



A NOVEL APPROACH FOR FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of writing this review on floating drug delivery system (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. These systems are useful to several problems encountered during the development of pharmaceutical dosage form. Our review article suggests that gastro retentive dosage forms can be the possible way to improve patients' compliance and robustness. This triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time. Several approaches such as floating drug delivery systems (FDDS), swelling and expanding systems, bio-adhesive systems, modified shape systems, effervescent system, high density systems or other delayed gastric emptying devices have been discovered till now. Various pharma companies opted advance technologies to make FDDS commercialized in large scale despite of several limitations. So, in future we hope to have a rational GRDF that's promises to be a potential approach for gastric retention

Keywords: floating drug delivery system, effervescent system, non-effervescent system, gastric retention.

INTRODUCTION

The most preferred route is the oral route especially for the administration of therapeutic drugs because low cost of therapy and ease of administration leads to higher level of patient compliance. More than 50% of the drug delivery systems available are to be administered through oral route. Reasons behind using oral route are that it is the most promising route of the drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and site of absorption of drug. High level of patient compliance is the major advantage of using the oral route.¹ To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems².

The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions³. These systems are useful in case of those drugs which are best absorbed in stomach for e.g. Albuterol. From the formulation and technological point of view, floating drug delivery system (FDDS) is considerably easy and logical approach in development of GRDDS. Therefore, this review article focuses on the current technological development in FDDS with special emphasis on the principal mechanism of floatation and advantages to achieve gastric retention and its potential for oral controlled drug delivery⁴. The retentive characteristics of the dosage form are not significant for the drugs that: Act insoluble in intestinal fluids, Act locally & Exhibit site-specific absorption. However, the system can be used for most of the drugs where controlled (sustained) release of the dosage form is desired by the oral route.

ANATOMY AND PHYSIOLOGY OF THE STOMACH:

The stomach is a muscular, hollow, dilated part of the digestion system which functions as an important organ of the digestive tract in some animals

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including vertebrates, echinoderms, insects (mid-gut), and molluscs. It is involved in the second phase of digestion, following mastication (chewing). The stomach is located between the esophagus and the small intestine. It secretes protein-digesting enzymes called proteases and strong acids to aid in food digestion, (sent to it via esophageal peristalsis) through smooth muscular contortions (called segmentation) before sending partially digested food (chyme) to the small intestines.⁵

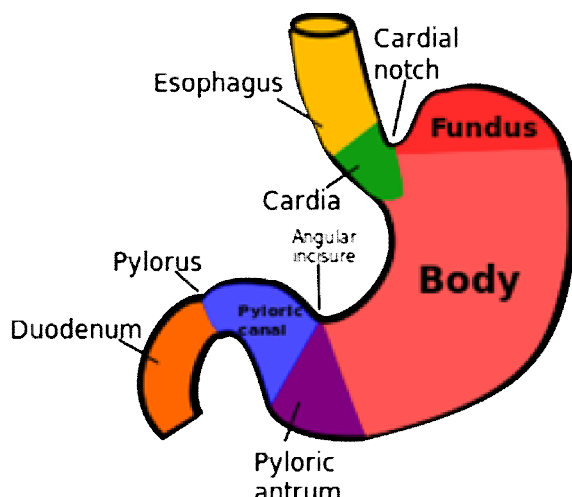


Fig. 1 Sections of the stomach

The capacity of the average stomach is about 1.12-1.70 liters. It normally expands to hold about one litre of food.⁵ The stomach is continuous with the esophagus at the cardiac sphincter and with the duodenum at the pyloric sphincter. It has two curvatures, the lesser curvature and greater curvature. The stomach can be divided into three parts: the fundus, the body and the pylorus or antrum. The distal end of the pyloric antrum is the pyloric sphincter, guarding the opening between the stomach and duodenum. When the stomach is inactive the pyloric sphincter is relaxed and open, and when the stomach contains food the sphincter is closed.^{6,7} Bolus (masticated food) enters the stomach through the esophagus via the esophageal sphincter. The stomach releases proteases (protein-digesting enzymes such as pepsin) and hydrochloric acid, which kills or inhibits bacteria and provides the acidic pH of two for the proteases to work. Food is churned by the stomach through muscular contractions of the wall called peristalsis – reducing the volume of the fundus, before looping around the fundus and the body of stomach as the boluses are converted into chyme (partially digested food). Chyme slowly passes through the pyloric sphincter and into the duodenum of the small intestine, where the extraction of nutrients begins. Depending on the quantity and contents of the meal, the stomach will digest the food into chyme anywhere between forty minutes and a few hours.⁸

GASTRIC EMPTYING:^{6,10,11}

The passage of a drug from stomach to the small intestine, called as gastric emptying, can also be a rate-

limiting step in drug absorption because the major site of drug absorption is intestine. For better drug dissolution and absorption, the gastric emptying can be promoted by taking the drug on empty stomach. Since gastric emptying is altered by several factors due to which large inter subject variations are observed, all biopharmaceutical studies. That require the drug to be taken orally are performed in volunteers on empty stomach. Several parameters are used to quantify gastric emptying:

1. Gastric emptying rate: is the speed at which the stomach contents empty into the intestine.
2. Gastric emptying time: is the time required for the gastric contents to empty into the small intestine. Longer the gastric emptying time, lesser the gastric emptying rate.
3. Gastric emptying $t_{1/2}$: is the time taken for half the stomach contents to empty.

APPROACHES TO GASTRIC RETENTION^{11,12,13,14}

Several approaches have been attempted in the preparation of gastro-retentive drug delivery systems. These include floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension systems and sachet systems.

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on.

HYDRO DYNAMICALLY BALANCED SYSTEMS (HBS)

It is also considered as a floating drug delivery system. These systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in acidic environment and also having specific site of absorption in the upper part of small intestine is achieved by these HBS systems. To retain in stomach for a prolonged period of time the dosage form must have bulk density of less than '1' and has to maintain its structural integrity and release drug constantly from the dosage form. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to potential danger of producing irritation.

Hydro – Dynamically balanced system (HBS) can be divided in the following:

1. Effervescent floating dosage forms
2. Non – Effervescent floating dosage forms
3. Low density approach

Effervescent Floating Dosage forms:

These are matrix type systems prepared with the help of swellable polymers such as Hydroxypropyl methyl-cellulose or polysaccharides and chitosan and various effervescent components like sodium bicarbonate, calcium carbonate, citric acid or tartaric

acid. These dosage forms are developed in such a way that, when they come in contact with gastric juice in the stomach, Carbon dioxide is liberated and is trapped in the swollen hydrocolloids. This provides buoyancy to the do-sage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet.¹⁵

Non-Effervescent FDDS: It is also known as swellable system. The non-effervescent FDDS works on the mechanism of polymer swelling, bioadhesion of the polymer to mucosal layer of GI tract. The most commonly used excipients for the preparations of non-effervescent FDDS are gel forming or swellable type hydrocolloids, poly-saccharides and matrix forming polymers like poly methacrylates, polycarbonates, polyacrylates polystyrenes and bioadhesion polymers like chitosan and carbopols. Hydro dynamically balanced tablets containing mixture of drug and hydrocolloids. Upon contact with gastric fluid, the tablet shell dissolved in gastric fluid followed by swelling of mixtures, formation of a gelatinous barrier and maintains bulk density less than 1.0, which remained buoyant on the gastric fluid for an extended period of time.

Low density approach: Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time. This type is also called as Hydro dynamically Balanced System (HBS).

High density approach: For preparing such type of formulations, the density of the pellets should be higher than the stomach fluid. It would be at least 1.50 g/ml. In this type, the drug can be coated or mixed with heavy, nontoxic materials such as barium sulfate, titanium dioxide, etc. The GI transit time can be extended from an average of 5.8-25 hours, depending more on density than on diameter of the pellets, although many conflicting reports Stating otherwise also abound in literature. Commonly used Excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5-2.4 g/cm³. However, no successful high density system has made it to the market.

Bioadhesive or mucoadhesive systems : These systems permit a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

Swelling and expanding systems: These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state¹⁶.

Raft forming system:

Raft forming systems have received much attention for the 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. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus⁵². 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.¹⁷

1. The most important parameters affecting gastric emptying and, hence, the gastric retention time of oral dosage forms include:

Density: Dosage form having density less than that of gastric fluid floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

Shape and size: The diameter of the dosage unit is equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with 9.9 mm.¹⁹

Single or Multiple unit formulation²⁰: 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;

Particle size: To pass through the pyloric valve into the small intestine, the particle size should be 1 to 2 mm.²¹

Caloric content: Gastric residence time can be increased by 4-10 hrs with a meal that is rich in proteins and fats.

Body posture: Gastric emptying is favored while standing and by lying on the right side since the normal curvature of the stomach provides a downhill path whereas lying on the left side or in supine position retards

Emotional state of subject: The influence of emotional factors on gastric motility and secretion may be either Augmentative or inhibitory depending upon whether the emotional experience is of an aggressive or a depressive.

Effect of drugs: Drug that retard gastric emptying includes poorly soluble antacids (Aluminum hydroxide), narcotic analgesics (Morphine) and tricyclic antidepressants (Imipramine, amitryptiline), domperidom and Anti emetics stimulates gastric emptying.

Exercise: physical activity retards gastric emptying.

Age: Elderly people, especially those over 70 years have a significantly longer GRT.²⁷

Disease states: Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote gastric emptying rate.

Nature of meal: decreasing the gastric emptying rate and prolonging drug release.²⁵

Fed or Unfed State: MMC is delayed and GRT is considerably longer.²⁶

CLASSIFICATION: 8, 10, 11

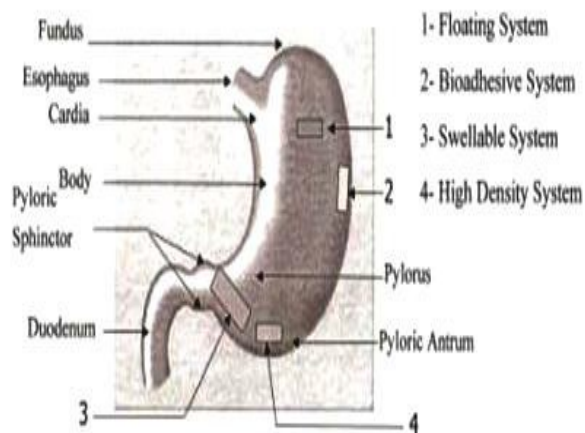
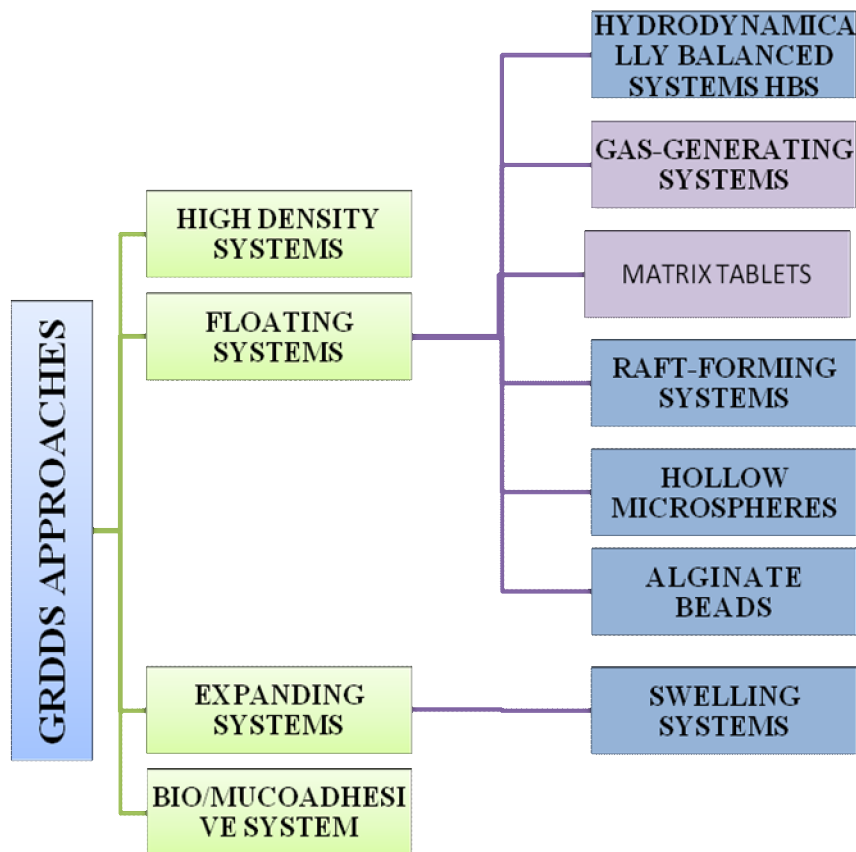


Fig 2: Various Approaches to Gastroretentive systems of system ensures no passage from gastric sphincter

Brand name	Delivery system	Drug	Category	Company name
Topalkan	Floating liquid alginate	Al – Mg	Antacid	Pierre Fabre Drug, France
Convicon	colloidal gel forming FDOS	Ferrous sulphate	Antianemic	Ranbaxy, India
Cifran OD	Gas-generating floating form	Ciprofloxacin	Antibiotic	Ranbaxy, India
Valrelease	Floating capsule	Diazepam	CNS depressant	Roche, USA
Madopar	Floating CR capsule	L-Dopa	Antiparkinsons	Roche Products, USA

Table 1: Marketed formulations available as GRDDS⁵

ADVANTAGES²²:

- a. Improves patient compliance by decreasing dosing frequency.
- b. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration.
- c. Better therapeutic effect of short half-life drugs can be achieved.
- d. Gastric retention time is increased because of buoyancy.
- e. Drug releases in a controlled manner for a prolonged period.
- f. Site-specific drug delivery to the stomach can be achieved.
- g. Enhanced absorption of drugs which solubilize only in the stomach.
- h. Superior to single unit floating dosage forms such as microspheres, releases drug uniformly and there is no risk of dose dumping.
- i. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

DISADVANTAGES^{23,24}

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. There are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
4. These systems also require the presence of food to delay their gastric emptying.
5. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery

Polymers and other ingredients:²⁸

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

Hydrocolloids (20%-75%):

They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives.

E.g. Acacia, pectin, Chitosan, agar, casein, bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan Gum (Gel rite®), Sodium CMC, MC, HPC.

Inert fatty materials (5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy.

E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Effervescent agents: **E.g.** Sodium bicarbonate, citric acid, tartaric acid, Di-SGC, CG (Citroglycine).

Release rate accelerants (5%-60%):

E.g. lactose, mannitol

Release rate retardants (5%-60%):

E.g. Dicalcium phosphate, talc, magnesium stearate

Buoyancy increasing agents (upto80%):

E.g. Ethyl cellulose

Low density material:

E.g. Polypropylene foam powder.

1. FUTURE POTENTIAL

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillin's, cephalosporin, amino glycosides and tetracycline) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

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