# FLOATING MICROSPHERES A NEW TREND IN THE DELIVERY OF GASTRO RETENTIVE MEDICATIONS

**Abstract**

There is no control over the delivery of conventional dose forms. Gastric resident time and gastric emptying are two crucial parameters that have a substantial impact on the drug's ability to treat certain conditions, and it produces differences in the drug's retention period. Drug levels in plasma change depending on the dosing type. As a result, among all gastro-retentive medication administration methods, the floating microsphere is one of the most dependable and creative methods to solve these issues. Due to their extreme appropriateness for targeting, floating microspheres are primarily gaining relevance. The main reason floating microspheres are becoming more and more popular is because of how well-suited they are for delivering medications to the stomach, dispersing them evenly over the gastric fluid to prevent variations in gastric emptying, and increasing drug release. Additionally, this technique greatly facilitates the development of oral formulations with controlled and delayed releases fostering changes in the pharmaceutical sector. The anatomy and physiology stomach, intestines, and components govern the retentive medication delivery method, according to the current review. This review's objective is to shed light on the latest literature regarding the value of Microspheres that float in new medication delivery systems, Formulation techniques, classification, and recent scientific developments in the formulations of floating microspheres using various drug classes.

**Keywords:** Floating microspheres, GRDDS, FDDS. GRT

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## I. INTRODUCTION

Hydro-dynamically balanced systems, also known as floating drug delivery systems (FDDS), are a type of gastro-retentive drug delivery system that has a bulk density lower than gastric fluids and floats in the stomach for an extended period of time without causing the gastric-emptying rate to increase. After the medication has been completely released from the floating system, the residual components of the dose form are expelled from the stomach. As a result, the GRT is improved, and variations in plasma drug concentration are better controlled.As a result, the GRT is enhanced, and variations in plasma drug concentration are better managed. Designing oral controlled release dose forms requires a thorough understanding of GI dynamics, which include colonic transit, small intestine transit, and stomach emptying. The development of dose forms is aided by knowledge of the extent and degree of drug absorption from certain GI tract locations as well as factors that control the absorption.[1]

Due to its lesser bulk thickness than GI fluid, the floating drug administration method maintains buoyancy in the stomach for an extended period of time without altering the rate of gastric emptying. In this process, the substance floats and is delayed until the medicine is released, allowing it to leave the body at the proper rate. This makes bacterial entry into the body more likely and produces efficient antibacterial medication concentration regulation.[2]

**Table 1: Benefits of Traditional Medication Administration Vs Gastrointestinal Retention**

| Traditional | Gastro Retentive Drug Delivery System |
|---|---|
| Not the ideal option for Insoluble medications at an alkaline pH Gastrointestinal medicines have a local effect. Medications that break down in the gut. Rapid-absorbing medications through the GIT | Very much preferred for Medications that quickly enter the GIT Medications that break down in the colon localized effects of gastrointestinal medicines |
| A technique for administering medications that have a specific window of absorption in the area around the small intestine | Adernate for the administration of drugs with a constrained window of ingestion in the area of the small intestine |
| Lower Patient adherence | Higher Patient adherence |

## II. BENEFITS OF FLOATING MICROSPHERES [4]

1. Improved receptor activation selectivity
2. Improved receptor bioavailability
3. Improved first-pass biotransformation.
4. Extended time over critical (effective) concentration
5. Targeted treatment for upper GIT local problems fewer changes in drug concentration decreased body counteractivity
6. Reduced colonic side effects and site-specific medication delivery
7. Less variation within and between subjects.
8. Reduces the body's natural defense mechanisms, increasing the drug's effectiveness.

 

9. Drug concentration fluctuations are kept to a minimum. As a result, undesirable effects that depend on concentration can be diminished.
10. With a continuous drug release method, the timing above with a crucial focus can be prolonged, improving pharmacological effects and therapeutic outcomes.
11. Flexibility in the creation of dosage forms.

## III. DISADVANTAGES OF FLOATING MICROSPHERES

1. First-pass effect-metabolized medications cannot be used with this sort of medication delivery system.
2. Medicines that aggravate ulcers and irritate the stomach mucosa are not appropriate for this administration method.
3. Drugs that have problems with solubility and stability in stomach fluid shouldn't be administered this way.

## IV. BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

The stomach is anatomically divided into three parts: the fundus, body, and antrum. The proximal portion, which is made up of the fundus and body, serves as a holding area for partially digested material, while the antrum is the primary location for mixing motions and serves as a pump for gastric emptying and full propulsion. Both when one is eating and when one is fasting, the stomach empties. In both situations, the motility pattern is understandable. The term "migrating myloelectric cycle" (MMC) or "interdigestivemyloelectric cycle" refers to the series of electrical events that occur during the fasting condition and every two to three hours, the stomach and intestines should cycle. This cycle comprises four Stages

**Stage I (basal phase)** It goes on from 40 to 60 minutes unusually constricted.

**Stage II (pre-burst phase)** Constrictions and period action potential persisted for 40 to 60 minutes. The regularity and magnitude also increase progressively once this Phase is completed.

**Stage III (burst phase)** It went on for 4 to 6 minutes. It has prolonged, strong contractions that are systematic. This wave causes the entire stomach's contents to be flushed into the small intestine.

**Stage IV** This pattern of digestion's motility is also known as phase II of the fasted state's continuous contractions. Between phases III and I of two subsequent cycles, it lasts for 0 to 5 minutes.

After ingesting a mixed meal, the contraction types to change afed from a fast condition. The contractions result in a reduction of the food fragments to a maximum of 1mm, after which causes them to be accelerated toward the pylorus.

## V. GASTRO-RETENTIVE MEDICATION DELIVERY FACTORS [7]

1. **Fed or non-fed state:** In general, the fed condition prolongs the drug's time at the site of absorption, which boosts absorption and improves stomach retention time. The amount of

 

time that food remains in the stomach depends on whether it appears or not. GRT is quite low during fasting because of the high motor activity that forces the stomach's undigested food into the intestine.

2. **Feeding frequency:** When meals are consumed in succession rather than all at once, the GRT increases by 400 minutes.

3. **Calorie and meal type:** The GRT extends from 4 to 10 hours when high-calorie foods like proteins and fats are consumed. Food containing indigestible polymers or fatty acid salts can affect the motility.

4. **The impact of posture, age, and gender:** People above the age of 70 have long GRT. GRT in women is lower than in men. No discernible difference exists between the upright and horizontal positions with regard to the GRT.

5. **The dosage form's density:** The density of a substance has a substantial impact on how quickly the stomach empties and regulates the buoyancy of a dose form. The best dose form for exhibiting good floating property is often one with less than 1.0 g/cm3 of density.

6. **Dosage form dimensions:** The dose form's enormous size might prevent it from passing quickly past the pyloric antrum and into the gut. The size of the dosage form determines the residence time of both floating and non-floating dosage forms. The dosage must move from the pylorus to the intestine.

7. **Dosage form shape:** For better stomach retention durations of up to 24 hours, dosage formulations with flexural moduli of 48 and 22.5 kilo pounds per square inch (KSI) are known to exist. When creating a floating medicine delivery system, shape is a key factor to take into account.

8. **Administration of drugs concurrently:** Metoclopramide and Cisapride are prokinetic drugs that lessen gastric retention. Gastric retention is enhanced by anti-cholinergic drugs including propantheline, atropine, and opiates like codeine.

9. **Absorption mechanism:** Orally administered medications are absorbed both passively and actively. Due to the fact that active and assisted transport systems are more prevalent in a particular area of the gastrointestinal tract, drugs absorbed by these mechanisms have increased regional specificity.

10. **Metabolic enzymes:** Regional variations in absorption are also influenced by the presence of particular enzymes in the G.I. tract. Phase-I metabolizing enzymes such as cytochrome P-450 are contained inside the intestinal epithelium; their activity decreases longitudinally along the small intestine, and their levels increase from the duodenum to the jejunum before decreasing in the ileum and colon. Drugs that are substrates for these enzyme experience variations in absorption due to this sporadic deposition of cytochrome P-450.

 

## VI. FLOATATION MECHANISM

To increase the length of Several techniques are utilized to reduce gastric retention time in the stomach. Due to their constant lower bulk density than gastric fluid, floating drug delivery systems (FDDS) float in the stomach for a longer period of time without having any effect on the rate at which the stomach empties. In this configuration, the drug floats on the stomach's contents and is expelled from the body at the desired rate.In order to maintain the submerged object, the gadget continually calculates the force F (a function of time). This device assists in adjusting the stiffness and robustness of the floating effect in the floating drug delivery system, which is important to prevent the drawback of erratic potentiality changes with a tendency to float.[8, 9]

$$F = F_{gravity} + F_{buoyancy} = (Df - Ds)\, gv$$

Where F is the total vertical force, Df is the fluid density, Ds is the object density, v is the volume, and g is the gravitational acceleration.

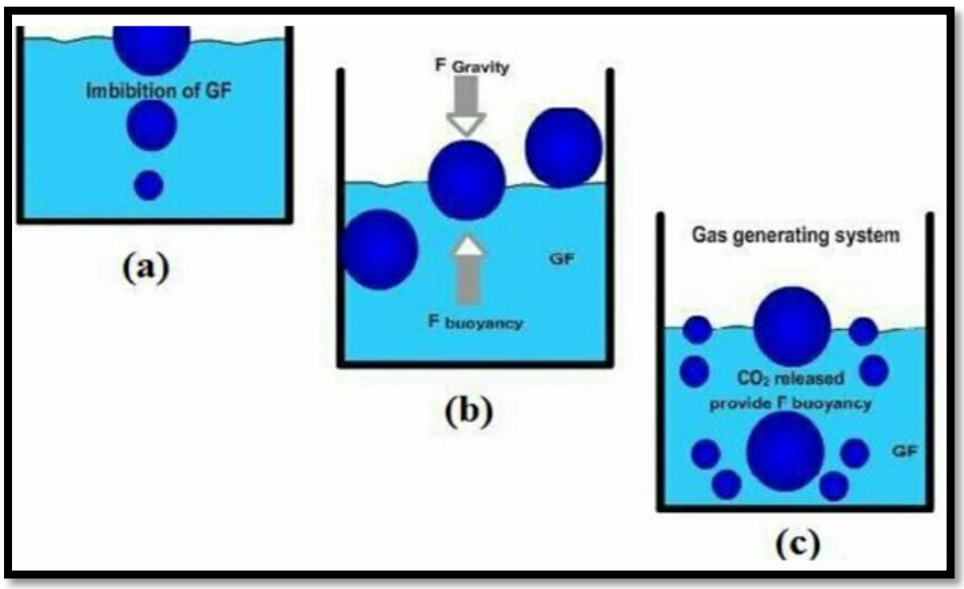


**Figure1: The Floating Microsphere's Mechanism**

## VII. POLYMERS UTILISED IN FLOATING MICROSPHERES[8]

Hydrophilic and hydrophobic polymers can be combined to create microspheres. For the creation of microspheres, various polymers, both biodegradable and not, have been used, including those with natural, semi-synthetic, and synthetic origins.

1. **Hydrophilic polymers:** The hydrophilic polymers used to create microspheres includealbumin, agar, chitosangelatine, egg starch, cellulose derivatives, and HPMC.

2. **Hydrophobic polymers:** The water-repellent polymers used to create microspheres include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters, etc.

 

3. **Biodegradable polymers:** These polymers progressively depart the administration site, yet via hydrolysis, it seems as though there was a response.

   Examples of this type of polymers used include polylactic acid (PLA), poly glycolic acid (PGA), polycaprolactone (PCL), and other broad classes including poly anhydrides and polyorthoesters.

4. **Non-biodegradable hydrophobic polymers:** Where they are used, eliminated, or originated from the administrative region, these inactive are inert. Ethyl cellulose (EC), cellulose acetate (CA), polyethylene vinyl acetate (PEVA), polyether urethane (PEU), polyethylene (PE), polydimethyl siloxane (PDS), polyvinyl chloride (PVC), Acrycoat, Eudragit S, and other non-biodegradable hydrophobic polymers are used to create microspheres.

5. **Hydrogels:** Where they are used, eliminated, or originate from the administrative region, these inactive are inert. Microspheres are produced using hydrophobic non-biodegradable polymers such as Acrycoat, Eudragit S, cellulose acetate (CA), ethyl cellulose (EC), polyethylene vinyl acetate (PEVA), polyether urethane (PEU), polyethylene (PE), polydimethyl siloxane (PDS), polyvinyl chloride (PVC), and polyethylene (PE).

6. **Soluble polymers:** These are uncross-linked polymers that melt in water and have a molecular weight of less than 75,000 Dalton. As molecular weight rose, the rate of dissolution dropped.These polymers can be used alone or in combination with hydrophobic polymers to make a product that deteriorates progressively over time. Co-polymers of methacrylic acid and acrylic acid methyl ester (Eudragit L), polyethylene glycol (PEG), polyvinylpyrrolidone or uncross linked polyvinyl alcohol, and hydroxyl propyl methyl cellulose are the soluble polymers used to create microspheres (Methocel).

## VIII. METHODS OF DEVELOPMENT FOR FLOATING MICROSPHERES

The manufacture of gastro-retentive floating microspheres can be done in a variety of ways. To explore the many viewpoints of floating microspheres, however, a lot of systematic researchers have widely used the ion tropic gelation method and the emulsion solvent evaporation methodology.

The best strategy is used to completely entrap the active components for creating floating controlled release microspheres. The choice of this approach depends on the type of the polymer, the API, and its intended purpose. The qualities of the formed microspheres as well as the regulated release rate from the dosage form are significantly influenced by the material characteristics and the procedure used.

1. **Solvent evaporation technique:** A floating multi-particulate dose shape can be constructed to create the full interior centre using solvent diffusion and evaporation techniques. The polymer is dissolved in a natural solvent, and the medication is either disseminated or dissolved inside the polymer solution. To create an o/w emulsion, it is then emulsified with the appropriate additive (surfactants or polymer) in an aqueous segment. Following the development of a strong emulsion, the natural solvent is evaporated either by developing the temperature below pressure or by non-forestall

 

stirring. After the solvent is removed from the droplet's o/w interface, polymer precipitation takes place, and a hollow gap forms to give rise to the floating dwellings. Polymers like cellulose acetate, polyethylene oxide, acrycoat, Eudragit, methocel, carbapol, polyacrylates, and polyvinyl chloride have all been researched for the creation of such systems.

2. **Ion-tropic gelation method:** The basis for this technique is the formation of beads by interactions between polyelectrolytes and counterions.Despite the fact that herbal poly electrolytes work as drug retardants and have coating qualities at drug centers, they chemically include high-quality anions. This is because alginates, CMC, and chitosan are frequently used to encapsulate drugs and even living cells.These anions specifically bind to the anion blocks, where they join the polyvalent cations to create a meshwork structure that causes gelation. The drug-loaded polymeric solution is dripped into the aqueous solution to create the hydrogel beads.

3. **Emulsion solvent diffusion:** This strategy is more effective than others.A natural solvent is used to dissolve the medication. Despite the fact that the organic solvent melts, polymers are disseminated in an aqueous solvent. As the natural solvent slowly diffuses from the emulsion droplets into the surrounding aqueous phase, the aqueous phase through which the medicine crystallizes diffuses into the droplets.

4. **The single emulsion method:** Using a single emulsion approach, this technology prepares proteins and carbohydrates to create microparticulate aggregates of natural polymers. Natural polymers are dispersed or dissolved in aqueous media with the help of a modification to the linking agent and exposed by dispersion in non-aqueous fluids, such as oil.

5. **Method of polymerization**

    - **Standard polymerization:** Regular polymerization is carried out with the aid of fantastic techniques like suspension, emulsion, precipitation, bulk, and micelles polymerization. Herbal polymers are created using the bulk polymerization resource.
    - **Cross-linking polymerization:** The interaction of many monomers at the interface results in a film of polymer that encompasses the majority of the two liquid phases that are irreducible and essentially encloses the dispersion.

6. **Phase separation coacervation technique:** It is totally predicated on the organic segment's idea that lowering the solubility of the polymer will have an effect on how quickly coacervates form. When an incompatible polymer is added to the solution, the first polymer phase separates, and the drug debris is submerged. The drug is still dispersed in the polymer's reaction.

## IX. MICROSPHERE CHARACTERIZATION

1. **Micrometric characteristics:** The produced microspheres can be distinguished from one another using their micrometric properties, such as microsphere particle size, bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose.

 

- **Bulk and Tapped density:** 50 cc of the graduated cylinder was used to measure the bulk and tapped densities. A glass funnel was used to filter a sample that had been precisely weighed. 100 mechanical taps were made on the sample that had been poured into the cylinder. Following that, the tapped volume was recorded, and the following formula was used to compute the bulk density and tapped density. The measurement was in $g/cm^3$.

  **Bulk density (ρb) =** Mass of microspheres (M)/Volume of microspheres after tapping (Vb)
  **Tapped density (ρt) =** Mass of microspheres (M)/Volume of microspheres after tapping (Vt)

- **Carr's compressibility index:** The Carr's Compressibility Index, Compressibility index (C.I.), or Carr's index value of microspheres was calculated using the following equation.

**% Compressibility index = (Tapped Density-Bulk Density/Tapped Density) ×100**

- **The Hausner's ratio:** The equation was used to compare the tapped density to the bulk density and find Hausner's ratio of microspheres.

**Hausner's ratio = (Tapped Density / Bulk Density) x 100**

- **Angle of repose:** The angle of repose is the largest angle that can be established between the surface of a powder pile and a horizontal surface.
  Tan θ = h/r
  where Tan θ = the angle of repose
  h = the height of the circle the powder heap forms
  r = the heap's radius

2. **Microspheres' particle size distribution:** A compound microscope was used to perform optical microscopy for the examination of the drug-loaded microspheres particle sizes. A calibrated ocular micrometer was used to measure the diameter of at least 300 Eudragit microspheres on a slide that was mounted on the microscope's stage. The average particle size of the microspheres was calculated by dividing the total size of the microspheres by the number of microspheres.

3. **Morphological investigation:** The surface morphology of the microspheres is examined using SEM. The powder is strewn across the tape that is fastened to an aluminum stub to create the SEM sample. In a high vacuum evaporator with an argon environment, a voltage of 20 kV, a current of 10 mA, and low pressure, the stubs are coated with a mixture of gold and palladium that is between 250 and 450 microns thick. Randomly selected coated samples are used for SEM photomicrographs.

 

4. **Calculating the microspheres yield in percentage :** Microspheres that had been completely dried were gathered and precisely weighed. The formulas below were used to calculate the % yield.

**%Yield=Weight of microspheresobtained/combined medication & polymerweight x100**

5. **Studies of buoyancy [14]:** The floating microspheres can be dispersed on a simulated stomach fluid (pH 1.2) containing the surfactant to conduct in-vitro floating experiments using a USP class II dissolving test device.At 37± 0.5°C, the medium is agitated at 100RPM.Both the floating and settling microsphere fractions are collected after predefined intervals of time, and a formula is used to determine the floating microspheresbuoyancy.

$$\text{Buoyancy}\,(\%) = \frac{Qf}{Qf + Qs} \times 100$$

where Qf and Qs, respectively, stand for the masses of floating or settling hollow microspheres.

6. **Effectiveness of Entrapment :** For testing, prepared microspheres corresponding to 100 mg of the medication were consumed. By repeatedly breaking up the microsphere and using aliquots of 0.1N HCl to extract, the amount of drug entrapped was calculated. A 100 ml volumetric flask was filled with 0.1 N HCl once the extract had been placed there. After filtering the solution, the absorbance at a certain wavelength was measured in comparison to a blank. The following formula was used to determine how much medication was trapped in the microsphere.

$$\%\ \text{Entrapment Efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \quad 100$$

7. **Drug content:** The drug content of microspheres was assessed by dispersing a 50 mg formulation in 10 mL acetone and mixing with a magnetic stirrer for 12 hours to wet the polymer and extract the drug. After achieving the necessary dilution with 0.1N HCl, the drug concentration in the ethanol phase was filtered through a Whatman filter and quantified spectrophotometrically at their relevant nm. Each conclusion was replicated three times. The formulas for estimating the yield and percentage of drug entrapment are as follows.

**% Drug loading = (Actual Durg content/ Weight of Microspheres)x100**

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