Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2013, Volume 1, Issue 9
ISSN : 2321–3647(online)

A Review On Floating Microspheres As Gastroretentive Drug Delivery System

Manjusha A.Gunjal* **Archana K Gaikwad[1]**
Aurangabad 431001, Maharashtra India.

ABSTRACT

The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time. Floating drug delivery systems (FDDS) have ability to prolong the gastric residence time after oral administration at proper site and release of drug controlled also useful to achieve desired peak plasma concentration and increase bioavailability. This review specify characteristics as well as evaluation of floating microspheres

Keywords: FDDS, Gastric emptying time, Buoyancy, *in vitro* release

*Corresponding Author Email: g29archana@yahoo.com
Received 27 November 2013, Accepted 09 December 2013

Please cite this article in press as: Gunjal MA. *et al.*, A Review on Floating Microspheres as Gastroretentive Drug Delivery System. American Journal of Pharmacy & Health Research 2013.

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance[1]. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period[2, 3].

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by using gastro-retentive dosage forms (GRDFs). It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug. It has several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered and reduction of administration frequency leading to improved patient compliances[4,5]

The concept of FDDS was described in the literature as early as 1986, when Davis discovered a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills

Floating microspheres are gastro-retentive floating drug delivery systems based on non-effervescent approach. These microspheres are characteristically free flowing powders having a size less than 200 μm and remain buoyant over gastric contents and for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[1]

Gastro retentive drug delivery system

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[4], low density (floating) systems that causes buoyancy in gastric fluid [5,6] , mucoadhesive systems that causes bioadhesion to stomach mucosa[7], unfoldable, extendible, or swellable systems which limits emptying of the

dosage forms through the pyloric sphincter of stomach[8,9], super porous hydrogel systems[10], magnetic systems[11] etc.

Basic gastro-intestinal tract physiology

The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus. The wall of the GI tract has the same general structure throughout most of its length, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus) [12] (**Figure 1**). Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid and air. Gastric emptying occurs during fasting as well as fed states. The GI tract is in a state of continuous motility consisting of two modes: inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) and is organized in cycles of activity and quiescence [13]. Each cycle lasts 90– 120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases[14].

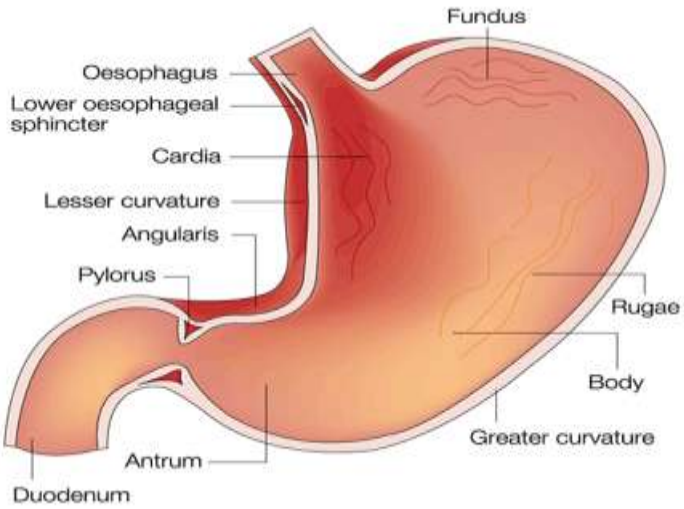

Fig. 1: Anatomy of stomach

The various phases are as below;

1. Phase I (basal phase)-Period of no contraction (30-60 minutes),
2. Phase II (preburst phase)-Period of intermittent contractions (20-40 minutes),
3. Phase III (burst phase)-Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave; includes intense and regular contractions for short

period. It is due to this wave that all the un-digested material is swept out of the stomach down to the small intestine (10-20 minutes),

4. Phase IV-Period of transition between phase III and phase I (0-5 minutes)[15]

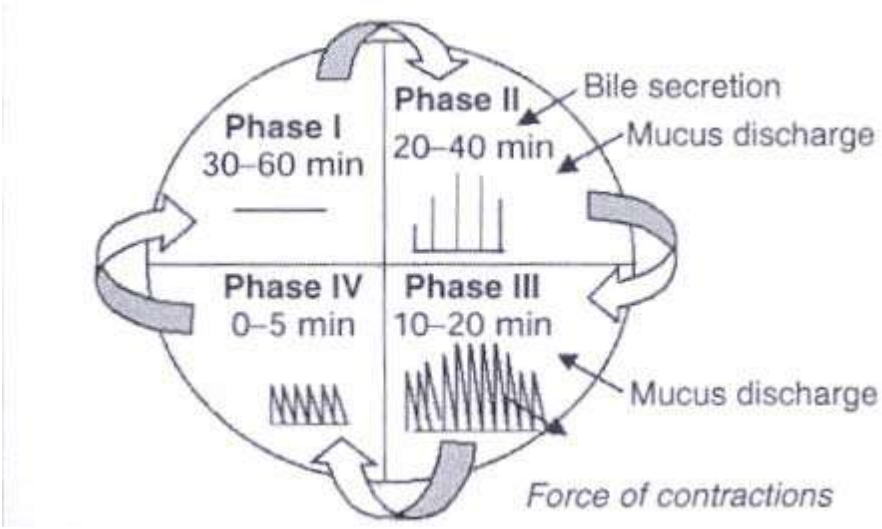

Fig. 2: Motility pattern in GIT

Approaches to gastric retention

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include:

a) Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, noneffervescent and effervescent systems.[16]

b) Bio/Muco-adhesive Systems:

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or

systemic effect.[17] Binding of polymers to the mucin/epithelial surface can be divided into three broad categories :–

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

c) Swelling and Expanding Systems:

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type system", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period[18].

d) High Density Systems:

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc[19].

e) Incorporation of Passage Delaying Food Agents:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14[20].

f) Ion Exchange Resins:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As

a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.[21]

g) Osmotic Regulated Systems:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.[22]

Floating drug delivery system

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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 from the system[22].

Suitable drug candidates for floating drug delivery systems

Sustained release in the stomach is useful as therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, where absorption occurs and contact time is limited, for example, material passes through the small intestine in as little as 1-3 h as shown in **Figure 3 (a)** and **(b).**

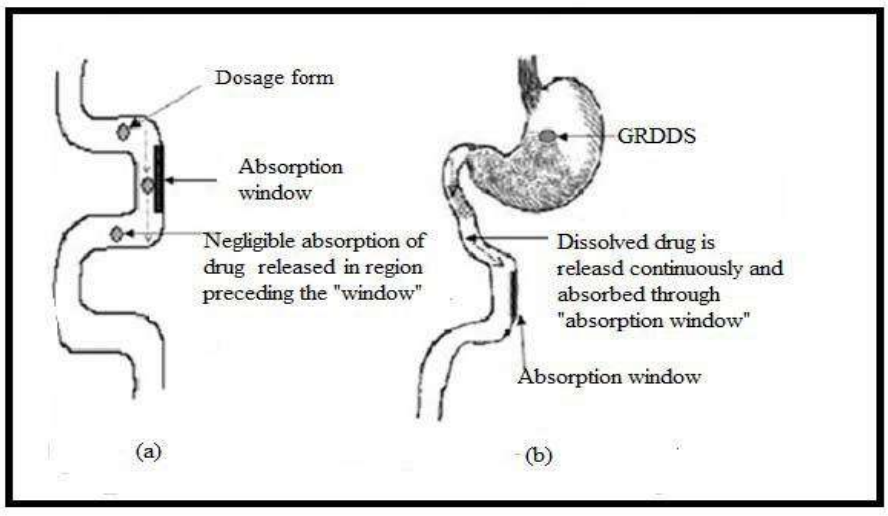

Fig. 3: Drug absorption in case of (a) conventional dosage forms (b) Gastroretentive drug delivery systems

In general, appropriate candidates for floating drug delivery system are the molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.[23]

1. Drugs with narrow absorption window in GI tract, e.g., Para aminobenzoic acid, furosemide, riboflavin in a vitamin deficiency and Levodopa.
2. Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.
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.
5. Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.

Classification of floating system

Single unit

Multiple unit

Raft forming system

Single unit

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug Delivered at a particular site of the gastro intestinal tract[24].

Types of single unit are as follows:

Noneffervescent systems

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules[25, 26]. For the preparation of these types of systems, the drug and the gel forming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Effervescent systems or gas generating systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate,

tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

Multiple units

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lower[27].

Noneffervescent systems

A little or no much report was found in the literature on noneffervescent multiple unit systems, as compared to the single unit effervescent systems. However, few workers have reported the possibility of developing such system containing Indomethacin, using chitosan as the polymeric excipient. A multiple unit hydrodynamically balanced system containing Indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio[15, 21].

Effervescent systems

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with non floating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h[15, 21].

Floating microspheres

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres.

Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, Eudragit® S and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer plasticizer ratio[23].

Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO_2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of the system which is less dense and floats on the gastric fluids[24]. Reckitt and Colman Products Ltd. have come out with such formulation in the treatment of H.pylori infections of GIT[28, 29].

Advantages of floating dosage form

1. These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.
2. The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
3. The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
4. Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.
5. Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response[30].

Limitations of floating drug delivery systems

1. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.
2. Drugs which have stability and solubility problems in GIT are not suitable candidates for these

types of systems.

3. Drugs such as Nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems[15, 30].

Floating microspheres

Floating microsphere can be defined as solid, approximately spherical particle ranging in size from 1 to 1000 um. The microspheres characteristically free flowing powder consisting of protein or synthetic polymers which are biodegradable in nature. Microspheres are small in size and therefore have large surface to volume ratio[31-33].

Mechanism of flotation of microspheres

When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy[34].

Mechanism of drug release from the microspheres

The mechanism of drug release from multiparticulates can occur in the following ways:

Diffusion: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating[35].

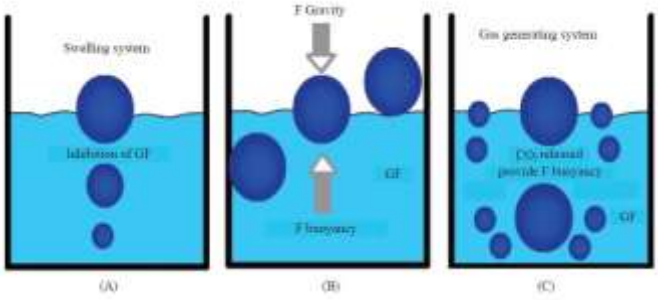

Figure 4: Mechanism of floating systems (A) Swelling system (C) Gas generating system

Formulation aspects

The design of novel controlled release dosage forms should take into account three important criteria, viz., drug, delivery, and destination. The various aspects which have to be considered while formulating FDDS (floating microspheres in particular) [21, 36] are;

a) Drug: the characteristics of the drugs which can be formulated as FDDS have already been discussed.

b) Polymer: low density polymers which have bulk density less than one, can be used for enhancing the buoyancy of the formulation are used in formulating FDDS.

c) Solvent: solvent system should be so chosen that it should yield good microspheres. Generally, water miscible organic solvents are chosen. It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres. e.g. ethanol, dichloromethane (DCM), acetonitrile, acetone, isopropyl alcohol (IPA), dimethyl formamide (DMF).

d) Processing medium: the processing medium is used to harden the drug polymer emulsified droplets. It should be such that it should give spherical droplets when the drug-polymer solution is poured into it, should not interact with the former; mainly used are liquid paraffin, polyvinyl alcohol and water.

e) Surfactant: these are used as stabilizers or emulsifiers, play the role of hardening the microspheres as well. e.g. tween 80, span 80 and SLS.

f) Cross linking agent: chemical cross-linking of microspheres can be achieved using cross linking agents such as formaldehyde, glutaraldehyde or by using diacid chlorides such as terephthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent.

g) Hardening agent: this helps to harden the microspheres formed in the processing medium. e.g. n-hexane, petroleum ether (in case the processing medium is liquid paraffin).

Polymers used in Microsphere

Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins etc[37].

Developmental Approaches of floating microspheres

Wide ranges of developmental techniques are available for the preparation of gastro retentive floating microspheres[38]. However, solvent evaporation technique and ionotropic gelation method have been extensively employed by large number of scientific investigators worldwide to explore the different vistas of floating microspheres. During the preparation of floating controlled release microspheres, the choice of optimal method has utmost relevance for the efficient entrapment of

active constituents. Selection of fabrication technique generally depends upon the nature of the polymer, the drug, and their intended use [39, 40]. Characteristic features of materials and the process engineering aspects strongly influence the properties of microspheres and the resultant controlled release rate. These techniques (i.e. solvent evaporation and ionotropic gelation)

a) Solvent Evaporation Technique

This technique is widely employed by large number of pharmaceutical industries to obtain the controlled release of drug [41]. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is carried out under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilisation [42]. For emulsion solvent evaporation, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

b) Oil-In-Water Emulsion Solvent Evaporation Technique

In this process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer [43]. In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties [44, 45]. Oil-in-water emulsion is widely used than water-in-oil due to simplicity of the process and easy cleans up requirement for the final product [46].

c) Oil-in-Oil Emulsification Solvent Evaporation Technique

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non aqueous emulsification solvent evaporation. In this technique, drug and polymers are codissolved

at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whatmann filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators. Span 60 is generally used which is non ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium [47, 48].

d) Ionotropic Gelation Method

In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions to form gel matrix. This technique has been generally employed for the encapsulation of large number of drugs. Polyelectrolyte such as sodium alginate having a property of coating on the drug core and acts as release rate retardant contains certain anions in their chemical structure. These anions forms meshwork structure by combining with polyvalent cations and induced gelation. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the aqueous solution of polyvalent cations as depicted in Figure 5.

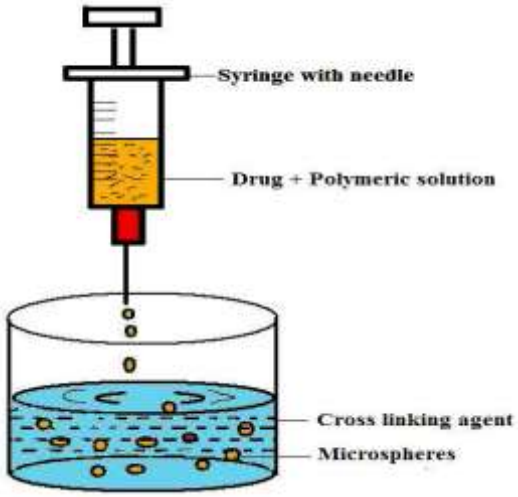

Fig. 5: Schematic representation of preparation of floating microspheres by ionotropic gelation

The cations diffuses into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microspheres formed are left into the original solution for sufficient time period for internal gelification and they are separated by filtration. Natural

polymers such as alginates can be used to improve drug entrapment and are widely used in the development of floating microspheres [49, 50].

Evaluation of floating microspheres.

Micromeritics:

Microspheres were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausner's ratio.

Particle size

The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer[51].

Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm^3) [52]

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Volume of sample}}$$

Tapped density

Accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm^3)[52]

$$\text{Tapped density} = \frac{\text{Weight of sample}}{\text{Tapped volume}}$$

Carr's index (%)

The Carr's index is frequently used as an indication of the flowability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability and below 15% of good flowability. Flow property of blend depends upon Compressibility index. The Carr's index is an indication of the compressibility of a powder. It is calculated by the formula. (Values as given in Table 1) [52]

$$\text{Carr}'\text{s index}(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 1: Carr's index as an indication of powder flow

Carr's index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Angle of repose (θ):

The angle of repose is indicative of flowability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by (Values as given in Table 2)[52, 53].

$$\tan \theta = h/r$$

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

Where, θ is angle of repose, h is height of the pile; r is the radius of the pile.

Table 2: Relationship between angle of repose (θ) and flowability

Angle of Repose(θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

Hausner's ratio:

The Hausner's ratio is an indication of the compressibility of a powder. It is calculated by the formula[52],

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

The Hausner's ratio is frequently used as an indication of the flowability of a powder. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. The observations for the flow properties determinations were recorded.

Percentage yield

Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula[54]

% yield = (actual weight of product/total weight of drug and Excipients) ×100

Drug entrapment efficiency (DEE)

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank.[23] The amount of drug entrapped in the microspheres was calculated by the following formula:

DEE = (amount of drug actually present/theoretical drug load expected) × 100

In vitro Buoyancy

Floating behavior of hollow microspheres was studied using a USP dissolution test apparatus II by spreading the microspheres (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microspheres were collected separately. The microspheres were filtered, dried and weighed. The percentage of floating microspheres was calculated using the following equation[54]

% buoyancy of microspheres = (weight of floating microspheres/initial weight of floating microspheres) x 100

Dissolution test (in vitro-drug release) of microspheres

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Microspheres equivalent to the drug dose are added to 900 ml of the dissolution medium and stirred at 100 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy.[54, 55]

Morphological Study using SEM

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM) .[54]

Stability Studies

Optimized formulation was sealed in aluminum packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the physical appearance and drug content.[54, 56]

Applications

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[57].

Marketed products of FDDS

Table 3: List of drugs explored for various floating dosage forms.

Dosage form	Drugs
Microspheres	Aspirin, Ibuprofen, Tranilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Capsules	Diazepam, Furosemide, L-Dopa and Benserazide
Tablets/Pill	Amoxycillin Trihydrate, Ampicillin, Diltiazem, p - Aminobenzoic acid,

CONCLUSION

Gastro retentive multiparticulates have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. This article gives an overview on method of preparation, and evaluation parameter for floating microsphere and will assist students for their further studies in development of floating microspheres.

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