

HOLLOW MICROSPHERE: A REVIEW

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ABSTRACT

The purpose of writing this review on Hollow microspheres is to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Hollow microsphere promises to be a potential approach for gastric retention. The recent developments of FDDS including approaches to design single-unit and multiple-unit floating systems, mechanism of floating microspheres, methods of preparation of hollow microsphere, list of polymers used in hollow microspheres, characterization of hollow microspheres, and their classification and formulation aspects are covered in detail.

Key-words: GRDFs, FDDS, Hollow Microspheres

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration¹. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion².

Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time.

However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability. Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed³.

Gastroretentive Drug Delivery Systems / Gastroretentive Dosage Forms (GRDFS)

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time i.e. Gastro retentive Dosage Forms (GRDFs)

These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages especially for drug exhibiting an 'absorption window' in the GI tract⁴. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption.

These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine⁵.

APPROACHES TO GASTRIC RETENTION^{6,7}

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These includes in fig. 1.

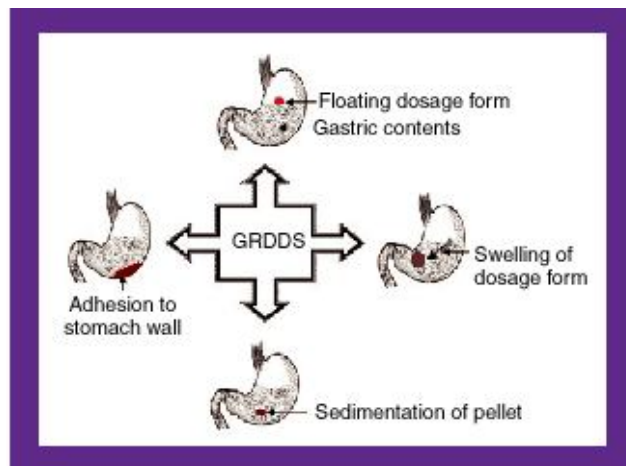


Figure 1: Illustration of types of gastroretentive drug delivery systems

a) Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating

systems can be classified into two distinct categories, non-effervescent and effervescent systems.

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 gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

Binding of polymers to mucin/epithelial surface can be divided into three broad categories:

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

c) Swelling and Expanding Systems :

These are 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 stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit tendency to remain logged at the pyloric sphincter.

d) High density systems :

These systems with a density of about 3 g/cm³ are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm³ acts as a threshold value after which such systems can be retained in the lower parts 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.

e) Incorporation of passage delaying food agents :

Food excipients 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.

f) 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.

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

Floating Drug Delivery Systems (FDDS) ^{8,9}:

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs).

Approaches To Design Floating Drug Delivery System

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

CLASSIFICATION OF FDDS :

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are

A. EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates (eg. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it float on the gastric fluid. These effervescent systems further classified into two types.

I. Gas generating systems

a. Intra gastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These are as shown in figure and formulated intimately mixing the CO₂ generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

b. Intra gastric bilayered floating tablets:

These are also compressed tablet as shown in figure and contains two layer i.e.,

- i) Immediate release layer and
- ii) Sustained release layer. (Fig.2)

c. Multiple Unit type floating pills :

These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable

membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. (Fig. 3 and 4)

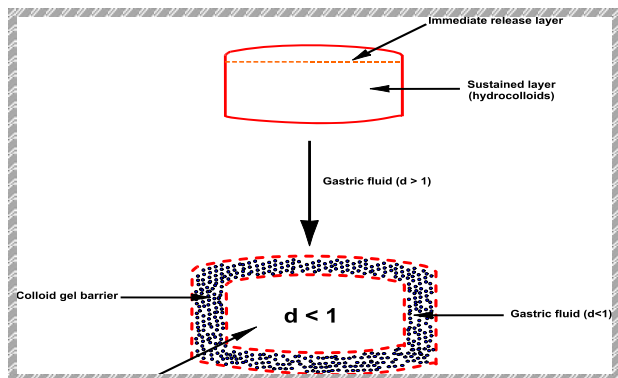


Figure 2: Intra gastric bilayer floating tablet.

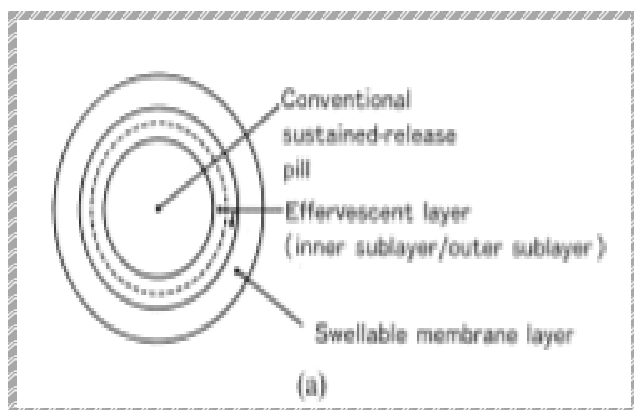


Figure 3: Multiple Unit of Oral FDDS

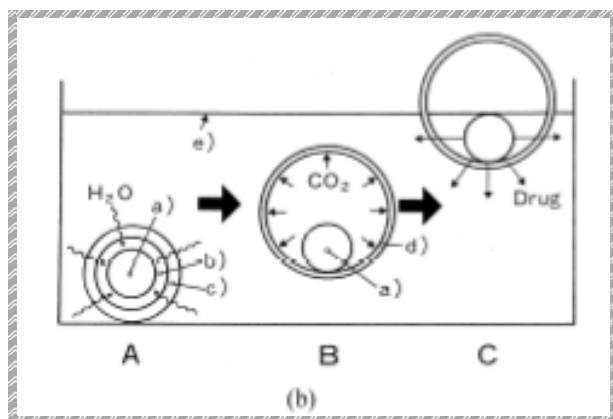


Figure 4: Working Principle of Effervescent FDDS

II. Volatile Liquid / Vacuum Containing Systems

a. Intra gastric floating gastrointestinal drug delivery system

These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporus compartment, as shown in fig. 5.

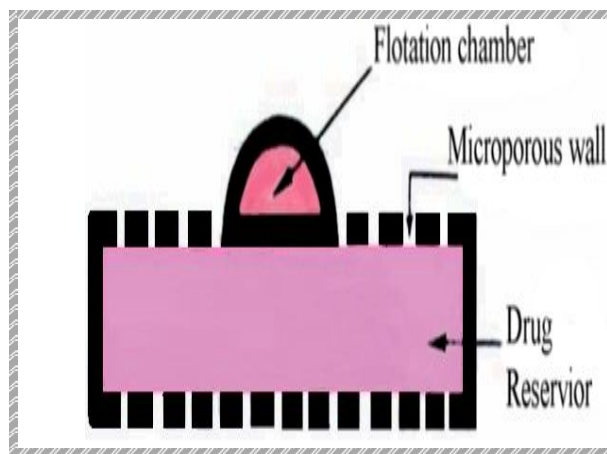


Figure 5: Intra gastric floating gastrointestinal drug delivery device

b. Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in fig. 6.

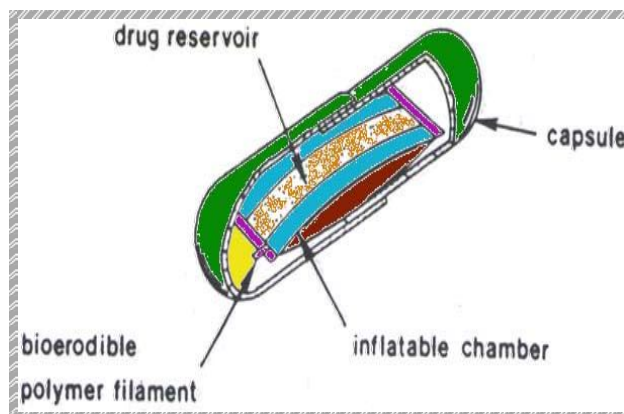


Figure 6: Inflatable gastrointestinal delivery system

c. Intra gastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra gastric 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 pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in fig. 7.

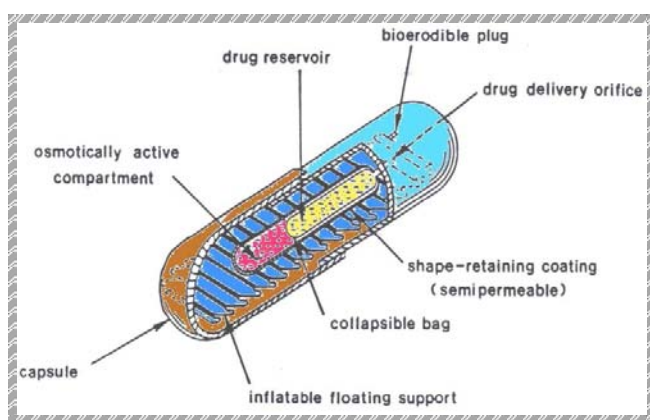


Figure 7: Intragastric osmotically controlled drug delivery system

B. Non effervescent systems

The Non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol.

The various types of this system are as :

1. Single layer floating tablets :

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer floating tablets :

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3. Alginate beads :

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow microspheres^{10,11} :

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.

DEVELOPMENT OF FLOATING MICROSPHERES

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach 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.

MECHANISM OF FLOATING 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 needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

METHODS OF PREPARATION OF HOLLOW MICROSPHERES

Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. 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.

LIST OF POLYMERS USED IN HOLLOW MICROSPHERES

Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene oxide.

CHARACTERIZATION OF HOLLOW MICROSPHERES

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties. Particle size is measured using an optical microscopy and mean particle size was calculated by measuring 200 to 300 particles with the help of calibrated ocular micrometer. True density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume

using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy.

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

The compressibility index was calculated using following formula :

$$I = V_b - V_t / V_b \times 100$$

Where, V_b is the bulk volume and V_t is the tapped volume. The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

Floating Behavior

Fifty milligrams of the floating microspheres were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy (\%)} = W_f / W_f + W_s$$

Where, W_f and W_s are the weights of the floating and settled microparticles

Table No. 1: Marketed Products of GRDFs

S. NO.	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	REMARKS
1.	Madopar [®]	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2.	Valrelease [®]	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
3.	Liquid Gaviscon [®]	Al hydroxide (95 mg), Mg carbonate (358 mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
4.	Topalkan [®]	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Convicon	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD [®]	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec [®]	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD [®]	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

Table No. 2: Various Types of Floating Drug Delivery Systems

Name of formulation	Name of drugs
Tablets	Ampicillin, Atenolol, Amoxycillin, Acetyl salicylic acid, Acetaminophen, Chlorpheniramine maleate, Ciprofloxacin, Captopril, Cinnarazine, Diltiazem, Fluoruracil, Isosorbide di nitrate, Riboflavin, Prednisolone, Theophylline.
Capsules	Nicardipine, Diazepam, Misoprostol, Propranolol, Verapamil.
Microspheres/Floating beads	Aspirin, Verapamil, Ibuprofen, Ketoprofen, Amoxicillin,
Granules	Riboflavin, Meloxicam, Nicardipine, Indomethacin, Diclofenac, Prednisolone.

In-Vitro Release Studies

The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at $37 \pm 1^\circ$ at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 μm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate.

In-Vivo Studies

The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs).

Table No. 1 and 2 give details about Marketed Products of GRDFs and Various Types of Floating Drug Delivery Systems

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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