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Review Article

FLOATING MICROSPHERE: A REVIEW

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ABSTRACT

Floating microspheres (Hollow Microspheres) are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micro meter. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilise only in stomach, Gastric retention time is increased because of buoyancy. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. In the present review preparation, methods, characterization, advantages, mechanism of drug release from microspheres, list of polymers, applications and list of the drugs formulated as floating microspheres are discussed.

Keywords: Floating microspheres, Gastro Retention, Short half-life, Solvent diffusion.

INTRODUCTION

Recent advances in novel drug delivery system to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. There are lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract).

To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability[1].

Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels.

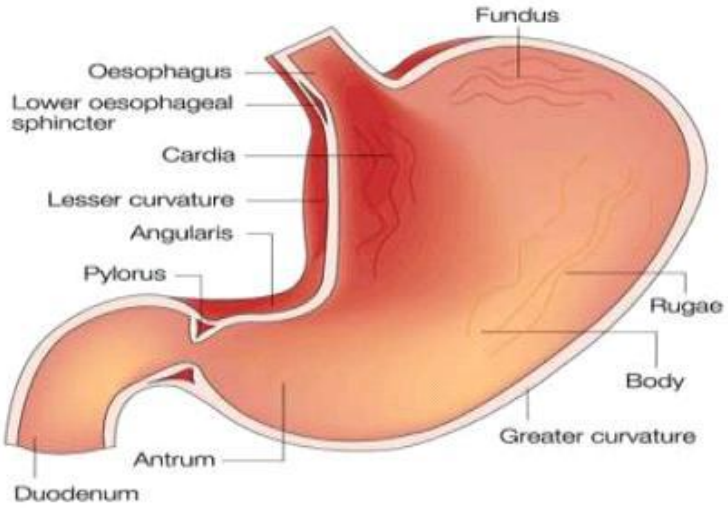

Fig. 1: Anatomy of stomach

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. 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 birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 micro meter. The Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Microspheres are small in size and therefore have large surface to volume ratios. The concept of incorporating quantities of materials within microspheres dates back to the 1930s and to the work of *Bungerberg de joing* and co-workers on the entrapment of substances within coacervates. The potential uses of microspheres in the pharmaceutical have been considered since the 1960's and have a number of applications [2].

The use of microspheres in pharmaceuticals have a number of advantages Viz., Taste and odour masking, conversion of oils and other liquids to solids for ease of handling, protection of drugs against environment (moisture, heat, light and oxidation), separation of incompatible materials, to improve flow of powders, production of sustained release, controlled release and targeted medications[3].

APPROACHES TO GASTRIC RETENTION:

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These includes in **fig.2.**

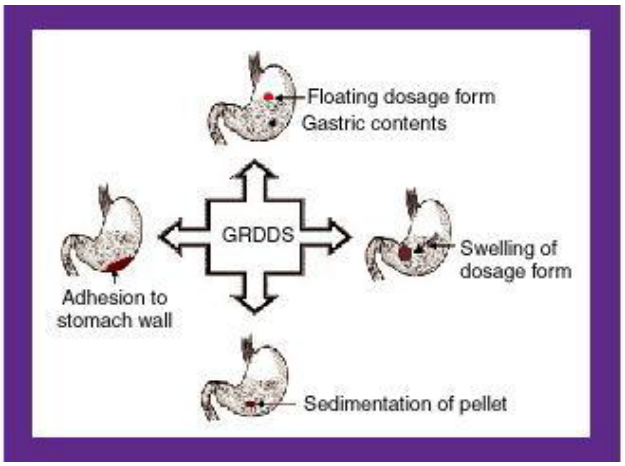

Fig. 2: Illustration of types of gastroretentive drug delivery systems

1. Floating Systems[4]

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

2. Bio/Muco-adhesive Systems[5]

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories:

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

3. Swelling and Expanding Systems[6]

These are dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit tendency to remain logged at the pyloric sphincter.

4. High density systems[7]

These systems with a density of about 3 g/cm3 are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6- 2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower parts of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

5. Incorporation of passage delaying food agents[5]

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

6. Ion exchange resins[5]

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

7. Osmotic regulated systems[5]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

Polymers Used In Hollow Microspheres[2]

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 are includes gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

• **Hydrophobic polymers**

These are 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.

ADVANTAGES OF FLOATING MICROSPHERES[8,2]

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilize only in stomach.
5. Drug release in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.
10. Improved receptor activation selectivity.
11. Extended time over critical (effective) concentration.
12. Less inter- and intra-subject variability.
13. Flexibility in dosage form design.

MECHANISM OF FLOTATION OF MICROSPHERES

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.[9]

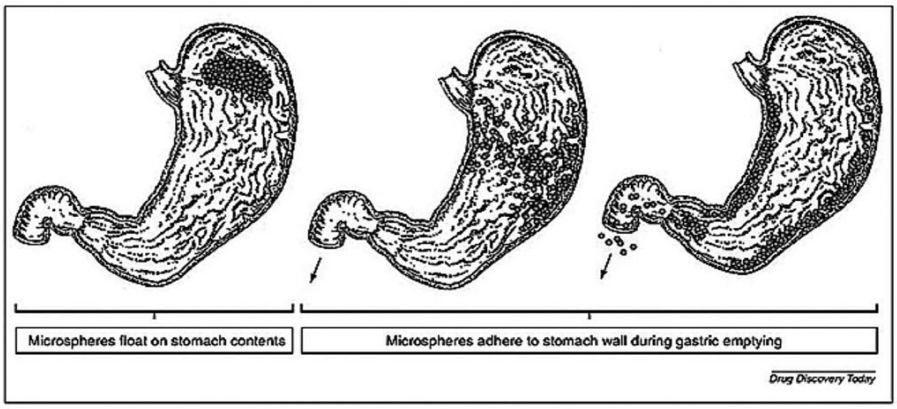

Fig. 3: Mechanism of gastro retention of floating microspheres having mucoadhesive polymer[10]

Mechanism of drug release from the microspheres (Fig. 4) [11]

The mechanism of drug release from multiparticulates can occur in the following ways: -

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

METHODS OF PREPARATION OF MICROSPHERES

1. Solvent Evaporation Method[12]

Floating multiparticulate dosage form can be prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants / polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, eudragit, Acrycoat, Methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonate.

2. Ionotropic Gelation Method [13]

Ionotropic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form beads. Since, the use of alginates, gellan gum, chitosan and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural poly electrolytes in spite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The schematic representation of ionotropic gelation method is shown in **Fig. 5**.

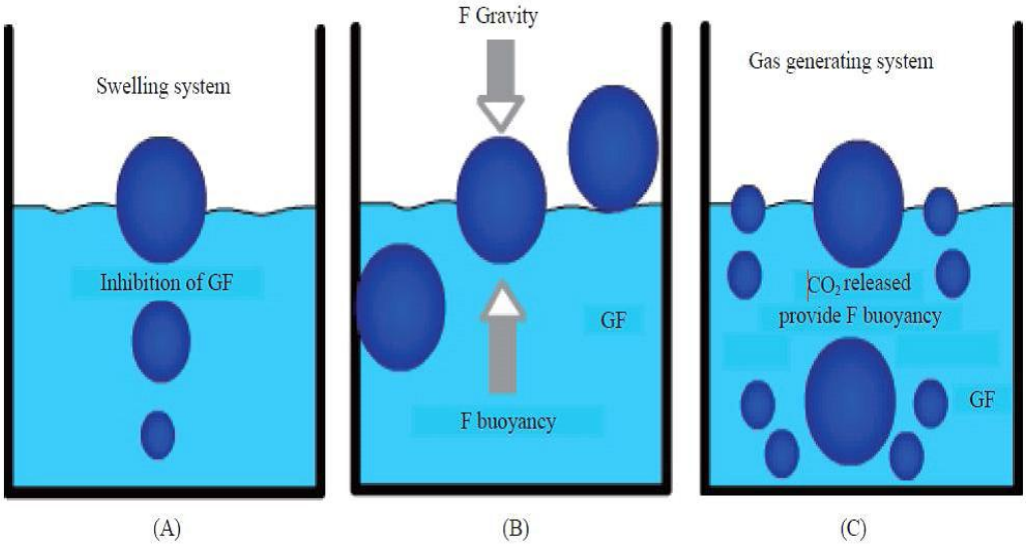

Fig. 4: Mechanism of floating systems (A) Swelling system (C) Gas generating system

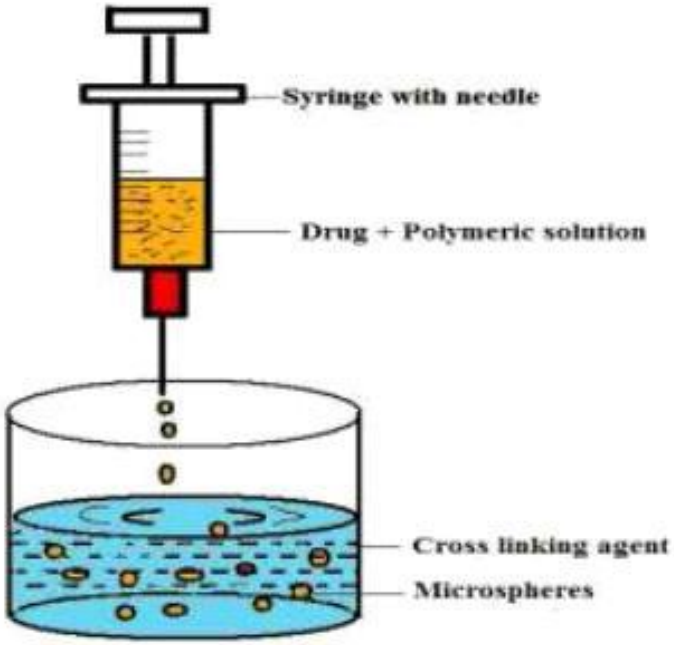

Fig. 5: Ionotropic gelation method

3. Emulsion Solvent Diffusion Method [13]

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible (**Fig. 6**). The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes.

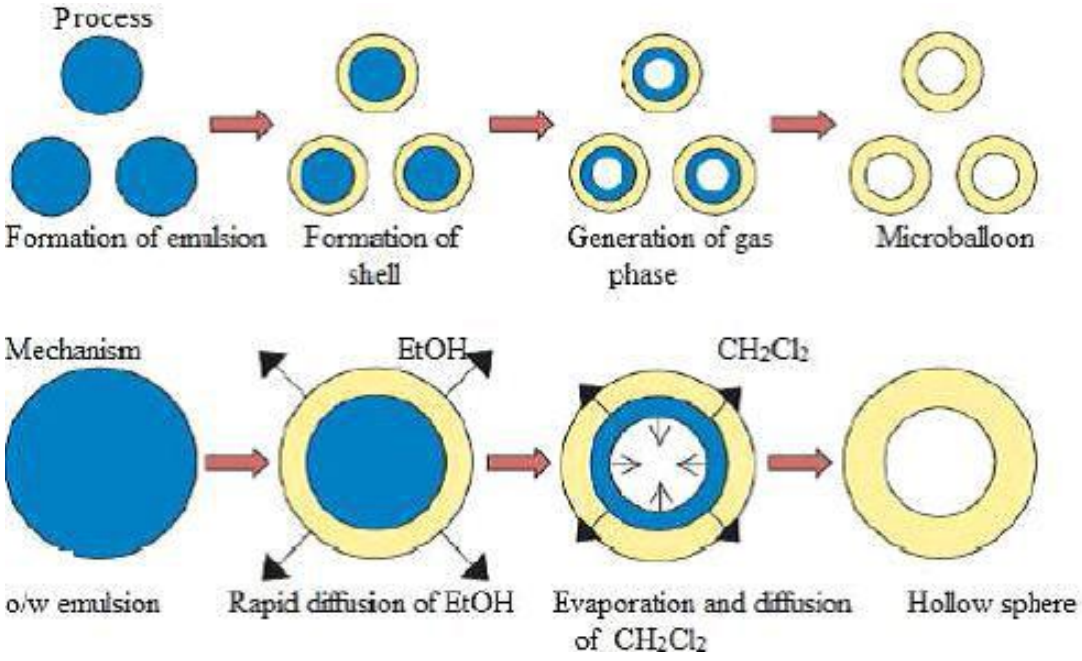

Fig. 6: Preparation technique (emulsion-solvent diffusion method) and mechanism of 'micro balloon' formation

4. Single emulsion technique[14]

In this method, micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil with the help of cross linking agent.

5. Double emulsion technique[14]

This method involves the formation of the multiple emulsions or the double emulsion such as w/o/w. This method can be used with the natural as well as synthetic.

6. Polymerization technique[14]

a) Normal Polymerization

Normal polymerization is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Pure polymers are formed by bulk polymerization.

b) Interfacial Polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

7. Phase separation coacervation technique[14]

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as coacervates. The drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles.

CHARACTERIZATION OF FLOATING MICROSPHERES

1. Particle size[1]

The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micro meter.

2. Bulk density[15]

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm. sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm3)

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Volume of sample}}$$

3. Tapped density[2]

The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100 taps as well as 1000 taps using tapped density apparatus.

$$\text{Tapped density} = \frac{\text{Weight of sample}}{\text{Tapped volume}}$$

4. Compressibility Index and Hausner Ratio[2]

Compressibility index and hausner ratio was calculated from the values of bulk density and tapped density by using following formulas:

$$\text{\% Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

5. Angle of Repose[15]

The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as

Tan θ = h/r

Therefore, θ = tan-1 h/r

Where, θ is angle of repose, h is height of the pile; r is the radius of the pile.

Table 1: Carr's Index as an Indication of Powder Flow

Carr's index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table 2: Relationship between angle of repose (θ) and flowability

Angle of Repose(θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

6. Percentage yield[15]

Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula.

% yield = (actual weight of product/total weight of drug and Excipients) ×100

7. Drug entrapment efficiency (DEE)[15]

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula:

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

8. Swelling studies[14]

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies may be determined by using dissolution apparatus, optical microscopy and other sophisticated techniques which include H1 NMR imaging, confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus was calculated as per the following formula.

$$\text{Swelling ratio} = \frac{\text{Weight of wet formulations}}{\text{Weight of formulations}}$$

9. Scanning Electron Microscopy (SEM)[16]

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure.

10. *In-vitro* buoyancy[14]

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 hrs. 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.

$$\text{Buoyancy}\,(\%) = \frac{W_f}{W_f + W_s} \times 100$$

Where Wf and Ws are the weight of floating and settled microsphere respectively

***11. In-vitro* drug release studies[16]**

For such type of studies USP dissolution apparatus at particular speed is used. Distilled water and dissolution fluid is maintained at 37±10C. Samples withdrawn at periodical intervals and are analyzed spectrophotometrically. The volume was replenished with the same amount of fresh medium to maintain the sink condition.

Applications of Floating Microspheres[2]

1. Floating microspheres are very effective approach in delivery of drugs that have poor bioavailability because of their limited absorption in the upper GIT. These systems efficiently maximize their absorption and improve the bioavailability of several drugs. e.g Furosemide, Riboflavin etc.
2. The floating microspheres can be used as carriers for drugs with so-calledabsorption 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.
3. Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of nonsteroidal anti-inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients..
4. 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. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
5. Hollow 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 sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. The development of such systems allow administration of nonsystemic, controlled release antacid formulations containing calcium carbonate and also locally acting antiulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
6. These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin frusemide and misoprostol. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.
7. These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system.
8. The drugs recently reported to be entrapped in hollow microspheres include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem, verapamil and riboflavin,

aspirin, griseofulvin, ibuprofen, terfenadine.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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