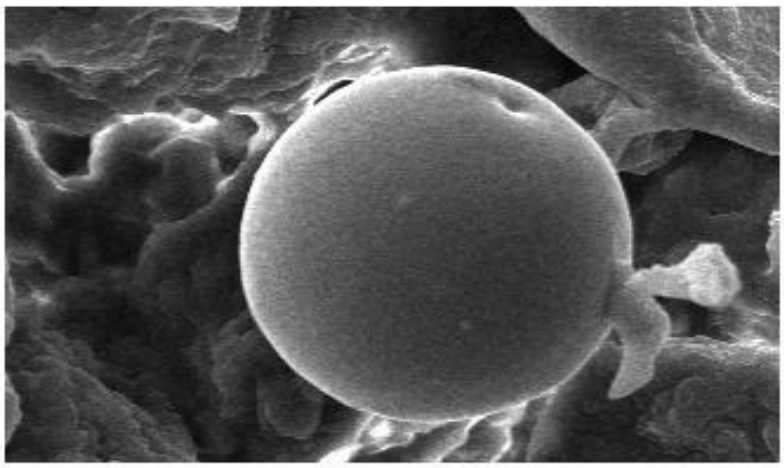


Fig. 3: SEM of optimized batch F1

The morphology of the microspheres was examined by SEM the view of the microspheres showed a spherical shape with a smooth surface morphology. The mean particle size increase with increase polymer concentration. The mean diameter of Rabeprazole sodium loaded floating microspheres was found to be 6.54 to 74.64 µm.

CONCLUSION

The Rabeprazole sodium floating microsphere formulated and performed the all evaluation parameters (micromeritic properties, percentage yield, particle size, drug entrapment efficiency, SEM, buoyancy and in vitro dissolution). In-vitro drug release of floating microspheres of rabeprazole sodium shows that when increase polymer(ethyl cellulose and HPMC K100M) concentration drug release increase with respect increased time. so this dosage form suppress acidic level for long time.

ACKNOWLEDGEMENT

I express my special gratitude to my parents who have borne my absence from home, and all responsibilities, with the grace I doubt I will ever be able to manage. I would love to thank to Regional College of Pharmacy, Jaipur management and faculties for providing information sources, library, internet and electronic facilities.

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