**FLOATING MICROSPHERES**

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

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**Abstract:**

Oral Conventional dosage forms offer no control over release of Drug from the dosage form which leads to variations in plasma drug levels, Gastric emptying and gastric resident time are two another important factors which have a significant effect on the therapeutic efficacy of drug and it causes changes in the retention time of the drug. Accordingly, Floating microspheres is one of the most dependable and inventive techniques among all the gastro retentive drug delivery system to overcome from these problems. Floating microspheres are mainly obtaining importance because of their vast suitability in the targeting of drugs to the stomach, undergo action and scattered uniformly over the gastric fluid to avoid the changes of gastric emptying and enlarge the liberation of the drug. This system also allows vastly in the fabrication of new controlled and delayed release oral formulations, thus Expanding revolutions in pharmaceutical Expansion. The present review in brief says the physiology of gastric Intestinal tract, Elements governs gastro retentive drug delivery system. The aim of this review is to illuminate the recent literature like the importance of floating microspheres in Novel drug delivery system, methods of Preparation, differentiation of Floating microspheres and recent scientific advances taken in the formulating floating microspheres by using different classes of the drugs.

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

**1.INTRODUCTION**

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems is type of Gastro retentive drug delivery system that possess a bulk density lesser than gastric fluids and remain floating in the stomach without arousing effect of gastric-emptying rate for a longer period. The drug is slowly liberated at a desired rate from the floating system and after the total release; the remaining materials of the dosage form is deported from the stomach. This leads to an improvement in the GRT and better control over changes in plasma drug concentration.

Thorough understanding connected with GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc. is the way for the designing of oral controlled release dosage forms. The amount and magnitude of drug absorption from single areas of GI tract and elements that directs the absorption helps for the preparation of dosage form.1

The method of floating drug delivery has a bulk thickness of less than GI fluid and therefore lasts for a prolonged duration of buoyancy in the abdomen without impacting the rate of gastric emptying. The material floats in this process and then it is delayed to release the material from the system at the critical rate after release of the drug. This raises the risk of bacterial invasion of the body and results in good control of bacterial drug concentrations.2

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

|  |  |
| --- | --- |
| Conventional | Gastro retentive drug delivery system |
| Not much Preferable for  Drugs which are poorly soluble at an alkaline PH  Drugs acting locally in the stomach.  Drugs which degrade in the colon.  Drugs having rapid absorption through GIT | Very much Preferable for  Drugs having rapid absorption through  GIT  Drugs which degrade in the colon.  Drugs acting locally in the stomach |
| Inadequate for delivery of drugs with  definite absorption window in small intestinal region | Adernate for delivery of drugs with N narrow absorption window in small  intestinal region |
| Less patient compliance | More patient compliance |

**II. ADVANTAGES OF FLOATING MICROSPHERES 4**

* Enhanced bioavailability
* Enhanced first-pass biotransformation
* Sustained drug delivery/reduced frequency of dosing
* Targeted therapy for local ailments in the upper GIT
* Reduced fluctuations of drug concentration
* Improved receptor activation selectivity
* Reduced counter-activity of the body
* Extended time over critical (effective) concentration
* Minimized adverse activity at the colon
* Site specific drug delivery
* Less inter- and intra-subject variability.
* Minimizes the counter activity of the body leading to higher drug efficiency.
* Fluctuations in drug concentration are minimized. Therefore, concentration dependent adverse effects can be reduced.
* Sustained mode of drug release enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
* Flexibility in dosage form design.

**III. LIMITATIONS 5**

* Drugs that cause ulcers and irritation to gastric mucosa are not applicable for this delivery system.
* Drugs which are metabolised by first pass effect are not applicable for this type of drug delivery system
* Drugs which build solubility and stability problems in the gastric fluid are not suitable for this delivery system.

**IV. BASIC GASTROINTESTINAL TRACT PHYSIOLOGY 6**

Anatomically, the stomach is split into three areas like Fundus, body and antrum. The proximal part made of fundus and body acts as a pool for un­digested substance, antrum is the main site for blending motions and work as a pump for gastric emptying, complete propelling movement. Gastric emptying takes place dur­ing fasting as well as in fed states. The pattern of motility can be understood in the two states. During the fasting state, an interdigestive series of electrical events takes place, cycling through both stomach and intestine every two to three hours which is called as migrating myloelectric cycle (MMC) or interdigestive my­loelectric cycle, which can be further divided into four phases.

1. Phase I (basal phase)

It continues from 40 to 60 minutes with unusual constrictions.

2. Phase II (preburst phase)

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

3. Phase III (burst phase)

It is also known as the housekeeper wave. It continuous for 4-6minutes. It contains severe and Systematic

contractions for ales Period of time. Due to this wave all the undigested material is wiped out of the Stomach

into the small intestine.

4. Phase IV

This is also called as digestive motility pattern and comprises continuous contractions as in phase II of the

fasted state. It continuous for 0 to 5 minutes and occurs between phases III and I of two successive cycles.

Following the intake of a mixed meal, types of contractions changes from fasted to fed state. The contractions

lead to reduce in size of food particles to less than 1 mm, which are then pushed towards the pylorus in a

suspension form. During the fed state, onset of MMC is slowed which leads to delaying of gastric emptying

rate. Scintigraphy studies has revealed that orally administered controlled-release dosage forms are subject to

basically two complications, like inconsistent gastric emptying rate and shorter gastric residence time. Other

different meth­ods have also revealed the gap imbalance in gastric emptying in humans under normal gravity

conditions are ultrasound, gastric aspiration, Magnetic resonance imaging (MRI) techniques, Epigastric

impedance, Pellet Gastric Empty­ing Test (PGET) and Octanoic acid breath test.

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

1. **Fed or unfed state**

The appearance and Non-appearance of food directs the gastric retention time, normally the fed state upgrades the gastric retention time and elevates the absorption of the drug by extending the drug to last at the site of the absorption. In the fasting state, the GI motility is decorated by strong motor activity which pushes the undigested material from stomach to intestine and hence GRT is very small.

1. **Frequency of feed:**

The GRT increases when meals taken successively than single meal, increases the GRT over 400 min.

1. **Caloric and Nature of meal**:

High caloric foods like proteins and fats increase the GRT from 4 to 10 hours. Food carrying fatty acid salts or indigestible polymers can influence the motility pattern of the stomach which leads to reduce in gastric emptying rate and thus elongated the release of the drug.

1. **Effect of age, gender and posture**

People with age above seventy have long GRT.GRT in females is less compared to male. The GRT is not affected due posture, no significant difference in the upright and horizontal position.

1. **Density of the dosage form:**

Density is significant factors which affect gastric emptying time and controls the buoyancy of dosage form. Mostly, dosage form with density less than 1.0 gm/cm3 is ideal for showing good floating property.

1. **Size of the dosage form:**

The giant size of the dosage form may not assign rapid movement through the pyloric antrum into the intestine. Residence time of Non-floating and floating dosage form depends on the size of the dosage form. To pass from pylorus to intestine the dosage must be in the size range of 1- 2 mm. Dosage forms containing a diameter of more than 7.5 mm show a better gastric residence time when compared with dosage form containing size 9.9mm.

1. **Shape of dosage form:**

Shape is a significant factor to plan a floating drug delivery system, tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are established to have better gastric retention time up to 24 hours.

1. **Concomitant drug administration:**

Prokinetic agents like Metoclopramide and Cisapride reduces the gastric retention. Anti-cholinergic like Propantheline, Atropine and Opiates like Codeine enhances the gastric retention.

**I. Mechanism of absorption:**

Drugs which are taken orally absorbed both by passive diffusion and non-passive absorption. Drugs absorbed by active and facilitated transport systems exhibit higher regional specificity due to the similarity of these mechanisms only in a peculiar area of gastro intestinal tract.

**J. Metabolic Enzymes:**

Enzymes present in specific location 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.MECHANISM OF FLOATATION**

To enhance the gastric retention time in the stomach various methods are used. The Floating drug delivery systems (FDDS) have every time lesser bulk density than gastric fluid and so encounter floatable in the stomach without showing any effect on the gastric emptying rate for a prolonged period. This set-up is floating on the stomach contents the drug is released slowly at the seek rate from the system. The apparatus handle by computing constantly the force equivalent to F (a function of time) that is used to maintain the submerged object. This apparatus helps in adjusting the floating drug delivery system concerning inflexibility and resilience of floating effect prompted in order to avert the disadvantage of unforeseeable propensity to float potentiality variability. 8, 9

F = F buoyancy-F gravity = (Df-Ds) gv

Where, F= total vertical force, Df = fluid density,

Ds =Object density, v = volume and g = acceleration due to gravity.



Figure 1: Mechanism of Floating Microsphere

**VII. POLYMERS USED IN FLOATING MICROSPHERES 8**

Microspheres can be formulated by taking both hydrophilic and hydrophobic polymers.

Both biodegradable and non-biodegradable Polymers have been using for the manufacture of microspheres and these involves polymers of natural, semi-synthetic and synthetic origin.

1. **Hydrophilic polymers**

Gelatine, agar, Egg albumin, starch, Chitosan, Cellulose derivatives; HPMC are the hydrophilic polymers used for manufacturing microspheres.

1. **Hydrophobic polymers**

Ethyl cellulose, Polylactic acid, PMMA, acrylic acid esters etc. are the hydrophobic polymers used for manufacturing microspheres.

1. **Biodegradable polymers**

These polymers disappear slowly from the site of administration; anyhow, due to hydrolysis it appears as a reaction. Biodegradable polymer used are Polylactic acid (PLA), poly glycolic acid (PGA), Polycaprolactone (PCL) and many generic classes such as the poly anhydrides and Polyorthoesters.

1. **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.

1. **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.

1. **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. DEVELOPMENTAL APPROACHES FOR FLOATING MICROSPHERES**

Large number of fabrication methods available for the formulation of gastro retentive floating microspheres. But Emulsion solvent evaporation technique and Ion tropic gelation method has been greatly used by a number of methodical investigators to research the various prospective of floating microspheres.

During the fabrication of floating controlled release microspheres, the use of best technique is taken for the thorough entrapment of active ingredients. Choice of this method trust upon the API and its planned use, nature of the polymer. Characteristic attributes of materials and the process taken greatly influence the formulated microspheres properties and also the controlled release rate from the dosage form.

1. **Solvent Evaporation Method**

To create the entire internal centre through solvent diffusion and evaporation methods floating multi particulate dosage shape may be prepared. In a natural solvent, the polymer is dissolved and within the polymer solution the drug is either dispersed or dissolved. Then it emulsified containing suitable additive (surfactants / polymer) into an aqueous segment to shape o/w emulsion. The natural solvent is evaporated after the formation of a strong emulsion either by through non-forestall stirring or developing the temperature below pressure. After solvent removal at the o/w interface of droplets polymer precipitation occurs and to impart the floating homes hollow space develops. For the development of such systems the polymers studied are cellulose acetate, polyethylene oxide, Eudragit, acrycoat, Chitosan, Methocel, Carbapol, Polyacrylates, polyvinyl acetate and polycarbonate.

**B. Ion tropic Gelation Method:**

This method is based on the ability of poly electrolytes to link with counter ions and to form beads. Because of the truth that, the usage of alginates, CMC and Chitosan for the encapsulation of drug and even cells, ion tropic gelation method has been broadly used for this cause the herbal poly electrolytes in spite, having belongings of coating at the drug centre and acts as drug retardants, contains high quality anions on their chemical form. Those anions paperwork meshwork structure by way of combining with the polyvalent cations and prompt gelation by using binding especially to the anion blocks. The hydro gel beads are produced by means of way of dropping a drug-loaded polymeric answer into the aqueous answer of polyvalent cations.

1. **Emulsion Solvent Diffusion Method**

This technique is more useful than other techniques. The medicament is dissolved within natural solvent. Polymers are dispersed in an aqueous solvent despite fact organic solvent is melting. Out of the emulsion droplets the natural solvent diffuses steadily in to the surrounding aqueous phase and in to the droplets the aqueous section diffuse through which drug crystallizes.

**D. Single emulsion technique**

Micro particulate corporations of natural polymers occur in this method i.e. By manner of single emulsion technique, the ones of proteins and carbohydrates are prepared. In aqueous medium the natural polymers are dispersed or dissolved and exposed through dispersion in non-aqueous medium like oil with the assist of change in linking agent.

**E. Double emulsion technique**

The formation of the more than one emulsion or the double emulsion entailed in this approach which consisting of multiple emulsion i.e., w/o/w. This method may be used with the natural as well as synthetic polymers.

**F. Polymerization technique**

**Normal Polymerization**

With the use of tremendous strategies as suspension, emulsion, precipitation, bulk and micelles polymerization regular polymerization is performed. With the resource of bulk polymerization herbal polymers are formed.

**Interfacial Polymerization**

On the interface it consists of the reaction of numerous monomers, to form a film of polymer contains most of the two immiscible liquid phases that basically envelops the dispersed.

**G. Phase separation coacervation technique**

It's far based completely on the precept in organic segment, lowering the solubility of the polymer to have an influence at the development of polymer rich phase known as coacervates. In an answer of the polymer, the drug remains dispersed and to the system, an incompatible polymer is added which makes first polymer to phase separate and immerse the drug debris 9

**IX. CHARACTERIZATION OF PREPARED MICROSPHERES**

1. **Micromeritic properties10:**

The prepared microspheres can be distinguished by their micromeritic 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 graduated cylinder. Carefully weighed amount of sample passed through a glass funnel. The sample poured in cylinder was tapped mechanically for 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 or Compressibility index (C.I.) or Carr's index value of microspheres was calculated according to the following equation

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

c) Hausner's ratio

Hausner's ratio of microspheres was identified by comparing the tapped density to the bulk density using the equation.

Hausner’s ratio = (Tapped density/Bulk density) ×100

d) Angle of repose

The maximum angle which is formed between the surface of a pile of powder and horizontal surface is called the angle of repose.

Tan θ = h/r

Where T =angle of repose

h = height of the circle formed by the powder heap

r=radius of heap

**B. Particle size distribution of microsphere**11

Particle Size Analysis: Particle size analysis of drug-loaded Eudragit microspheres was performed by optical microscopy using a compound micro-scope. The slide containing Eudragit microspheres was mounted on the stage of the microscope and diameter of at least 300 particles was measured using a calibrated ocular micrometre. The average particle size of microspheres was determined by the total size of the microspheres divided by the number of microspheres

**C. Morphological study using scanning electron microscopy (SEM) 12**

SEM technique is used for determining the surface morphology of the microspheres. The SEM sample is prepared by sprinkling the powder on the tape stuck attached to an aluminium stub. The stubs are coated using the mixture of gold and palladium at a thickness of 250–450Å under an argon atmosphere in a high vacuum evaporator at a voltage of 20 KV, current 10 mA, and low pressure. Photomicrographs are taken on the random screening of coated samples using SEM.

**D. Determination of % yield of microspheres 13**

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formulae given below.

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

**E. Buoyancy studies 14**

In vitro floating tests can be performed in USP type II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid (pH 1.2) containing the surfactant. The media is stirred at 100 rpm at 37± 0.5°C. After specific intervals of time, both the fractions of microspheres (floating and settled microspheres) are collected and buoyancy of the floating microspheres is determined by using formula



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

**F. Entrapment Efficiency 15**

Formulated microsphere equivalent to 100 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microsphere and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to 100 ml volumetric flask and the volume was made up using 0.1 N HCl. The solution was filtered and the absorbance was measured at Specific nm against blank. The amount of drug entrapped in the microsphere was calculated by following formula

Amount of drug actually present

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

Theoretical drug load expected

**G. Drug content** 16

The drug content of Microspheres was identified by dispersing 50 mg formulation in 10mL acetone, followed by mixing with a magnetic stirrer for 12hours to wet the polymer and to extract the drug. After filtration through a Whatsman filter, the drug concentration in the ethanol phase was determined spectrophotometrically at their relevant nm by making desired dilution with 0.1N HCl. Each determination was made in triplicate. The percentage drug entrapment and yield are to be calculated as follows:

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

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