FLOATING MICROSPHERES: A REVIEW

Dr. A. Ankarao*, G. Divya, V. Jyothi, G. Gowri Sindhu and Erick

Department of Pharmaceutics, K. L. College of Pharmacy, Koneru Lakshmaiah Educational Foundation (KLEF), Vaddeswaram, Guntur District, Andhrapradesh, India.

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 micrometer. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. Various gastro retentive dosage forms are available, including tablets, capsules, pills, laminated films, floating microspheres, granules and powders. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. 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 solubilize 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. 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. Floating microspheres are gastroretentive drug delivery systems based on a non – effervescent approach. Hollow microspheres, micro balloons 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 1000µm. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuation in plasma drug concentration. The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier characteristics. The floating microspheres not only prolong the gastric retention time but also controls the space in the stomach by maintaining the delivery system positioned at a steady site and their by properly delivering the drug.

Advantages of Floating Microspheres
- Floating dosages systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery.
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- Improve drug absorption because of increase gastric residence time and more time spent by the dosage form at its absorption site thereby increasing bioavailability of encapsulated drug.
- Controlled or sustained drug delivery system.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro oesophageal reflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.
- Less frequent dosing.
- Possibly reduced side effects of drugs for prolonged administration.
- Avoiding peak and valley curves in plasma drug concentration.
- Site-specific drug delivery.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect.
- Better therapeutic effect of short half-life drugs can be achieved.
- Improved receptor activation selectivity.
- Extended time over critical (effective) concentration.
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.

Disadvantages of Floating Microspheres
- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first – pass metabolism, may not be desirable.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as drug delivery systems.
Factors Affecting Gastric Retention

There are several factors that can affect gastric emptying of an oral dosage form which include:

- **Density**
  Density is an important parameter for gastric emptying time and also determines the buoyancy of dosage form; a density of < 1.0 gm/cm³ is ideal for exhibiting good floating property.

- **Size**
  The mean residence time of floating and non-floating dosage form depends on the size of the dosage form. To pass the dosage form from the pylorus to intestine, it should be in the range of 1 to 2 mm.

- **Shape of dosage form**
  Shape is an important parameter to design a single unit dosage form, tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better gastric retention time up to 24 h compared to other shapes.

- **Fed or unfed state**
  Under Fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.

- **Age**
  Elderly people, especially those over 70, have a significantly longer; floating. Disease condition such as diabetes and Crohn’s disease etc also affect drug delivery.

- **Single or multiple unit formulation**
  Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Gender**
  Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.
• **Diseased state of the individual**
  Biological factors also affect the gastric retention.

  *e.g.* Crohn's disease, gastrointestinal disease and diabetes. Concomitant drug administration. Anti-cholinergics like atropine and propentheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

**Formulation aspects**

• **Absorption window**
  Site of absorption also favours the development of this formulation. Drugs having site of absorption in the stomach and upper part of the small intestine are good candidates to be encapsulated in floating microspheres.

• **Shorter biological half-life**
  Drugs having shorter biological half life’s favours for the formulations.

• **Solubility**
  Drug having better solubility in acidic environment and also having specific site of absorption in the upper part of the small intestine. Drug having stability at gastric pH.

• **Dose**
  Drugs that are used locally in stomach like Ranitidine hydrochloride, Famotidine (H2-receptor antagonist). It is widely used / prescribed in duodenal ulcers, gastric ulcers, zollinger ellisons syndrome, gastrooesophageal reflux disease and erosive esophagitis.

• **Polymer**
  Low density polymers which have bulk density less than one, can be used for enhancing the buoyancy of the formulation are used in formulating FDDS.

**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.
Mechanism of drug release from the microspheres

- 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**
   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

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 show.
3. Emulsion Solvent Diffusion Method

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. 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.

![Diagram of Emulsion Solvent Diffusion Method](image1)

4. Single emulsion technique

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.

![Diagram of Single Emulsion Technique](image2)
5. Double emulsion technique
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
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
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

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

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/cm$^3$)

\[
\text{Bulk density} = \frac{\text{weight of sample}}{\text{volume of sample}}
\]

3. Tapped density

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

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

\[
\text{Compressibility Index} = \frac{Tapped \ density - bulk \ density \times 100}{Tapped \ density}
\]
Hausner ratio = \( \frac{\text{tapped density}}{\text{Bulk density}} \)

5. Angle of Repose

The angle of repose \( \theta \) of the microspheres, which measures the resistance to particle flow, was calculated as \( \tan \theta = \frac{h}{r} \). Therefore, \( \theta = \tan^{-1} \left( \frac{h}{r} \right) \). Where, \( \theta \) is angle of repose, \( h \) is the height of the pile; \( r \) is the radius of the pile.

Carr's Index as an Indication of Powder Flow

<table>
<thead>
<tr>
<th>Carr’s index</th>
<th>Types of flow</th>
</tr>
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<tbody>
<tr>
<td>5-15</td>
<td>excellent</td>
</tr>
<tr>
<td>12-16</td>
<td>good</td>
</tr>
<tr>
<td>18-21</td>
<td>Fair to possible</td>
</tr>
<tr>
<td>23-35</td>
<td>poor</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Extremely poor</td>
</tr>
</tbody>
</table>

Relationship between angle of repose (\( \theta \)) and flowability

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Very poor</td>
</tr>
</tbody>
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6. Percentage yield

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.

\[ \% \text{ yield} = \left( \frac{\text{actual weight of product}}{\text{total weight of drug and Excipients}} \right) \times 100 \]

7. Drug entrapment efficiency (DEE)

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:

\[ \text{DEE} = \left( \frac{\text{amount of drug actually present}}{\text{theoretical drug load expected}} \right) \times 100 \]
8. Swelling studies
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.

9. Scanning Electron Microscopy (SEM)
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.

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

10. 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 agitation 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.

Applications of Floating Microspheres
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
   a. 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-called absorption windows, these substances,
3. For example: antiviral, antifungal and antibiotic
4. Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of no steroidal anti-
inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients.

5. Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs.

6. 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.

7. 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.

8. 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.

9. 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.

REFERENCES


