**FLOATING MICROSPHERES**

**A NOVEL EMERGING TREND IN GASTRO RETENTIVE DRUG DELIVERY**

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**ABSTRACT:**

There is no control over the delivery of conventional dose forms. Gastric emptying and gastric resident time are two crucial parameters that have a substantial impact on the therapeutic efficacy of the Drug and it produces differences in the retention time of the drug. Drug from the dosage form causes variations in plasma drug levels. As a result, among all the gastro-retentive drug delivery systems, 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 controlled and delayed release oral formulations, fostering revolutions in the pharmaceutical industry. The physiology of the gastric intestinal tract and elements govern the retentive medication delivery system, according to the current review. This review's objective is to shed light on recent literature regarding the value of floating microspheres in novel drug delivery systems, preparation techniques, classification, and recent scientific developments in the formulations of floating microspheres using various drug classes.

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

**1. 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. This leads to an improvement in the GRT and better control over changes in plasma drug concentration. 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, such as stomach emptying, small intestine transit, colonic transit, etc. 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

The method of floating medication delivery lasts for an extended duration of buoyancy in the belly without affecting the rate of gastric emptying because its bulk thickness is smaller than that of GI fluid. In this procedure, the substance floats, and when the medicine is released, the substance is delayed to escape from the system at the necessary rate. This increases the possibility of bacterial infiltration of the body and leads to effective bacterial drug concentration management.2

**Table 1: Advantages of Conventional v/s Gastro retentive drug delivery system 3**

|  |  |
| --- | --- |
| **Conventional** | **Gastro retentive drug delivery system** |
| Not very preferred for  Medications that are insoluble at an alkaline PH  Locally acting medications for the stomach.  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.  Drugs acting locally in the stomach |
| Insufficient for administering medications with a specific window of absorption in the small intestine area | Adernate for the distribution of medications with a limited window of absorption in the small intestine area |
| Patient compliance is lower | Patient compliance is higher |

**II. ADVANTAGES OF FLOATING MICROSPHERES 4**

* Improved receptor activation selectivity
* Improved receptor bioavailability
* Improved first-pass biotransformation Extended time over critical (effective) concentration Targeted therapy for local conditions in the upper GIT Reduced fluctuations of drug concentration Reduced counter-activity of the body
* Reduced colonic side effects and site-specific medication delivery
* Less variation within and between subjects.
* Reduces the body's natural defence mechanisms, increasing the drug's effectiveness.
* Drug concentration fluctuations are kept to a minimum. As a result, undesirable effects that depend on concentration can be diminished.
* The period over a critical concentration can be extended with sustained mode of drug release, which enhances the pharmacological effects and improves clinical results.
* Flexibility in the creation of dosage forms.

**III. LIMITATIONS 5**

* Drugs that aggravate the stomach mucosa and induce ulcers are not suitable for this delivery technique.
* First-pass effect-metabolized medications cannot be used with this sort of drug delivery system.
* Drugs with solubility and stability issues in stomach fluid should not be administered using this method.

**IV. BASIC GASTROINTESTINAL TRACT PHYSIOLOGY 6**

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 "interdigestive myloelectric cycle" refers to the series of electrical events that occur during the fasting condition and cycle through the stomach and intestine every two to three hours. This cycle comprises four phases

**Phase I (basal phase)**

It continues from 40 to 60 minutes with unusual constrictions.

**Phase II (pre-burst phase)**

It continued for 40 to 60 minutes with period action potential and constrictions. As this Phase is completed, the regularity and magnitude also rise progressively.

**Third Phase (burst phase)**

Another name for it is the housekeeping wave. 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.

**Phase 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.

The sorts of contractions shift from a fasted to a fed condition after consuming a mixed meal. The contractions cause the food particles to get smaller—to less than 1 mm—and are subsequently pushed in the direction of the pylorus.

**V.FACTORS AFFECTING GASTRO-RETENTIVE DRUG DELIVERY** 7

1. **Fed or non-fed state**

In general, the fed state improves the stomach retention time and increases the absorption of the drug by extending the drug to last at the site of absorption. The appearance and non-appearance of food directs the gastric retention time. As a result of the intense motor activity that drives the undigested material from the stomach to the intestine while fasting, GRT is quite low.

**B. Feeding frequency:**

When meals are consumed in succession rather than all at once, the GRT increases by 400 minutes.

**C. 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.

**D. 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.

**E. 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 a density less than 1.0 gm/cm3.

**F. 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.

**G. Dosage form shape:**

Dosage forms with flexural moduli of 48 and 22.5 kilo pounds per square inch (KSI) are known to have better stomach retention times of up to 24 hours. Shape is an important consideration when designing a floating drug delivery system.

**H. Administration of drugs concurrently:**

Metoclopramide and cisapride are prokinetic drugs that lessen gastric retention. The gastric retention is enhanced by anti-cholinergic drugs including propantheline, atropine, and opiates like codeine.

**I. Absorption mechanism:**

Orally administered medications are absorbed both passively and actively. Due to the commonality of these mechanisms only in a particular area of the gastrointestinal tract, drugs absorbed via active and assisted transport systems demonstrate increased regional specificity.

**J. Metabolic Enzymes:**

Enzymes present in specific locations in G.I. tract also lead to regional changes in absorption. Intestinal epithelium encloses phase-I metabolizing enzymes like cytochrome P-450, their action reduces longitudinally along the small intestine, and their levels increasing from duodenum to the jejunum and then reducing in the ileum and colon. This intermittent deposition of cytochromeP-450 makes variabilities in the absorption of drugs that are substrate to this enzyme.

**VI. FLOATATION MECHANISM**

Various techniques are employed to prolong gastric retention time in the stomach. The floating drug delivery systems (FDDS) are floating in the stomach for a longer period of time without having any impact on the gastric emptying rate due to their constant lower bulk density than gastric fluid. The medication is released from the system slowly at the desired rate in this setup while floating on the contents of the stomach. The device controls by continuously calculating the force F (a function of time) that is applied to sustain the submerged object. This device aids in the floating medication delivery system's adjustment with regard to the rigidity and robustness of the floating effect, which is necessary to avoid the drawback of unpredictable propensity to float potentiality variations. 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 MICROSPHERES8**

Hydrophilic and hydrophobic polymers can be combined to create microspheres.

For the creation of microspheres, both biodegradable and non-biodegradable polymers have been used, including those with natural, semi-synthetic, and synthetic origins.

1. **Hydrophilic polymers, first**

The hydrophilic polymers used to create microspheres include gelatine, agar, egg albumin, starch, chitosan, cellulose derivatives, and HPMC.

**B. Hydrophobic polymers**

The Polymers that repel water used to make microspheres include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters, etc.

1. **Biodegradable plastics,**

These polymers slowly leave the administration site; however, because of hydrolysis, it appears as a response. Polylactic acid (PLA), poly glycolic acid (PGA), polycaprolactone (PCL), and several general classes such the poly anhydrides and polyorthoesters are examples of biodegradable polymers that are employed.

**D. Non-Biodegradable Hydrophobic Polymers**

These dormant are inert in the place of use and are abolished or originated from the region of administration. Non-Biodegradable Hydrophobic Polymers used for preparing microspheres are Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene vinyl acetate (PEVA), Polyether urethane (PEU), Polyethylene (PE), Polydimethyl siloxane (PDS) and Polyvinyl chloride (PVC), Acrycoat, Eudragit S etc.

**E. Hydro gels:**

These polymers tuff but do not melt when gets in contact with water. Hydro gels are dormant, unstayed from the site of administration, and acts by forming a rate limiting barrier to the transport and release of drugs. The hydro gels that are used for preparing microspheres are cross-linked Poly vinyl alcohol (PVA), Poly acryl amide, Poly hydroxy ethyl methyl acryl ate (PHEMA), Cross linked Poly vinyl pyrrolidone (PVP) etc.

**F. Soluble polymers**

These are with molecular weight (less than 75,000 Daltons) un-cross-linked polymer melt in water. The rate of dissolution weakened with elevating molecular weight. These polymers can be used as alone or in combination with hydrophobic polymers so that device slowly destroys over time. The soluble polymers taken for preparing microspheres are co-polymers of Methacrylic acid and acrylic acid methyl ester (Eudragit L), Polyethylene glycol (PEG), Poly vinyl pyrrolidone or uncross linked poly vinyl alcohol, hydroxyl propyl methyl cellulose (Methocel).

**VIII.METHODS OF DEVELOPMENT FOR FLOATING MICROSPHERS**

There are numerous fabrication techniques for creating gastro-retentive floating microspheres. However, a number of systematic researchers have extensively applied the emulsion solvent evaporation approach and the ion tropic gelation method to examine the diverse perspectives of floating microspheres.

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.

**A. 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 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.

1. **Ion-tropic Gelation Method:**

This technique relies on polyelectrolytes' propensity to connect with counterions and produce beads. In spite of the fact that the herbal poly electrolytes have properties of coating at the drug centre and operate as drug retardants, they contain high quality anions in their chemical form. This is because alginates, CMC, and Chitosan have been widely employed for the encapsulation of drugs and even cells. These anions cause gelation by specifically attaching to the anion blocks and forming a meshwork structure with the polyvalent cations. The hydro gel beads are made by dripping a drug-loaded polymeric solution into the aqueous solution.

**C. Emulsion Solvent Diffusion**

This method is more effective than others. A natural solvent is used to dissolve the medication. Despite the fact that the organic solvent is melting, polymers are dispersed in an aqueous solvent. The natural solvent slowly diffuses from the emulsion droplets into the surrounding aqueous phase, and the aqueous portion through which the medication crystallizes diffuses into the droplets.

**D. The single emulsion method**

This approach, which prepares proteins and carbohydrates using a single emulsion procedure, results in microparticulate conglomerates of natural polymers. Natural polymers are dispersed or dissolved in aqueous media and exposed through dispersion in non-aqueous media, such as oil, with the aid of a modification to the linking agent.

**F. 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 immiscible liquid phases and essentially encloses the dispersion.

**G. Phase separation coacervation technique**

It is based entirely on the organic segment's principle that reducing the solubility of the polymer will have an impact on the formation of the polymer-rich phase known as coacervates. The drug is still disseminated in the polymer's response, and when an incompatible polymer is added to the solution, the first polymer phase separates and the drug debris is submerged.9

**IX. CHARACTERIZATION OF MICROSPHERES**

**A. Micromeritic properties10:**

The prepared microspheres can be distinguished by their micrometric properties like microsphere particle size, Bulk density, Tapped density, Carr’s compressibility index, Hausner’s ratio, and angle of repose.

**a) Bulk and Tapped density**

Bulk and tapped densities were measured by using 50 ml of the graduated cylinder. A carefully weighed amount of sample passed through a glass funnel. The sample poured in the cylinder was tapped mechanically 100 times. Then tapped volume was noted down and bulk density and tapped density were calculated by using the following formula. It was expressed in g/cm3.

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

b) **Carr's Compressibility Index**

The following equation was used to compute Carr's Compressibility Index, Compressibility index (C.I.), or Carr's index value of microspheres.

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

**c) 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) ×100

**d) 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 T =angle of repose

h = height of the circle formed by the powder heap

r=radius of heap

1. **Microsphere particle size distribution11**

A compound microscope was used to perform optical microscopy for the particle size analysis of drug-loaded Eudragit microspheres. A calibrated ocular micrometre was used to measure the diameter of at least 300 Eudragit microspheres on a slide that was mounted on the microscope's stage. The overall size of the microspheres divided by the quantity of microspheres yielded the average particle size of the microspheres.

**C. Scanning electron microscopy morphological investigation (SEM)12**

To analyze the surface morphology of the microspheres, SEM is used. The powder is sprinkled over the tape that is fastened to an aluminium 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 at a thickness of 250–450. SEM is used to randomly choose coated samples for photomicrographs.

**D. Calculating the microspheres' yield in percentage 13**

Microspheres that had been completely dried were gathered and precisely weighed. The formulas below were used to calculate the % yield.

Percentage Yield = Weight of obtained microspheres/Total weight of drug and polymer x100

**E. Studies of buoyancy 14**

Spreading the floating microspheres on a simulated stomach fluid (pH 1.2) containing the surfactant allows for the performance of in vitro floating tests in USP type II dissolving test equipment. At 37±0.5 °C, the medium is agitated at 100RPM. Both the fractions of microspheres (floating and settling microspheres) are collected after predetermined amounts of time, and the buoyancy of the floating microspheres is calculated using a formula.



Where, Qf and Qs, respectively, represent the masses of floating and settled hollow microspheres.

**F. Effectiveness of Entrapment 15**

For testing, prepared microspheres corresponding to 100 mg of the medication were consumed. By repeatedly crushing the microsphere and extracting with aliquots of 0.1N HCl, 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.

Amount of drug actually present

% Entrapment Efficiency = -------------------------------------- 100

Theoretical drug load expected

**G. Drug content**

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, the drug content of microspheres was determined. The drug concentration in the ethanol phase was then filtered through a Whatman filter and measured spectrophotometrically at their relevant nm by creating the required dilution with 0.1N HCl. Three duplicates of each determination were made. The formulas for calculating the % drug entrapment and yield are as follows

% Drug loading = (Actual drug content/Weight of microspheres) X 100

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