



Review Article

FLOATING MICROSPHERES: A NOVEL APPROACH IN DRUG DELIVERY SYSTEM

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KEY WORDS

Floating microspheres, Hollow microspheres, Gastro Retention, Short half-life, Solvent diffusion.

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ABSTRACT

Floating microspheres (Hollow Microspheres) are gastro-retentive drug delivery systems based on non effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micrometer. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilise only in stomach, Gastric retention time is increased because of buoyancy. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose, scanning electron microscopy, in vitro floatability studies, in vivo floatability studies in dogs, in-vitro drug release studies and stability studies etc. In the present review preparation methods, characterization, advantages, mechanism of drug release from microspheres, applications and list of the drugs formulated as floating microspheres are discussed.

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INTRODUCTION

Recent advances in novel drug delivery system to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. There are lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). (1)

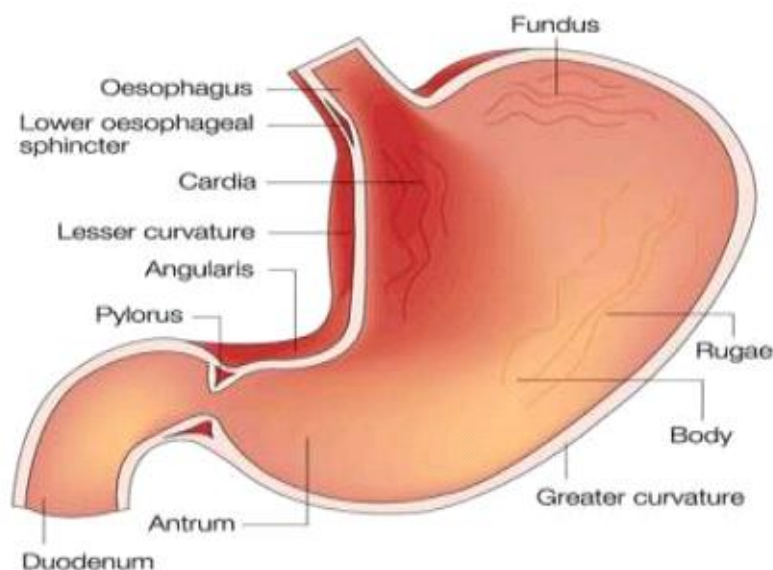


Fig. 1: Anatomy of stomach

To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. (2, 3) Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 micrometer. The Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs.

Microspheres are small in size and therefore have large surface to volume ratios. The concept of incorporating quantities of materials within microspheres dates back to the 1930s and to the work of *Bungerberg de joing* and co-workers on the entrapment of substances within coacervates. The potential uses of microspheres in the pharmaceutical have been considered since the 1960's and have a number of applications. (4, 5) The use of microspheres in pharmaceuticals have a number of advantages Viz., Taste and odor masking, conversion of oils and other liquids to solids for ease of handling, protection of drugs against environment (moisture, heat, light and oxidation), separation of incompatible materials, to improve flow of powders, production of sustained release, controlled release and targeted medications. (6)

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)

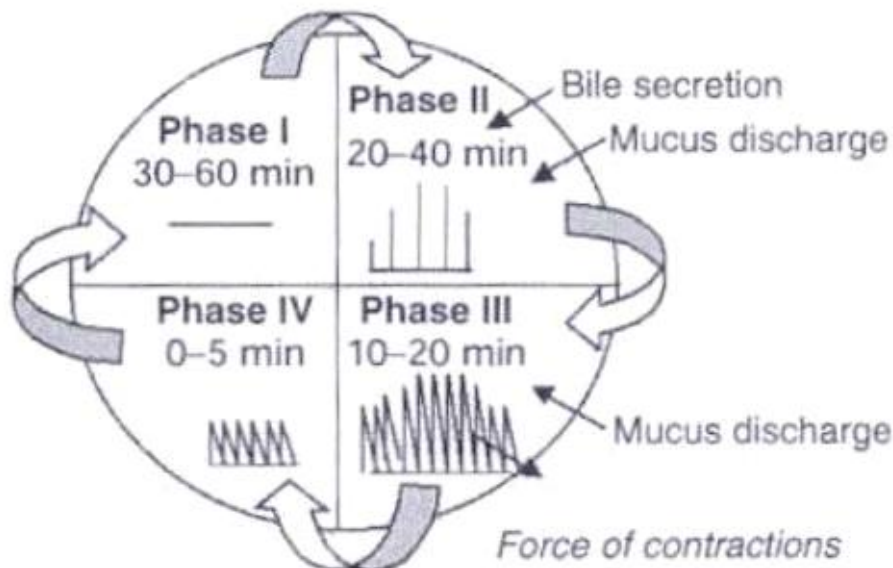


Fig. 2: Motility pattern in GIT

APPROACHES TO GASTRIC RETENTION

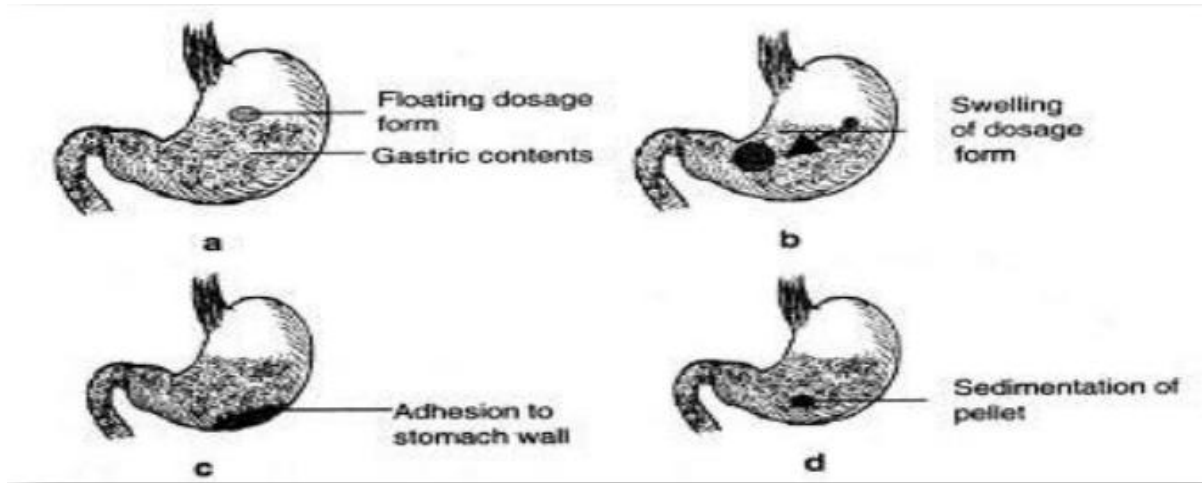


Figure 3: Mechanism of various gastro retentive drug delivery systems in stomach

A systematic flowchart of the approaches is shown in Fig. 4

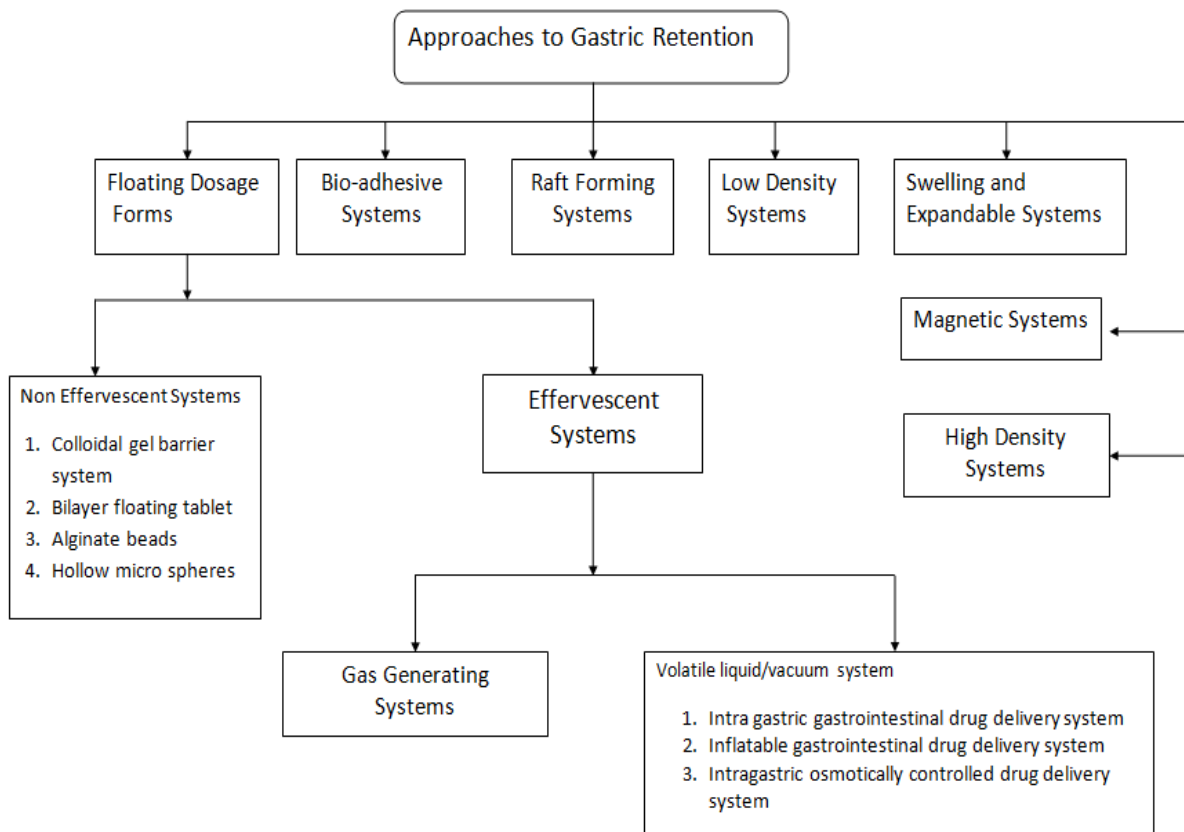


Fig. 4: Approaches to gastric retention

Floating Drug Delivery Systems (FDDS)

These 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. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. (7, 8)

$$RW \text{ or } F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) Gv$$

Where, RW = total vertical force, D_f = fluid density, D_s = object density, V = volume and g = acceleration due to gravity.

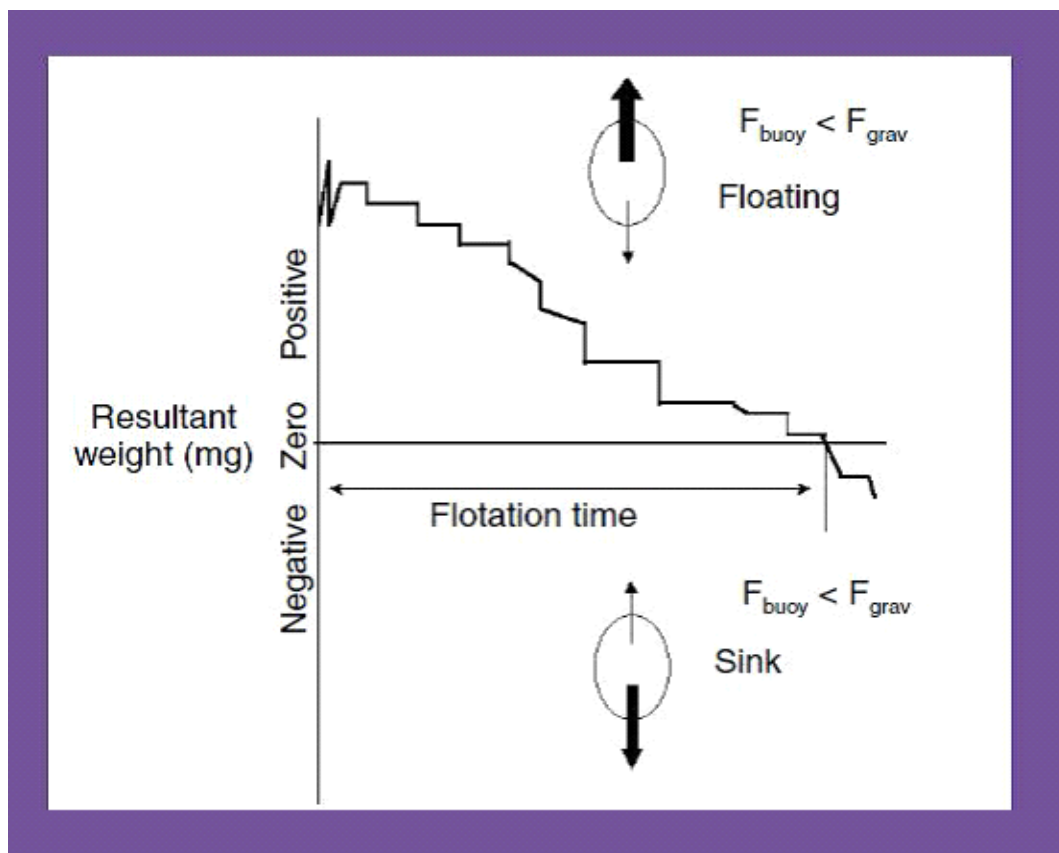


Fig. 5: Effect of resultant weight during buoyancy on the floating tendency of FDDS

Bioadhesive systems or mucoadhesive systems

These enable the localized retention of the system in the stomach. Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbophil, carbopol, lectins, chitosan and gliadin, etc. (9, 10)

Swelling and expanding systems

These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration. The expandable GRDF's are usually based on three configurations: a small ('collapsed') configuration which enables convenient oral intake; expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter; and finally another small form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.

High density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. (11, 12)

Raft systems

Raft forming systems incorporate alginate gels. These have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating. These systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The 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. This raft floats on gastric fluids because of low bulk density created by the formation of CO₂. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of *helicobacter pylori* (*H. Pylori*) infections in the GIT. (13)

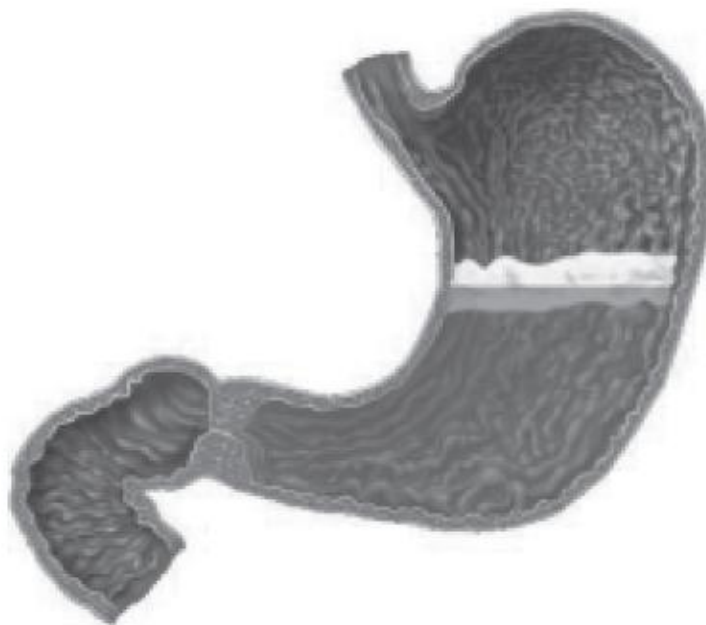


Fig. 6: Barrier formed by a Raft Forming System

Magnetic systems

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito *et al* used this technique in rabbits with bioadhesive granules containing ultrafine ferrite (g-Fe₂O₃). They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

Large single unit dosage forms

These dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.

Co-administration of gastric emptying delaying drugs

This concept of simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug has not received the favour of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices.

Incorporation of passage delaying food agents

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

Ion exchange resins

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are 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 is 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. (14-19)

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. (20)

TYPES OF FLOATING DRUG DELIVERY SYSTEM: -

FDSS can be divided into two systems:

1. Effervescent systems
2. Non-effervescent systems

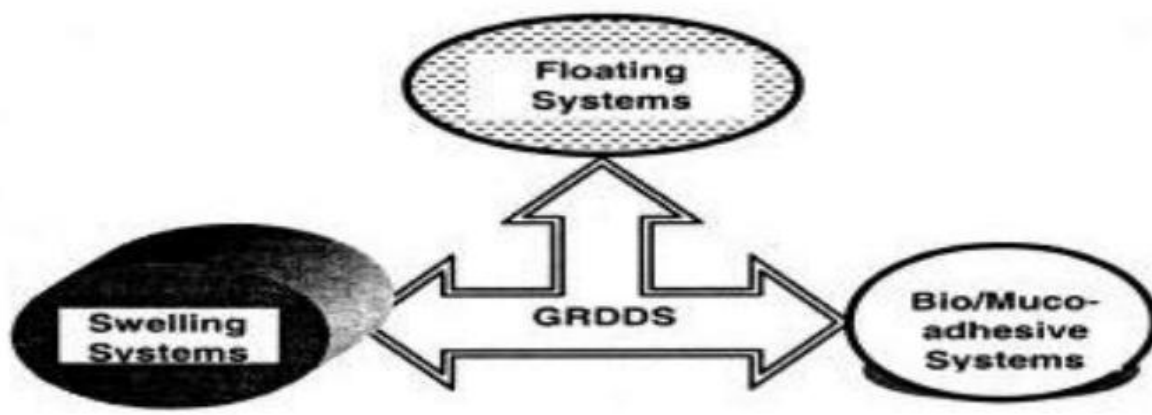


Fig. 7: Classification of gastroretentive drug delivery system

Effervescent Systems

Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible 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.

Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. These buoyant systems can be prepared by using 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 to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. 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.

Non-Effervescent Systems

This type of system, after swallowing, swells 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 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.

Colloidal gel barrier systems

Hydro-dynamically balanced system (HBS) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain 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, NaCMC, Polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and 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.

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 undissolved 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.

Alginate beads

Multiple units floating dosage forms have been developed from freeze-dried 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 12 h.

Hollow microspheres

Hollow microspheres (microballons), 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 polymer 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 in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h in vitro. (21-28)

FACTORS AFFECTING GASTRIC RETENTION

Density

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm.

Shape

The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT, 90 to 100% retention at 24 hours compared with other shapes.

Fed or Unfed State

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. Single or multiple unit formulation: Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Nature of the meal

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

Caloric Content

GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.

Age

Elderly people, especially those over 70 years have a significantly longer GRT.

Posture

GRT can vary between supine and upright ambulatory states of the patients.

Diseased state of the individual

Biological factors also affect the gastric retention e.g. Crohn's disease, gastrointestinal diseases and diabetes. Concomitant drug administration: Anti-cholinergics like atropine and propenthenline opiates like codeine and prokinetic agents like metoclopramide and cisapride.(29-35)

SUITABLE DRUG CANDIDATES FOR FLOATING DRUG DELIVERY SYSTEM

Sustained release in the stomach is useful for 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, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 h as shown in **Fig. 8 (a)** and **(b)**.

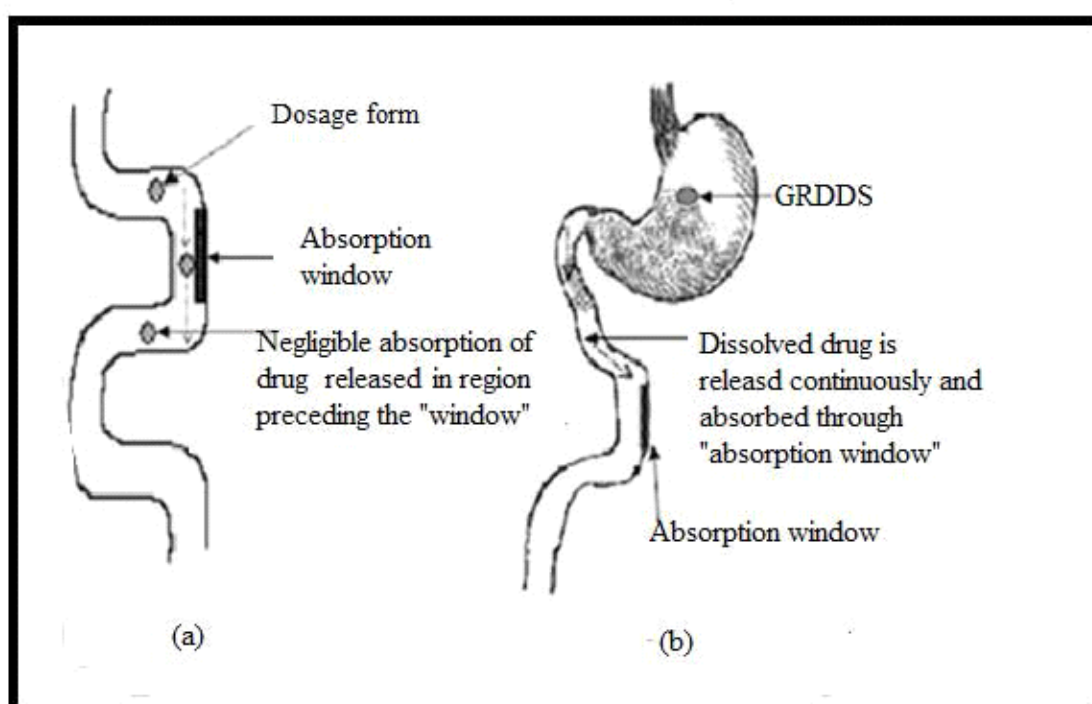


Fig. 8: Drug absorption in case of (a) conventional dosage forms (b) Gastroretentive drug delivery systems

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.

- a) Drugs with narrow absorption window in GI tract, e.g., Para aminobenzoic acid, furosemide, riboflavin in a vitamin deficiency and Levodopa.
- b) Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.
- c) Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- d) Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- e) Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate. (36, 37)

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.

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. (38, 39)

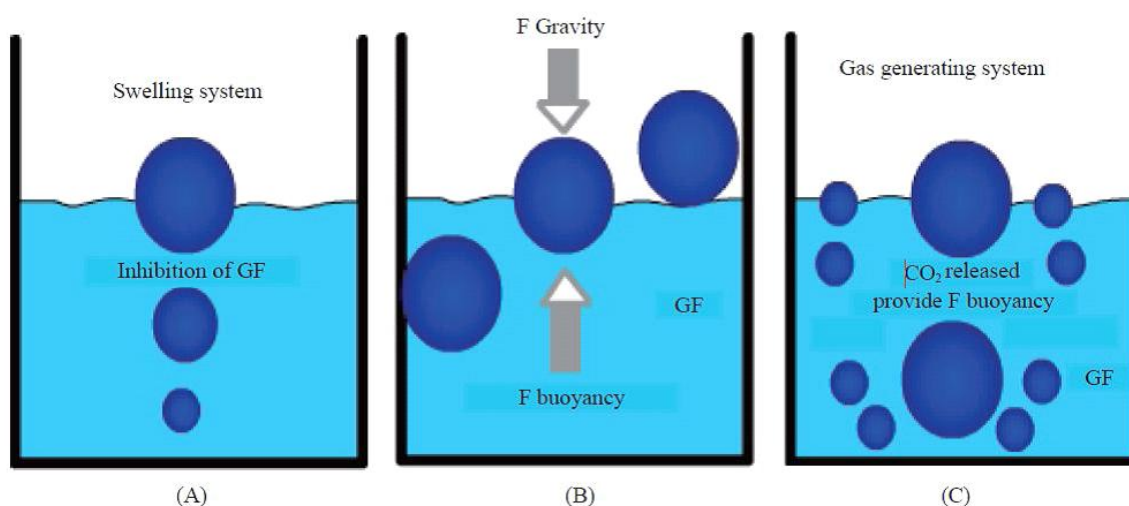


Fig. 9: Mechanism of floating systems (A) Swelling system (C) Gas generating system

METHODS OF PREPARATION OF MICROSPHERES

Solvent Evaporation Method

Floating multiparticulate dosage form can be 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 suitable additive (surfactants / polymer) 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 oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, eudragit, Acrycoat, Methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonate.

Ionotropic Gelation Method

Ionotropic gelation is based on the ability of poly electrolytes 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 poly electrolytes in spite, 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. The schematic representation of ionotropic gelation method is shown in **Fig. 10**.

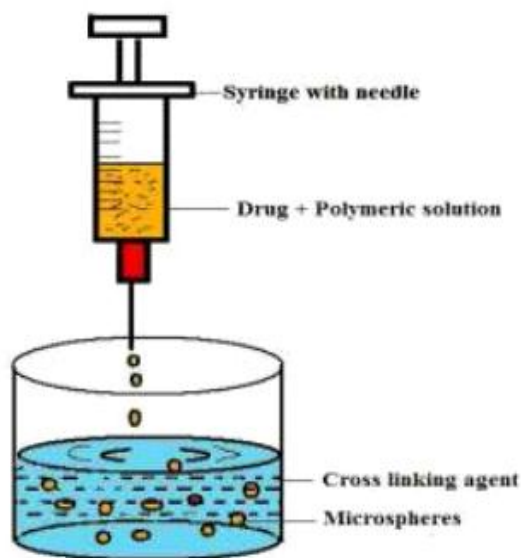


Fig. 10: Ionotropic gelation method

Emulsion Solvent Diffusion Method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion

droplets even though the organic solvent is miscible (**Fig. 11**). The organic solvent diffuses gradually out of the emulsion droplets into the surrounding aqueous phase and the aqueous phase diffuses in to the droplets by which drug crystallizes. (40, 41, 42)

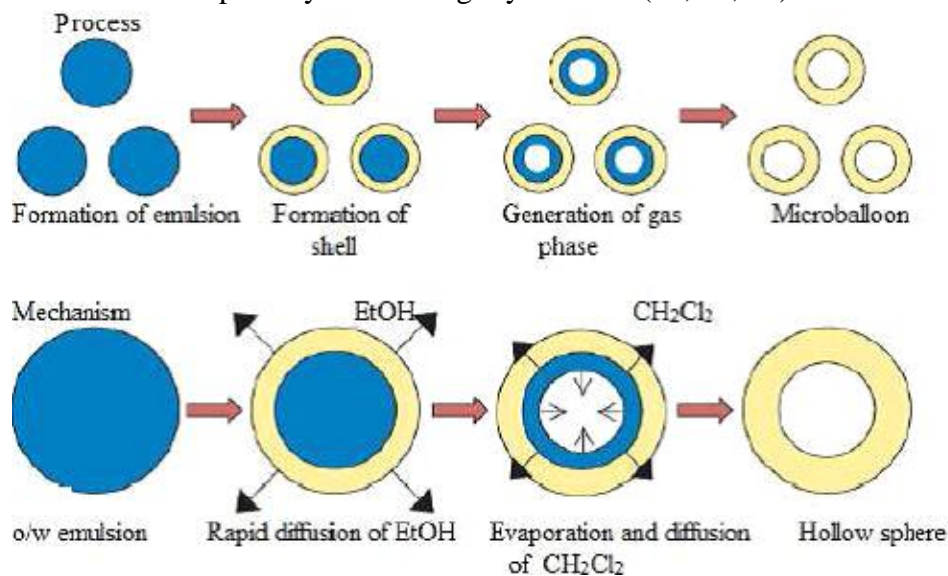


Fig. 11: Preparation technique (emulsion-solvent diffusion method) and mechanism of 'microballoon' formation

EVALUATION OF FLOATING MICROSPHERES

Micromeritics

Microspheres were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausners 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.

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/cm³)

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

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/cm³)

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

Carr's index (%)

The Carr's index is frequently used as an indication of the flowability of a powder. A Carr's 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)

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

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).

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

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

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,

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

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.

$$\% \text{ yield} = (\text{actual weight of product} / \text{total weight of drug and Excipients}) \times 100$$

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. The amount of drug entrapped in the microspheres was calculated by the following formula:

$$\text{DEE} = (\text{amount of drug actually present} / \text{theoretical drug load expected}) \times 100$$

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.

$$\% \text{ buoyancy of microspheres} = (\text{weight of floating microspheres} / \text{initial weight of floating microspheres}) \times 100$$

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 °C. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy.

Morphological Study using SEM

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

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. (43, 44)

APPLICATIONS

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.

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 misoprostol. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

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.

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. (44, 45)

Table 3: Marketed Products of FDDS.

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

CONCLUSION

Floating microspheres has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. Optimized multi-unit floating microspheres are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse diseases. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Increased sophistication of

this system will ensure the successful advancements in the avenue of gastro retentive microspheres therapy so as to optimize the delivery of molecules in a more efficient manner.

REFERENCES

1. Praveen N, Sheefali M, Deepika S. Floating Systems: A Novel Approach towards Gastroretentive Drug Delivery Systems. *Int J Pharmacy and Pharm Sci.* 2010; 2 (3): 27.
2. Audumbar DMi, Ritesh SB. A Review on Gastroretentive Floating Drug Delivery System. *American Journal of Pharmtech Research.* 2015; 5(2): 107-132.
3. Brahamankar D, Jaiswal SB. *Biopharmaceutics and Pharmacokinetics: A Treatise.* 1st Edition. 1995; pp. 399.
4. Chawla G, Gupta P, Koradiav, Bansal AK. Gastro Retention: A Means to Address Regional Variability in Intestinal Drug Absorption. *Pharmaceutical Technology.* 2003; pp. 50-52.
5. Kavitha K, Sudhir KY, Tamizh MT. The Need of Floating Drug Delivery System. *Research Journal of Pharmaceutical, Biological and Chemical Sciences.* 2010; 1(2): 396.
6. Shaha SH, Patel JK, Pundarikakshudu K. An Overview of a Gastro-Retentive Floating Drug Delivery System. *Asian Journal of Pharmaceutical Sciences.* 2009; 4(1): 65-80.
7. Fujimori J, Machida Y, Nagai T. Preparation of a Magnetically-Responsive Tablet and Configuration of its Gastric Residence in Beagle Dogs. *STP Pharma Sci.* 1994; 4: 425-30.
8. Katakam VK, Somagoni JM, Reddy S, Eaga CM, Rallabandi BRC Yamsani MR, et al. Floating Drug Delivery Systems: A Review. 2010; 4(2): 610-647.
9. Ramdas TD, Hosmani A, Bhandari A, Kumar B, Somvanshi S. Novel Sustained Release Gastro retentive Drug Delivery System: A Review. 2011; 2(11): 26-41.
10. Rocca G, Omidian H, Shah K. Progresses in Gastroretentive Drug Delivery Systems. *Pharma Tech.* 2003; 3(2):152-156.
11. Arunachalam A. Floating Drug Delivery System: A Review. *Int. J. Res. Pharm. Sci.* 2011; 2(1): 76-83.
12. Deshpande AA., Shah NH., Rhodes CT., Malick W. Development of a Novel Controlled-Release System for Gastric Retention. *Pharm.Res.*1997; 14: 815-819.
13. Lenaerts VM, Gurny R. Gastrointestinal Tract-Physiological Variables Affecting the Performance of Oral Sustained Release Dosage Forms. In: Lenaerts V, Gurny R, Editors. *Bioadhesive Drug Delivery System.* Boca Raton, FL: CRC Press; 1990.
14. Urguhart J, Theeuwes F. Drug Delivery System Comprising a Reservoir Containing a Plurality of Tiny Pills. US Patent. 4 434 153. 1994; 2: 28.
15. Garg R, Gupta GD. Gastro retentive Floating Microspheres of Silymarin: Preparation and in vitro Evaluation *Trop J Pharm Res.* 2010; 9(1): 59-66.
16. Huang HP, Ghebre-Sellassie I. Preparation of Microspheres of Water-Soluble Pharmaceuticals. *J. Microencapsul.* 1989; 6(2): 219-225.
17. Gattani YS, Bhagwat DA, Maske AP. Formulation and Evaluation of Intra-gastric Floating Drug Delivery System of Diltiazem Hydrochloride. *Asian J. Pharm.* 2008; 2(4): 228-231.
18. Hincal AA, Calis S. In: *Handbook of Pharmaceutical Controlled Release Technology.* New York: Marcel Dekker. 2005; 329 -343.
19. Sam TM., Gayathri DS, Prasanth VV, Vinod B. *The Inter J Pharmaco.* 2008; 6(1):21-32.
20. Patil JS, Kamalapur MV, Marapur SC, Kadam DV. *Dig J Nano and Bio.* 2010; 5(1): 241-248.
21. Harsoliya MS, Patel VM, Pathan JK, Ankit, Meenakshi, Ali. Formulation of Floating Microspheres of Ritonavir by Crosslinking-Technique: Effect of Nahco as Gas Forming Agent. *Inter J Pharm & Bio Arch.* 2012; 3(1):108-111.
22. Wells J. *Pharmaceutical Preformulation, the Physicochemical Properties of Drug Substances.* In: M.E. Aulton (Ed), *Pharmaceutics- The Science of Dosage Form Design.* 2nd Ed.;Churchill Living-Stone, CN, London. 2002; 113-138.
23. Trivedi P, Verma A, Garud N. Preparation and Characterization of Aceclofenac Microspheres. *Asian J. Pharm.* 2008; 2:110-115.
24. Prakash K, Raju PN, Shanta KK, Lakshmi MN. Preparation and Characterization of Lamivudine Microcapsules Using Various Cellulose Polymers. *Trop J Pharm Res.* 2007; 6(4): 841-847.
25. Sarode SM, Mittal. Srivastava AK, Ridhurkar DN, Wadhwa S, Floating Microspheres of Cimetidine: Formulation, Characterization and in Vitro Evaluation. *Acta Pharm.* 2005; 55: 277-285.
26. Sanjay SPI, Ray S, Thakur RS, Formualtion and Evaluation of Floating Drug Delivery System Containing Clarithromycin for Helicobacter Pylori. *Acta Poloniae Pharmaceutica - Drug Research.* 2006; 63(1): 53-61.

27. Patel A, Ray S, Thakur RS. In vitro Evaluation and Optimization of Controlled Release Floating Drug Delivery System of Metformin Hydrochloride. *DARU Journal*. 2006; 14(2): 57-64.
28. Fabregas JL, Garcia N. Invitro Studies on Buccoadhesive Tablet Formulations of Hydro Cortisone Hemisuccinate. *Drug Dev.Ind.Pharm*. 1995; 21(14): 1689-1696.
29. Rathbone MJ, Purve R, Ghazati FA, In Vivo Techniques for Studying the Oral Mucosa Absorption Characteristics of Drugs in Animals and Humans. In Rathbone, M.J. (Ed.). *Oral Mucosal Delivery Systems*, Marcel Dekker Inc. Newyork. 1996; 121-156.
30. Lu MF. Delivery of Rennin Inhibitors Through Mouth Mucosa. *Drug Dev.Ind.Pharm*. 1996; 22(11): 1167-1171.
31. Yukimatsu K, Nozaki Y. Development of a Transmucosal Controlled Release Device for Systemic Delivery of Antianginal Drugs Pharmacokinetics and Pharmacodynamics. *Drug Dev.Ind.Pharm*. 1994; 20(4): 503-534.
32. Hussain, MA, Aungst BJ, Kearney A. Buccal and Oral Bioavailability of Naloxone and Naltrexone in Rats. *Int. J.Pharm*. 197; 36:127.
33. Soppimath KS. Microspheres as Floating Drug Delivery Systems to Increase Gastric Retention of Drugs. *Drug Metab. Rev*. 2001; 33: 149-160.
34. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating Microspheres of Cimetidine: Formulation, Characterization and In Vitro Evaluation. *Acta Pharm*. 2005; 55: 277-285.
35. Stanley SD. Formulation Strategies for Absorption Windows. *DDT*. 2005; 10: 249-257.
36. Streubel A, Siepmann J, Bodmeier R. Floating Microparticles Based on Low Density Foam Powder. *Int. J. Pharm*. 2002; 241: 279-292.
37. Sarode. Formulation and Evaluation of Floating Microspheres of Glipizide. *J. Chem. Pharm. Res*. 2011; 3(3): 775-783.
38. Sunil K, Govind P, Agrawal, Narendra KJ. Evaluation of Porous Carrier-Based Floating Orlistat Microspheres for Gastric Delivery. *AAPS Pharmscitech*. 2006; 7(4): E54–E62.
39. Kapil K, Rai AK. Development and Evaluation of Floating Microspheres of Curcumin. *Tropical Journal of Pharmaceutical Research*. 2012; 11(5): 713-719.
40. Pooja J, Kantilal V, Hiral B. Formulation and Evaluation of Controlled Release Floating Microspheres of Tolperisone Hydrochloride. *Asian Journal of Pharmaceutics*. 2012; 6(3): 190-197.
41. Singh A. Formulation and Evaluation of Floating Microspheres of Famotidine. *International Journal of Pharmtech Research*. 2010; 2(2): 1415-1420.
42. Bathini ST, Durgaramani S, Shalini DP. Formulation and in Vitro Evaluation of Clarithromycin Floating Microspheres for Eradication of Helicobacter Pylori. *Der Pharmacia Lettre*. 2011; 3(6): 90-101.
43. Amol V. Pande, Pravin D. In Vitro and In Vivo Evaluation of Ethyl Cellulose Based Floating Microspheres of Cefpodoxime Proxetil. *Int J Pharm Biomed Res*. 2010; 1(4): 122-128.
44. Satish V, Shirolkar, Mukund.G, Tawar, Nishant. S. Gandhi, Nilesh B. Development and Evaluation of Floating Microspheres of Pioglitazone Hydrochloride Using Ethyl Cellulose. *Der Pharmacia Lettre*. 2010; 2(5): 261-277.
45. Sudha MT, Naveen KK. At preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery *International Journal of Pharma Research and Development*. 2010; 2(8): 120-121.