



## A REVIEW ON FLOATING MICROSPHERES

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### ABSTRACT

The purpose of writing this review on floating microspheres is to compile the recent literature with special focus on the principle mechanism of floatation to achieve gastric retention. Recent advances indicate that floating microspheres are especially suitable for achieving sustained or delayed release oral formulations with flexibility of blending to attain different release patterns, low risk of dose dumping as well as reproducible and short gastric retention time. One of the approaches toward this goal is to develop the floating microspheres so as to increase the gastric retention time. In this review, the current status of floating microspheres including hollow microspheres (micro balloons) and their characterization, advantages, disadvantages, mechanism and method of preparation for gastric retention of drug are discussed. This review also summarizes *the in-vitro* dissolution study to evaluate the performance and applications of floating microspheres.

**Keywords:** Floating microspheres, Floating Drug Delivery System, Gastro Retention, Bioavailability, Hydro dynamically Balanced Systems.

### INTRODUCTION<sup>1-7</sup>

The primary aim of oral controlled drug delivery is the most preferable route of drug delivery system is to achieve better bioavailability and release of drug from the system which should be predictable and reproducible, easy for administration, patient compliances and flexibility in formulation for effective therapy or to improve therapeutic efficiency of the drug through improved bioavailability. Gastro retentive dosage forms significantly extend for the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Gastric retention can be achieved by the mechanism of mucoadhesive or bioadhesion systems, expansion system, high density systems, magnetic systems, super porous hydrogels, raft forming systems, low density system and floating ion exchange resins. Floating drug delivery systems or hydro dynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The drug is released slowly at a desired rate from the system and drug residual systems are emptied from the stomach. This results in increase in the gastric residence time and a better control of qualification in plasma drug concentration. Microspheres are small spherical particles, with

diameters in the micrometer range (typically 1 $\mu$ m to 1000 $\mu$ m). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material<sup>5</sup>.

Hollow microspheres, microballoons or floating microparticles are terms used synonymously for floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core. These are free-flowing particles, with size ranging from 1 to 1000 $\mu$ m. have developed non-effervescent hollow polycarbonate microspheres by using an emulsion solvent evaporation method. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than one. This property results in delayed transit through the stomach. The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time:

### Advantages of Floating Microspheres<sup>7-9</sup>

- a. Enhanced bioavailability
- b. Enhanced first-pass biotransformation
- c. Sustained drug delivery/reduced frequency of dosing
- d. Targeted therapy for local ailments in the upper GIT
- e. Reduced fluctuations of drug concentration
- f. Improved receptor activation selectivity
- g. Reduced counter-activity of the body
- h. Extended time over critical (effective) concentration
- i. Minimized adverse activity at the colon
- j. Site specific drug delivery
- k. Less inter- and intra-subject variability.
- l. Minimizes the counter activity of the body leading to higher drug efficiency.
- m. Fluctuations in drug concentration are minimized. Therefore, concentration dependent adverse effects can be reduced.
- n. Sustained mode of drug release enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
- o. Flexibility in dosage form design.
- p. Extend patent protection, globalize product, and provide new business opportunities.

### Disadvantages of Floating Microspheres<sup>7-9</sup>

- a. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- b. Not suitable for drugs that have solubility or stability problem in GIT.
- c. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- d. Drugs which are irritant to gastric mucosa are also not suitable.
- e. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- f. The dosage form should be administered with a full glass of water (200-250 ml).

### Polymers Used In Floating Microspheres<sup>14,15</sup>

A number of different substances both biodegradable as well as nonbiodegradable have been investigated for the preparation of microspheres; these materials include polymers of natural origin or synthetic origin and also semisynthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

#### • Hydrophilic polymers

These include gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

#### • Hydrophobic polymers

These include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

#### • Biodegradable polymers

These materials also slowly disappear from the site of administration; however it occurs in response to a chemical reaction such as hydrolysis. Example: Polylactic acid (PLA), poly glycolic acid (PGA), Polycaprolactone (PCL) and several generic classes such as the poly anhydrides and poly orthoesters.

#### • Non-Biodegradable Hydrophobic Polymers

These materials are inert in the environment of use, are eliminated or extracted intact from the site of administration. Example: Polyethylene vinyl acetate (EVA), Polydimethyl siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) and Polyvinyl chloride (PVC), Acrycoat, Eudragit S etc.

#### • Hydrogels

These polymers swell but do not dissolve when brought in contact with water. As with the hydrophobic polymers, hydrogels are inert, removed intact from the site of administration, and function by forming a rate limiting barrier to the transport and release of drugs. Example: Polyhydroxy ethyl methyl acrylate (PHEMA), cross-linked poly vinyl alcohol (PVA), cross linked poly vinyl pyrrolidone (PVP), poly acryl amide etc.

#### • Soluble polymers

These are moderate molecular weight (less than 75,000 Daltons) uncross linked polymers that dissolve in water. The rate of dissolution decreases with increasing molecular weight. These materials can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time. Example: polyethylene glycol (PEG), uncross linked poly vinyl alcohol or poly vinyl pyrrolidone, hydroxyl propyl methyl cellulose (Methocel) and copolymers of methacrylic acid and acrylic acid methyl ester (Eudragit L) etc.

### Approaches of floating microsphere<sup>10,11</sup>

- High density system.
- Floating system.
- Expandable system.
- Super porous hydrogels.
- Magnetic system
- Mucoadhesive or bioadhesive system.

### Methods of preparation

Following methods are used for preparation of floating microspheres

- Spray Drying
- Solvent Evaporation
- Ionic gelation method
- Single emulsion technique
- Double emulsion technique
- Phase separation co-acervation technique
- Spray drying and spray congealing
- Quasi emulsion solvent diffusion

### Spray Drying<sup>10</sup>

In Spray Drying technique, the polymer is first dissolved in a suitable volatile organic solvent. The drug in the solid form is then dispersed in the polymer solution with high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100µm.

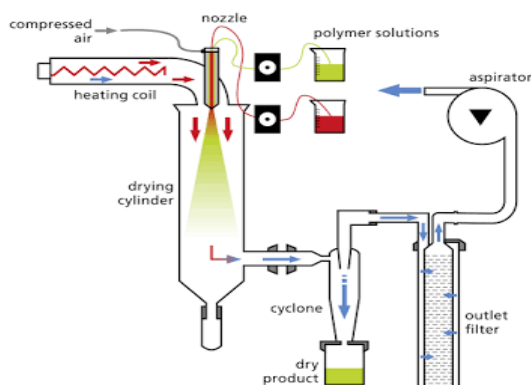


Figure 1: Spray drying

### Solvent Evaporation<sup>10,11</sup>

The solvent Evaporation process is carried out in a liquid manufacturing vehicle phase. The microcapsule coating is dispersed in a volatile

solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. The core material mixture is dispersed in the liquid manufacturing vehicle phase with agitation to obtain the appropriate size microcapsule.

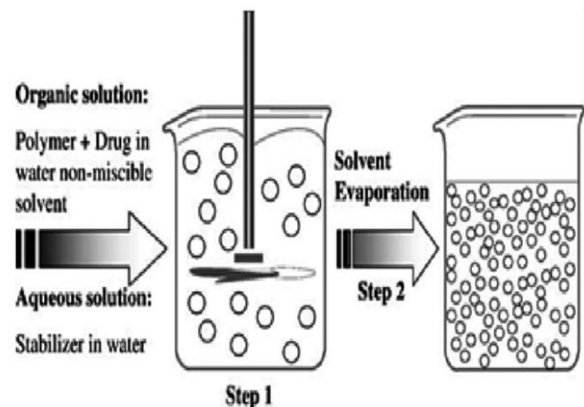


Figure 2: Solvent evaporation method

### Ionic gelation method

In this method cross-linking agent & polymer alone or in combination with copolymers were dispersed in the purified water to form a homogeneous polymer mixture. The drug was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous dispersion. The gelation medium was prepared by dissolving calcium chloride in 2% glacial acetic acid. The homogenous alginate solution was extruded using syringe needle into the gelation medium. Then, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr.

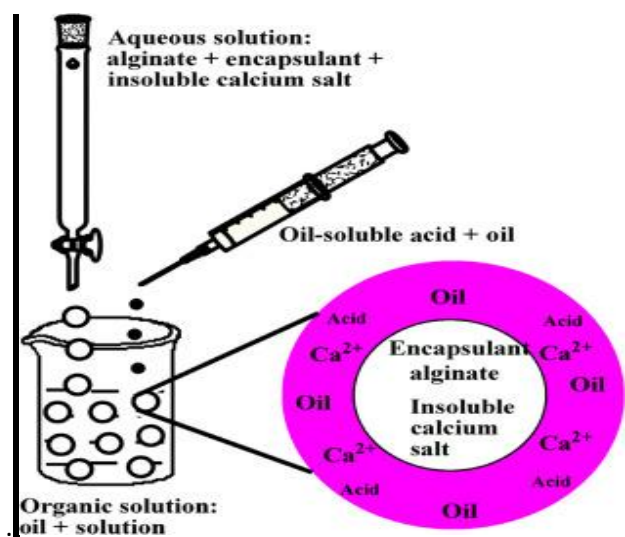


Figure 3 Ionic gelation method.

### Single emulsion technique

The natural polymers are dissolved or dispersed in the aqueous medium followed by dispersion in the non-aqueous medium like oil. In the next step, the cross-linking of the dispersed globule is carried out. The cross-linking can be achieved either by means of heat or by using the chemical crosslinkers.

### Double emulsion technique

Double emulsion method involves the formation of the multiple emulsions or the double emulsion type w/o/w and is best suited for water-soluble drugs, peptides, proteins and the vaccines. The continuous phase has generally consisted of the polymer solution that eventually encapsulates the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization results in the formation of a double emulsion.

### Phase separation coacervation technique

In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes the first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of a polymer. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates.

### Spray drying and spray congealing<sup>12,13</sup>

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying leads to the formation of porous microparticles.

### Quasi-emulsion solvent diffusion

Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol, and polymer. At first, the internal phase is manufactured at 60°C and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then

washed and dried by vacuum oven at 40°C for a day.

### Mechanism of Flotation of Microspheres<sup>14</sup>

When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy.

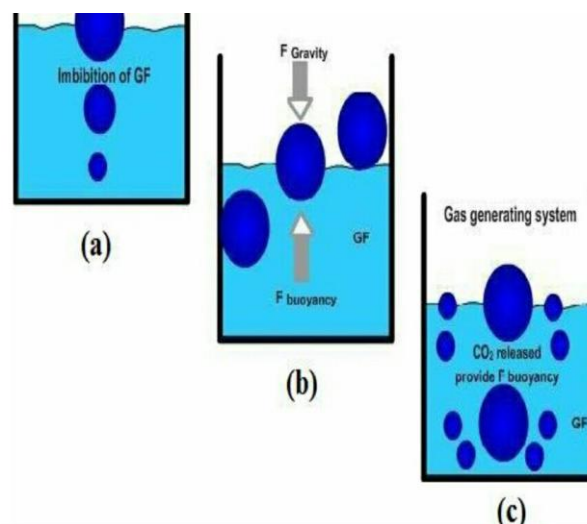


Figure 4: mechanism of floating microsphere

### Evaluation of floating microspheres<sup>15-20</sup>

Following parameter are used for the floating microspheres

#### Particle size analysis

The size will be measured using an optical microscope and the mean particle size will be calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

#### 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 repose.

$$\tan \theta = h / r$$

Where  $\theta$  = angle of repose

H = height of the circle formed by the powder heap

R = radius of heap



### Percentage yield

The prepared floating microspheres will be calculated by dividing actual weight of product to total amount of all non-volatile components that will be used in the preparation of floating microspheres and is represented by following formula.

Percentage yield = actual weight of microspheres / total weight of excipient and drug × 100

### Entrapment efficiency

Accurately weighed quantity of floating microspheres from all batches will be accurately weighed and crushed. The powdered microspheres will be dissolved in ethanol (5ml) in volumetric flask (100ml) and made the volume with 0.1 N HCL. filtered through whatmann filter paper. After filtration the sample will be observed by UV spectrophotometer and the absorbance will be measured against 0.1 N HCL as a blank. The percentage drug entrapment will calculated as follows.

% drug entrapment = Calculated drug concentration / theoretical drug concentration × 100

### Percentage buoyancy

Microspheres will be spread over a surface of USP dissolution apparatus type II field with 900ml 0.1 N HCL (pH 1.2). The medium is to be agitated with a paddle rotating at 50 rpm for 12hrs. The floating and settled portion of microspheres will be recovered separately. The microspheres will be dried and weighed. Percentage buoyancy will be calculated as the ratio of the mass of the microspheres that remain floating and the total mass of the microspheres.

Buoyancy (%) =  $W_f / (W_f + W_s) \times 100$

### Scanning electron microscopy (SEM)

The shape and surface morphology of the beads were studied using electron microscope. Beads were mounted directly on to the SEM sample stub using double – sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001mm of Hg). The beads were viewed at an accelerating voltage of 10KV.

### In – vitro release study

A modified USP dissolution apparatus type I (basket) will be used to study in vitro drug release from the microspheres. This will be carried out separately at 100 rpm in 0.1N HCL (pH 1.2) and in

phosphate buffer as dissolution media (900ml) maintained at  $37 \pm 1^\circ$  C samples (2ml each) will be withdrawn at intervals and analyzed spectrophotometrically. The release medium will be replenished with the same amount of fresh medium to maintain sink conditions.

### Applications of Floating Microspheres<sup>9,12</sup>

#### Sustained Drug Delivery

These systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

#### Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g. riboflavin and furosemide. Floating microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the submucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.

#### Absorption Enhancement

Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption.

#### As a drug carriers

The floating multiparticulates can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa. Pharmacokinetic advantages and future potential: As sustained release systems, floating dosage forms offer various potential advantages evident from several recent publications. Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently

thereby maximizing their absorption and improving their absolute bioavailabilities.

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