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Review Article

An Overview on Gastro Retentive Floating Microspheres

Shah Chainesh*[1], Aundhia Chintan[1], Ramani Vinod[2], Shah Nirmal[1], Chauhan Sachin[1], A. K.Seth[1], Ghelani Tejas[1], Vegada Rajnikant[1].
[1] Sumandeep Vidyapeeth, Piparia, Waghodiya. Vadodara.Gujarat
[2] C.K. Pithawalla Institute of Pharmaceutical Science & Research, Surat. Gujarat.
***Corresponding Author** Email ID: chainesh_26@yahoo.com*
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ABSTRACT
Once important aspect for successful controlled oral drug delivery is it's complete absorption through gastrointestinal tract (GIT) mainly by passive diffusion. Oral controlled dosage form are not suitable for many drug having narrow therapeutic window in upper part of GIT (stomach and small intestine) due to less transit time in these anatomical portion thus drug is release in short time in non-absorbing distal segment of GIT, which ultimately lead to poor bioavailability of drugs. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time. Floating Drug delivery system (FDDS) are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. This review also summarizes various sophisticated and modern evaluation parameter for floating microspheres. Thus floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

Key words: Floating drug delivery systems, GIT, residence time, in-vitro, hydro dynamically balanced systems.

An overview on Gastroretentive dosage form[1, 2]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is available asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention (GRT) time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability and improves solubility of drugs that are less soluble in high pH environment. Gastric retention to provide new therapeutic possibilities and substantial benefits from patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

Basic Gastrointestinal System Physiology [3,4]

Anatomically the stomach is divided into three regions:
Fundus, Body and Antrum (pylorus). The proximal part made of fundus and body acts as reservoir for undigested materials, where as the antrum is the main side for mixing motions and acts as a pump for gastric by propelling action. Gastric emptying occurs in both the fasting and fed states. During the fasting state and inter digestive series of electrical events take place with cycle both through stomach and intestine every 2-3 hrs, which is called as inter digestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided into four phases after the ingestion of mixed meal, the pattern of contractions changes from fastest to that of fed state which is also termed as digestive motility pattern.

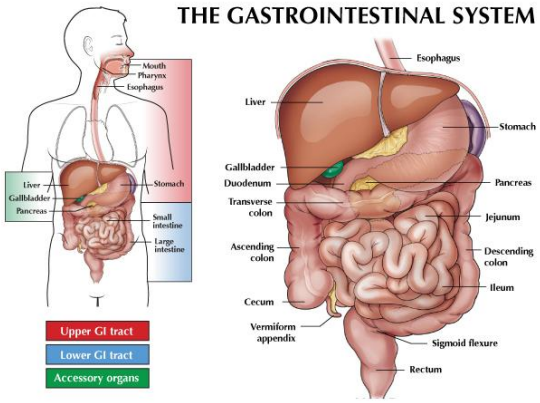

Figure 1 Basic Gastrointestinal System

Various phases of transition of dosage form: [3,4]

1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst Phase)-last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3 – (Burst Phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles (show in Figure 2).

After the ingestion of a mixed meal, the pattern of contraction changes from fasted to that of fed state which also termed as digestive motility pattern.

Factors affecting the gastric emptying [5]

1. Density, size and shape of the dosage.
2. Concomitant ingestion of the food and its nature, caloric content and frequency of intake.
3. Simultaneous administration of drugs acting as anticholinergic agent (e.g. atropine, propentheline), opoides (e.g. codeine)andprokinetic agents (e.g. metoclopromide, isapride).
4. Biological factor such as gender, posture, age, sleep, body weight, physical activity and disease states (e.g. diabetes, crohn's disease).

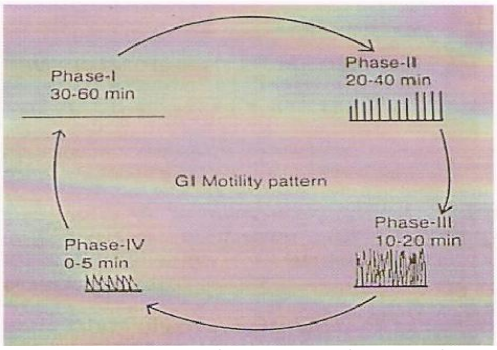

Figure 2 Various Phases of Transition of Dosage form.

Approaches for gastric retention

To formulate a successful gastro-retentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS)/ floating drug delivery system, low-density systems, raft systems incorporating alginate various system is floating on the gastric contents, the drug is released approaches that have been adopted to increase the retention of an oral dosage from in the stomach, includes: floating systems, swelling and expanding systems, bio adhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices. [6]

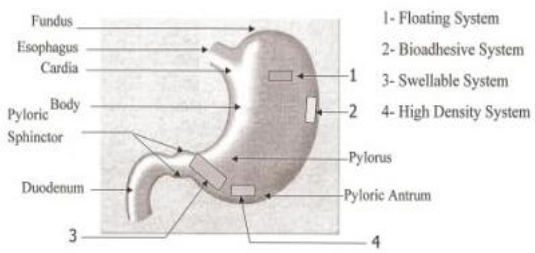

Figure 3 Various Drug Degestroretentive Drug Delivery Systems

FDDS or HBS have a bulk density lower than the gastric fluids and thus remain buoyant the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the drug is released, the residual system is emptied from the stomach. Swelling type dosage from are such that after swallowing, these products swell to an extent that prevents their exit from stomach through the pylorus. Bio adhesive system is used to localize a delivery device within the lumen and cavity of the body to enhance drug absorption process. These bio adhesive polymers adhere to the epithelial surface of the GIT. High density formulations include coated pellets, which have density greater then that of stomach contents. Here the drug is cited by inert heavy materials like zinc oxide, barium sulphate and iron powder. Modified shapes molded from elastic polymer or elastomer also extend the GRT. Gels, bio adhesive or muco adhesive system, high density system, super porous hydro gels and magnetic systems.

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the system is eliminated from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentrations. The floating sustained release dosage forms exhibit most of the characteristics of hydrophilic matrices and are known as 'hydro dynamically balanced system'(HBS) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gel like barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 h) in the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than of the gastric contents. Many studies have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drug and improved effects in clinical situations. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy IN parallel with formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performance of floating forms. [7]

Based on the buoyancy mechanism, FDDS can be classified into:

(1) Single unit floating dosage systems;
(2) Multiple unit floating dosage system;
(3) Raft forming system

1. Single unit floating dosage (Effervescent) systems [8,9,10,11]

a) Volatile liquid containing system

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber containing liquid which contains a liquid e.g. ether that gasifies at body temperature to cause the infatuation of the chamber in the stomach. The device may also consist of a biodegradable plug made up of PVA, polyethylene; etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b) Gas-generating systems

These buoyant delivery systems utilize effervescent reactions between carbonate / bicarbonate salts and citric / tartaric acid to liberate CO_2, which gests entrapped in the gellified hydrocolloid layer of the system thus decreasing its specific gravity and making it to float over chime. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan,

effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

2. Multiple unit floating (non- effervescent) system [8,9,10,11]

In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of the gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome this, multiple unit floating systems were developed, which reduce the inter-subjects variability in absorption and lower the probability of dose-dumping. Reports have described the development of both non-effervescent and effervescent multiple unit systems. More research has been focused on this gastro-retentive floating drug delivery system investigators are still exploring the field of hollow microspheres, capable of floating on the gastric fluid, and having improved gastric retention properties. This type of system after swallowing, unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative's integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

a) Colloidal gel barrier systems

Hydro dynamically balance system (HBS) was first design by sheth and tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, Na CMC, polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

b) Microporous compartment system

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un dissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

c) Alginate beads:

Multiple unit floating dosage forms have been developed from freeze-fried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40 for 24 h, leading to the formation of porous system, which can maintain a floating force over.

d) Hollow microspheres

Hallow microspheres (Micro balloons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed internal cavity in microspheres of the polymer with drug. The micro balloons floated continuously over the surface of the acidic dissolution media containing surfactant for greater than 12 h in vitro.

3) Raft forming systems [8,9,10,11]

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and other disorder. The mechanism involved in the draft formation includes of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called raft. This raft floats on gastric fluid because of the low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense able float on the gastric fluids.

Floating Microspherers

In case of conventional therapy, drug administered not only interact with targeted cells but also with normal healthy cells which often results in toxic effects and this conventional therapy also includes frequent administration of therapeutic agent which reduces patient compliance. The therapy also involves administration of high concentration of therapeutic agent in order to maintain its effect. All such problem associated with conventional therapy can be overcome by controlled drug delivery systems (Microspheres, Microcapsules, Nanoparticles, Implants etc.) [12]

The population of patient with chronic disease or complications of other disease has been recently increasing. These situations necessitate taking drug for long period and or multiple medicines simultaneously, which can lead to increase in non-compliance. The problem would be worse

for drugs with short biological half-life. One method to solve such problems is to find a dosage form capable of releasing the drug gradually. [13]

In this regard novel drug delivery systems (NDDS) have many benefits, which includes improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved site specific delivery to reduce unwanted adverse effects. Microparticulate drug delivery system has been used as one of the methods to deliver drugs in a controlled manner and posses many advantages such as high bioavailability, rapid kinetic of absorption as well as avoidance of hepatic first pass effect and improvement of patient compliance. **[13]**

Between 1940s and 1960s, the concept of microencapsulation technology began as an alternative means of delivering drugs. In continued quest for the more refined systems, in 1980s polymer/membrane technology came to be known at forefront. Further the process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposomes, bioerodible polymers, implants, monoclonal antibodies and various particulate carriers (e.g. nanoparticles and microspheres, etc). [4]

The microparticulate delivery systems are considered and accepted as a reliable means to deliver the drugs to target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effect(s).[14]

The term microcapsules, is defined as a spherical particle with size varying 50 nm to 2 nm, containing core substance. Microspheres are in strict sense, spherical empty particles. However, the term microcapsules and microspheres are often used synonymously. In addition some related terms are used as well. For example, essentially "micro beads" and "beads" are used alternatively.[14]

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving sustained or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. One of the approaches toward this goal is to develop the floating multiparticulate so as to increase the gastric retention time. Such systems have more advantages over the single-unit dosage forms. The development of floating multiparticulate involves different solvent evaporation techniques to create the hollow inner core. [15.16]

Multiparticulate drug delivery system applies specially to multiple particles such as pellets, beads, microspheres, microcapsules. In recent years, multiparticulate dosage forms or microparticles have gained in popularity for a variety of reasons. Considerable research efforts have been spent on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet (Figure 4).[15,16]

The system is based on the expansion of the core (non effervescent FDDS or low density approach), which lead to floating due to low density. Also the air entrapped by the swollen polymer confers buoyancy to this dosage forms. Multiparticulate carriers (microspheres) are defined as homogeneous, monolithic particles in the size range of about 0.1-1000 μm and are widely used as drug carriers for controlled release. Multiparticulate carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact in formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using various polymers. However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling gastroretentive and bio adhesion characteristics to multiparticulates and developing gastroretentive bio adhesive multiparticulates. These multiparticulates have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site. **[17]**

It is stated that, 'the multiparticulates' float on the stomach contents, and then adhere to the mucous linings as the stomach empties (Figure 2). The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the stomach.[17]

The microspheres are characteristically free flowing powders consisting of protein or synthetic polymers, which are biodegradable in nature, and ideally having a particles size less than 200 μm. solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release or drug.**[18]**

Methods of Preparation of Microspheres:

The microspheres can be prepared by using any of the several techniques as follows:

1. Solvent evaporation method: [19,20,21]

Floating multiparticulate dosage form was 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 Polyvinyl alcohol 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 o/w interface of droplets, forming cavity

and thus making them hollow to impart the floating properties.

2. Ionotropic gelation method: [22]

Ionotropic gelation is based on the ability of polyelectrolytes 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 polyelectrolytes inspite, 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. Biomolecules can also be loaded into these beads under mild conditions to retain their three dimensional structure.

3. Emulsion solvent diffusion method: [23,24,25]

In this method solution of polymer and drug in ethanol methylene chlorideis poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles.

4. Single emulsion technique: [23,24,25]

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 mediumlike oil with the help of cross linking agent.

5. Double emulsion technique: [23,24,25]

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 surfactant.

6. Polymerization technique: [26,27]

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 co-acervation technique: [28]

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.

But the choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use and the duration of therapy.

Characterization of Micorshpere

The characterization of the Microparticulate carriers is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. The microspheres have different microstructures, which depends on their method of preparation and condition during preparation. These microstructures determine the release and the stability of the carrier.

A number of other parameters are generally evaluated for the characterization of microspheres.

1. Yield of microspheres: [29,30,31,32]

The prepared microspheres with a size range of 251-µm were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\text{Percentage Yield} = \frac{\text{Weight of microspheres Recovered}}{\text{Weight (drug + polymer)}} \times 100$$

2. Particle size: [30,31]

The particle size was measured by microscopic technique. In this method suspension of floating microspheres was prepared using castor oil. A drop of suspension was mounted on a slide and observed under optical microscope about 600 particles were measured with the help of the eye piece micrometer. All the microspheres in a field were counted.

3. Bulk density: [31,32,33,34]

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

$$\text{Bulk Density } (\rho_b) = \frac{\text{Weight of powder}}{\text{Bulk Volume}}$$

4. Tapped density: [31,32,33,34]

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

$$\text{Tapped Density } (\rho_p) = \frac{\text{Weight of powder}}{\text{Tapped Volume}}$$

5. Carr's (Compressibility) index: [31,32,33,34]

This parameter was calculated from bulk density (the ratio of weighed quantity of microspheres to its volume), DP, and tapped density as follows:

$$\text{Carr's Index} = \frac{(\rho_p - \rho_b)}{\rho_p} \times 100$$

6. Hausner, s ratio: [31,32,33,34]

Hausner, s ratio of microspheres was determined by comparing tapped density to bulk density using the equation:

$$\text{Hausner's Ratio} = \frac{\rho_p}{\rho_b}$$

7. Angle of repose: [34]

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface.

$$\theta = \tan^{-1} h/r$$

8. Scanning electron microscopy: [35]

Dry microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then picture of microsphere were taken by SEM.

9. Swelling studies: [36]

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.

10. *In-vitro* buoyancy: [37,38,39]

Microspheres (300mg) were collected. lution 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 was calculated as the ratio of the mass of the microspheres that remained f loating and the total mass of the microspheres

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

Where,

W_f is the weight of floating microspheres after drying.

W_s is the weight of settled microspheres.

11. Drug entrapment efficiency: [38,40]

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 spectro random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV. photometer against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula:

$$\text{Drug Encapsulation efficiency} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

12. In-vitro drug release studies: [31,32,33,34,36,37,41]

For such type of studies USP dissolution apparatus at particular speed is used. Distilled water and dissolution fluid is maintained at 37±1 ^{0}C. 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.

Table No 1 Marketed Products [44]

Brand Name	Delivery System	Drug (dose)	Company Name
Valrelease	Floating Capsule	Diazepam (15 mg)	Hoffmann-LaRoche, USA
Madopar HBS (Prolopa HBS)	Floating, CR Capsule	Benserazide (25 mg) & L-Dopa (100 mg)	
Liquid Gaviscon	Effervescent Floating Liquid alginate Preparation	Al hydroxide (95mg) Mg Carbonate (358 mg)	Glaxo Smithkline, India
Topalkan	Floating liquid alginate preparation	AI – Mg antacid	Pierre Fabre Drug, France
Almagate Float Coat	Floating dosage form	AI – Mg antacid	
Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India

Advantages of Floating Microspheres: [42,43]

Multiunit controlled-release drug delivery systems such as microcapsules and microspheres are becoming popular because they;

The advantages of hollow microspheres include

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. Better therapeutic effect of short half-life drugs can be achieved.
4. Gastric retention time is increased because of buoyancy.
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Enhanced absorption of drugs which solubilise only in stomach.
8. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
9. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

Disadvantages of Floating Microspheres: [42,43]

1. They are not suitable candidates for drugs with stability or solubility problem in stomach.
2. FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200-250 ml) of water to be taken together with FDDS.
3. Drugs having irritant effect on gastric mucosa are not suitablecandidates for FDDS.
4. Drugs which are absorbed along the entire GIT and which undergofirst pass metabolism may not be desirable e.g. nifedipine.

Criteria for selection of drug candidate for floating microsphere:[43]

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Drugs having narrow absorption window in GI tract, e.g., Riboflavin in a vitamin Deficiency and Levodopa, paraaminobenzoic acid, furosemide.
2. Drugs those are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements and Chlordiazepoxide.
3. Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
4. Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole, captopril, ranitidine HCl,
5. Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.
6. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil hydrochloride

Applications of floating Drug Delivery System:[45]

1. Sustained Drug Delivery

HBS system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, hence, can be overcome with these systems. These systems have bulk density of <1, as a result of which they can float on the gastric contents.

2. Site specific drug delivery

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin furosemide and misoprostal. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

3. Absorption enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

4. Maintenance of constant blood level

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

CONCLUSION

Floating drug delivery system can provide sufficient gastric retention which may help to provide sustained release dosage form with enhanced absorption. This article gives an overview on method of preparation, and evaluation parameter for floating microsphere and will assist researchers for further studies in development of gastroretensive drug delivery system.

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