



Formulation and Evaluation of Floating Microspheres of Acebutolol

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ABSTRACT

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration patient compliance and flexibility in formulation. Throughout the gastrointestinal tract, these considerations have led to the development of a unique oral controlled release dosage form with Gastro retentive properties. Gastro retentive dosage forms (GRDFs) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. There are different types of gastro retentive dosage forms the formulation of floating microspheres is solvent diffusion evaporation technique. Acebutolol is commonly prescribed as angiotensin drug. Gastric retention time is increased because of buoyancy and site-specific delivery in stomach can be achieved. Pre formulation studies have done to formulate the floating microspheres, Acebutolol as API and three polymers were used namely Cellulose Acetate (F1), EdurgitS100 (F2), Acrycoat S100 (F3). For the above formulations all the evaluation parameters (SEM studies, buoyancy studies, the in vitro studies, Floating time) were conducted. The microspheres were placed in 6.8 pH phosphate buffer containing surfactant tween 80 to stimulate gastric condition. The drug release from floating microspheres found to be 84.22 ± 0.29 , 75.19 ± 1.99 , 67.59 ± 1.97 for F1, F2, and F3 respectively.

Keywords: GRDFs, pH, microspheres, SEM, in vitro studies, buoyancy studies, 6.8 pH phosphate buffer, edurgitS100, cellulose acetate, acrycoatS100.

INTRODUCTION

Microsphere is a term used for small spherical particles, with diameters in the micrometer range (typically $1\mu\text{m}$ to $1000\mu\text{m}$ (1mm)). Microspheres are sometimes referred to as micro-particles¹. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Floating microspheres are spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins, natural or synthetic polymers. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

One requisite for successful performance of oral controlled drug delivery system is that drug should have good absorption throughout the gastrointestinal tract, preferably by passive diffusion. These considerations have led to the development of a unique oral controlled release dosage form with Gastro retentive properties¹. After oral administration, such a dosage form (DF) would be retained in the stomach and releases the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.

There are different types of dosage forms, which are being administered through different routes. However, oral route is the most preferred route of administration as it more natural and enjoys better patient compliance. Majority of the drugs are having site specific absorption in the G.I.T and parameters like pH dependent solubility, stability and ionization of the drug in different portions of the G.I.T influence such absorption. Gastric retention time is one of the important factors, which adversely affect the performance of these drugs when administered by an oral controlled drug delivery system.

One of the most feasible approaches for retaining the dosage forms in stomach for a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time using gastro-retentive dosage forms that will provide us with new and important therapeutic options.

Many attempts have been made in the recent years to provide a dosage form with a longer retention time. These approaches include floating drug delivery systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high density systems and other delayed gastric emptying devices. Compared to these approaches, the gastric retentive floating drug delivery systems (GRFDDS) developed has provided several advantages. Furthermore, the buoyancy action provided by the GRFDDS seems to offer a greater safety for clinical uses than some of the above-



mentioned approaches.

In the present investigation, the drug Acebutolol has been selected for the formulation of GFDDS. Acebutolol is one of the commonly prescribed angiotensin drugs. The absorption of Acebutolol is erratic in patients due to the impaired gastric emptying. Gastric retention time is increased because of buoyancy and site-specific delivery in stomach can be achieved.

MATERIALS AND METHODS

Materials

Acebutolol purchased from goldfish pvt. Ltd, EudragitS100, Cellulose Acetate, Acrycoat S100, ethyl acetate, dichloromethane purchased from S.D. fine-chem ltd., Mumbai. Isopropyl alcohol, ethanol purchased from goldfish pvt.ltd.

Method

Pre formulation Studies

It is defined as the determination of physical, chemical and mechanical properties of a new drug substance alone and when combined with excipients². The overall objective of preformulation studies is to generate information useful in developing stable, safe and effective dosage form.

Solubility

The solubility of the drugs as the number of milliliters of solvent in which 1 gram of solute will dissolve. One gm. of Model drug was dispersed in the solvent and based on the following table solubility was determine

Melting point

Melting point of Model drug was determined by capillary method. Fine powder of Model drug was filled in glass capillary tube (previously sealed on one end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt³.

Drug polymer compatibility studies

Study was carried out using FT-IR spectrometer by the KBr pellet method in the wavelength region between 4000 and 400cm⁻¹. FT-IR Spectra of Acebutolol and Polymers with Acebutolol were obtained. The spectrum was studied for specific peaks of drug and polymer.

Calibration Curve of Acebutolol

Preparation of 6.8 pH Phosphate Buffer

50ml of 0.2M Potassium Di-hydrogen Ortho Phosphate Solution was taken in a 200ml volumetric flask, to which 22.4ml of 0.2M Sodium hydroxide was added. Then volume was made up to the mark with distilled water and pH was adjusted to 6.8 with dilute sodium hydroxide solution⁴.

Preparation of Acebutolol Standard Stock Solution (100µg/ml)

A Standard Stock solution of Acebutolol was prepared by dissolving accurately weighed 10mg of Acebutolol in 6.8 pH Phosphate buffer solution in a 100ml volumetric flask and the volume was made up to 100ml by using 6.8 pH Phosphate buffer solutions.

Determination of λ_{max} of Acebutolol

From the standard stock solution 1ml was taken into 10ml volumetric flask. The volume was made up to 10ml with 6.8 pH Phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200-400nm. The λ_{max} was found to be 233nm and used as analytical wavelength.

Calibration Curve of Acebutolol

From the Standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made up to 10 ml with 6.8 pH Phosphate buffer so as to get concentration of 2, 4, 6, 8, 10, 12 µg/ml. The absorbance of the solution was measured at 233 nm. This procedure was performed in triplicate to validate calibration curve. A calibration graph was plotted.

Preparation of Floating Microspheres:

1. Floating microspheres loaded with Acebutolol were prepared using solvent diffusion evaporation method using Cellulose acetate (F1), EudragitS100 (F2) and Acrycoat S100 (F3).
2. Drug and polymer in proportion of 1:2 were dissolved in 1:1 mixture of solvent system of Ethyl Acetate and Acetone for Cellulose Acetate, dichloromethane and ethanol for Acrycoat S100; dichloromethane, ethanol and Isopropyl Alcohol (1:1:1) For Eudragit S100.
3. This clear solution was poured slowly in a thin stream into the aqueous solution of 0.05% Polyvinyl Alcohol⁵.
4. The emulsion was continuously stirred for 3 hours at a speed of 500 rpm at 27±2° C.
5. 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.

Evaluation parameters

Particle size analysis

Particle size and shape of the microspheres was determined by optical microscopy. The freshly prepared microspheres were examined on an optical microscope and the size of microspheres was measured by pre-calibrated ocular micrometer and stage micrometer. About 100 particles of each formulation were observed and measured.



Micrometrics properties

The prepared microspheres are characterized by their micrometric properties, such as microsphere size (mean particle size), Bulk density, Tapped density, Carr's compressibility index, Hausner's ratio and angle of repose⁶.

Bulk and Tapped density

Bulk and tapped densities were measured by using 50 ml of graduated cylinder. Accurately weighed amount of 5g of sample passed through a glass funnel. The sample poured in cylinder was tapped mechanically for 3 times and 100 times for calculating bulk volume (V_b) and tapped volume (V_t) respectively. Then tapped volume was noted down and bulk density and tapped density were calculated. It was expressed in g/cm^3 ⁷.

$$\text{Bulk density} = \frac{\text{mass}}{\text{volume}} \quad \text{Eq. (1)}$$

$$\text{Tapped density} = \frac{\text{mass}}{\text{tapped volume}} \quad \text{Eq. (2)}$$

Carr's Compressibility Index

Compressibility index (C.I.) or Carr's index value of microspheres was calculated according to the following equation

$$\% \text{ Compressibility index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad \text{Eq. (3)}$$

The value given below 5% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

Hausner's ratio

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad \text{Eq. (4)}$$

Angle of repose

The maximum angle which is formed between the surface of a pile of powder and horizontal surface is called the angle of repose⁸.

$$\tan \theta = h/r \quad \text{Eq. (5)}$$

Where θ = angle of repose

h = height of the circle formed by the powder heap

r = radius of heap

In vitro buoyancy

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 mL of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the

microspheres that remained floating and the total mass of the microspheres^{9,10}.

Incorporation efficiency (IE)

To determine incorporation efficiency floating microspheres were dissolved in a minimal amount of dichloromethane and the drug was extracted into a suitable aqueous media (0.1 N hydrochloric acid) by evaporating dichloromethane¹¹. The solution was filtered through 0.45 m membrane, diluted suitably and analysed for drug content spectrophotometrically at 278 nm using 0.1 N hydrochloric acid as blank.

In vitro drug release studies

Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of 6.8 pH Phosphate buffer as dissolution medium maintained at $37 \pm 0.5^\circ \text{C}$. Medium was stirred at 50 rpm for a period of 30 minutes. Samples were withdrawn at every 1 min interval up to 30 min, replacing the same amount with the fresh medium¹². Samples were suitable diluted with 6.8 pH and analyzed for drug content at 233 nm¹³. Cumulative percent drug release of Acebutolol was calculated and plotted against time.

Data Analysis

To analyze the mechanism of the drug release kinetics of the dosage form, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer - peppas model and plotted as:

1. Cumulative percent drug released Vs. time (Zero order plots)
2. Log cumulative percent drug remaining Vs. time (First order plots)
3. Cumulative percent drug release Vs. square root of time (Higuchi plots)
4. log cumulative percent drug release Vs. log time (Korsmeyer-Peppas Plots)

RESULTS AND DISCUSSION

Pre-formulation Studies

The following studies were performed for model drug.

Solubility

It is soluble in water and sparingly soluble in methanol and practically insoluble in Ethanol^{14,15}.

Melting Point

The melting point of obtained drug sample was found to be 158-159°C.

FT-IR Spectroscopy

The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Acebutolol. The spectrum of Acebutolol showed the following functional groups at their frequencies^{16,17, and 18}.



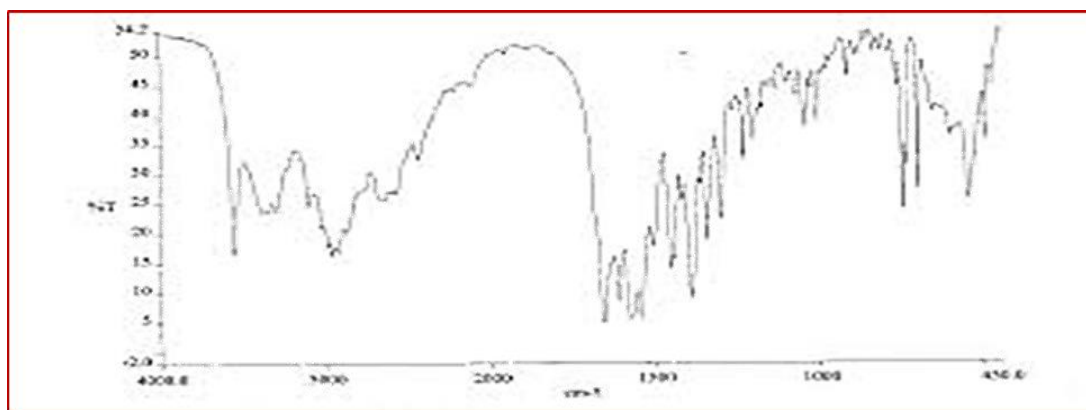


Figure 1: FT-IR Spectrum of Acebutolol

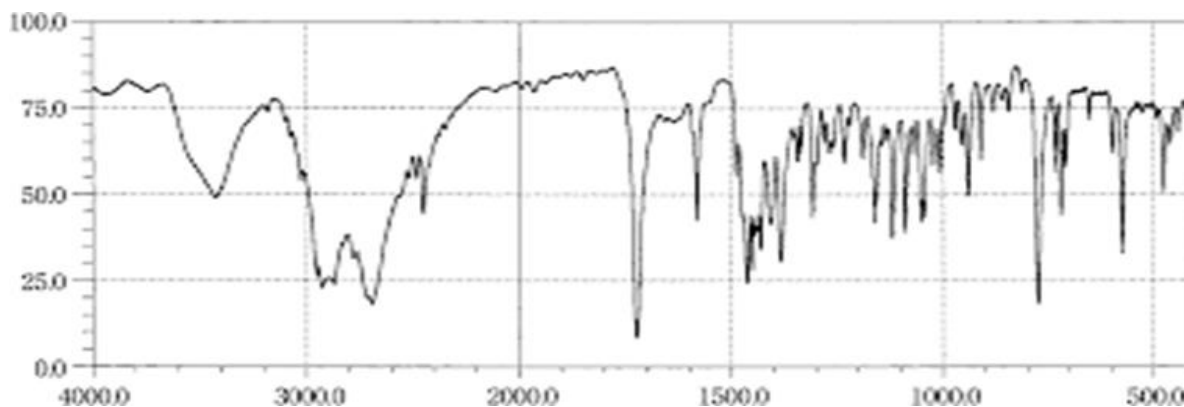


Figure 2: FT-IR Spectrum of Acebutolol with EudragitS100

Formulation of Floating Microspheres

Table 1: Composition of different formulations

Formulation code	Drug: polymer	Solvent mixture	Concentration of PVA(%w/v)	Stirring speed(rpm)
F1	1:2	1:1	0.05	500
F2	1:2	1:1	0.05	500
F3	1:2	1:1	0.05	500

Solvent mixture: F1-ethyl acetate and acetone for cellulose acetate; F2- dichloromethane, ethanol and isopropyl alcohol (1:1:1) for Eudragit S100; F3- dichloromethane and ethanol for acrycoat S100.

Characterization of microspheres

Spectroscopic studies

The size of microspheres was determined using microscope fitted with an ocular micrometre and stage micrometre. Scanning electron microscopy (SEM) was performed to characterize the surface of the formed microspheres. Microspheres were mounted directly onto sample stub and coated with gold film (~200 nm) under reduced pressure.

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: F1 > F3 > F2. The percentage yield of floating microspheres was found to be: F1 > F3 > F2. Percentage incorporation efficiency was in the range of 64.31 % to 84.62%, cellulose acetate microspheres entrapped maximum amount of the drug shown in Table 2.

Flow property: Angle of repose, hausner’s ratio, and Carr’s index were determined to predict flow ability. A

Table 3: *In vitro* release for floating microspheres

Time (hrs.)	F1	F2	F3
1	15.21 ±0.21	13.45 ±0.49	10.68 ±0.28
2	24.22 ±1.24	22.89 ±0.57	15.72 ±0.68
4	35.66 ±0.99	31.66 ±0.24	21.39 ±0.17
6	47.96 ±0.65	43.78 ±0.98	28.59 ±0.95
7	58.49 ±0.29	48.16 ±0.57	35.22 ±0.24
8	67.39 ±1.67	53.68 ±0.24	40.68 ±0.55
9	76.48 ±0.55	63.45 ±0.36	56.27 ±0.97
10	81.22 ±0.33	73.88 ±0.29	61.66 ±1.22
12	84.22 ±0.29	75.19 ±1.99	67.59 ±1.97

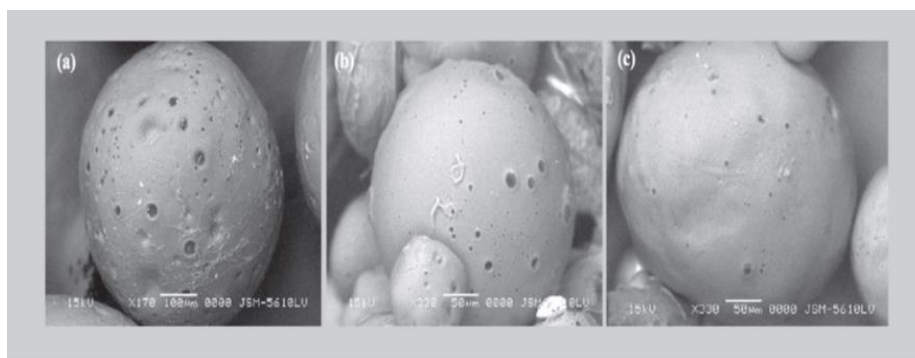


Figure 3: SEM photomicrographs of floating microspheres

In vitro buoyancy and Incorporation efficiency (IE)

Table 2: Flow properties, In Vitro Buoyancy and Incorporation efficiency (IE), particle size of Floating Microspheres

Formulation code	Buoyancy (%)	Incorporation Efficiency (%)	Particle Size(μm)	Angle of repose	Hausner's ratio	Carr's index
F1	65.84	81.24	304.45	21.2	1.14	0.140
F2	43.25	62.37	287.16	26.7	1.13	0.149
F3	58.21	70.34	221.84	26.8	1.11	0.147

Table 4: Kinetic Model fitting data for Optimized Formulation (F1)

Formulation type	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	Peppas n value
F 1	0.9922	0.6553	0.974	0.988	0.719

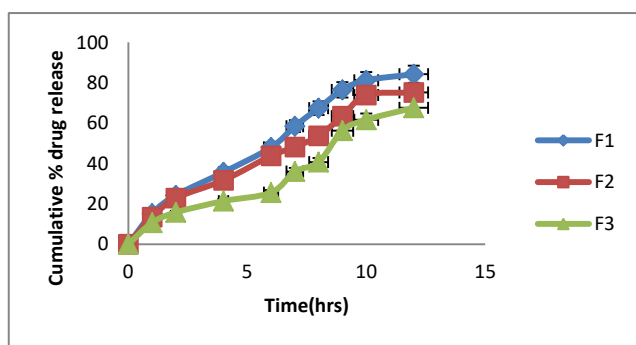


Figure 4: In Vitro Drug Release for Floating Microspheres (F1-F3)

In vitro release for floating microspheres

Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of 6.8 pH Phosphate buffer as dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$. Medium was stirred at 50 rpm for a period of 30 minutes^{19, 20}. The drug release from floating microspheres was found to be 84.22 ± 0.29 , 75.19 ± 1.99 , 67.59 ± 1.97 at the end of 12h for F1, F2 and F3 respectively.

CONCLUSION

Floating microspheres of Acebutolol were prepared by a solvent diffusion-evaporation method. The nature of polymer influenced the physical characteristics as well as floating behaviour of the microspheres. *In vitro* buoyancy

and *in vivo* studies confirmed the excellent floating properties of cellulose acetate microspheres. The drug release was sufficiently sustained and non-Fickian transport and it follows zero order kinetics of the drug from floating microspheres was confirmed. Hence the floating microspheres of Acebutolol prepared with cellulose acetate, may provide a convenient dosage form for achieving best performance regarding flow, release and floating properties.

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