

A Review on Floating Drug Delivery System

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Abstract: *This review on floating drug delivery systems (FDDS) was written with the intention of gathering the most recent research with a particular focus on the main mechanism of flotation to induce stomach retention. Stomach retention duration and drug delivery behaviour are known to be significantly impacted by variations in stomach physiology (such as, gastric pH, motility), which display both intra- and inter-subject variability. Floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, high-density systems, and other delayed gastric emptying devices are now being employed to extend the GRT. This overview discusses the most recent and present FDDS innovations, including commercial products and patented distribution systems. The most current advancements in FDDS are reviewed in depth, including the physiological and formulation factors influencing stomach retention, design methods for single-unit and multiple-unit floating systems, and their categorization and formulation characteristics. This study also provides an overview of research that assessed the effectiveness and uses of floating systems.*

Keywords: Floating, Stomach, Gastric PH, Motility.

I. INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract (Yie W. Chein et al, 1992, Sanjay Garg et al, 2003).

Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa (Hirtz, 1985). Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the gastric emptying are summarized. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

Basic GIT Physiology:

Anatomically the stomach is divided into three regions-

Body, Antrum (pylorus), and Fundus. While the antrum is the primary site for mixing motions and serves as a pump for gastric emptying by propelling actions, the proximal part made of fundus and body serves as a reservoir for undigested materials (Yie W. Chein et al., 1992; Sanjay Garg et al., 2003). Both when one is fasting and when one is eaten, the stomach empties. The interdigestive myoelectric cycle, also known as the migrating myoelectric cycle (MMC), is a sequence of electrical events that occur during the fasting state and cycle through the stomach and intestine every two

to three hours. The pattern of contractions changes from a fasting condition to a fed state following the consumption of a mixed meal, which is-

1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles (Fig1).

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

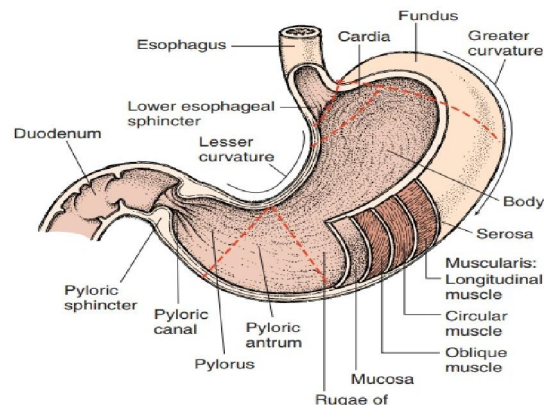
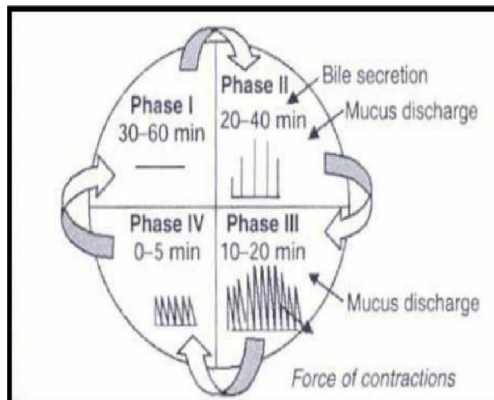


Fig 1: Gastrointestinal Motility Pattern Fig 2: structure of Stomach

A FLOATING DRUG DELIVERY SYSTEM:

Definition:

Floating systems, also known as dynamically regulated systems, are low-density systems with enough buoyancy to float above the gastric contents and remain buoyant in the stomach for an extended length of time (Yie W. Chein et al, 1992). This leads in extended stomach retention duration and improved regulation of plasma medication concentration variations. Many buoyant systems based on grains, powders, capsules, tablets, laminated films, and hollow Microspheres have been created [1].

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the system is eliminated from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentrations. The floating sustained release dosage forms exhibit most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' (HBS) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gel like barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 h) in the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many studies have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved effects in clinical situations. The results obtained have also demonstrated that the presence of gastric contents is needed to allow the proper achievement of the buoyancy retention effect. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are the most popular, especially hydroxyl propylmethyl cellulose (HPMC). Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy [2]. In parallel with formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performance of floating forms. These assessments were carried out either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the transit through the GI tract. When a floating capsule is administered to subjects who have consumed a fat and protein meal, it remains buoyant at the surface of the gastric contents in the upper part of the stomach and moves to the lower region progressively as the meal empties from

the stomach. The reported gastric retention times range from 4 to 10 h. Pharmacokinetic and bioavailability evaluation studies confirm the favourable effect of this prolonged gastric residence time [3].

ADVANTAGES AND DISADVANTAGES OF FDDS:

Advantages	Disadvantages
i. Also at the alkaline pH of the intestine, floating drug types such as capsules or tablets will stay in the solution for an extended period ⁴ .	i. Various Factorlike gastric motility, pH and presence of food influences the gastric retention and these are never constant. So, the buoyancy can't be predicted ⁵ .
ii. Thedrugswhich are absorbed through the stomachfor them the gastro-retentive system is advantageous. e.g. Ferrous salts, and antacids ⁴ .	ii. The drugs which cause irritation to the gastric mucosa are not suitable for formulating the floating drug delivery system ⁵ .
iii. When an acidic substance like aspirin meets the stomach wall, it causes discomfort. As a result, HBS/FDDS formulations could be useful for administering aspirin and other comparable medications ⁴ .	iii. In sleeping subject, the gastric emptying of floating tablets may occur at random. Hence the patient should avoid the floating tablet dose just before going to bed ⁶ .
iv. FDDS dosage forms are beneficial in cases of diarrhoea and vigorous intestinal movement because they keep the drug in a floating state in the stomach ,allowing for a better response ⁴ .	iv. Drugs having solubility and stability problem in gastric fluids are not suitable for formulating floating drug delivery system ⁶ .
v. For drugs ingested through the stomach, the FDDS is beneficial, e.g.:ferrous salts, antacids Improved drug absorption due to increased GRT and more time spent on its absorption site by the dosage type ⁴ .	v. For the drug to float and work efficiently, it requires high level of field in the stomach ⁷ .
	vi. The drugs which undergo first pass metabolism are not suitable for preparing the floating drug delivery system ⁶ .
	vii. The drugs which are unstable in the acidic environment of stomach are not suitable forformulating the floating drug delivery system ⁷ .

II. MECHANISM OF FLOATING DRUG DELIVARY SYSTEM:

The system is floating on the stomach contents (see figure 3(a)), and the delayed medication release occurs at the required rate while the system is floating on the gastric contents. The remaining system is then removed from the stomach after the release. However, in addition to the proper degree of floating force (F), minimum quantities of stomach contents are required to meet the buoyancy retention principle and to maintain the dose form buoyant over the meal surface. A unique device for determining resultant weight (RW) has been disclosed in the literature to assess the floating force kinetics. Its functioning entails measuring a force. F (in terms of time) is similar to keeping the thing underwater. If RW is on the positive side, the item floats better (see picture 3(b)).This apparatus optimises FDDS while avoiding unforeseen intragastric buoyancy capacity fluctuations, which are important to stability and durability[9]

$$RW = \text{buoyancy} - \text{gravity} = (D_f - D_s) gV$$

Where,

F = total vertical force, D_f = fluid density, D_s = object density, V = volume, and g = gravity acceleration.

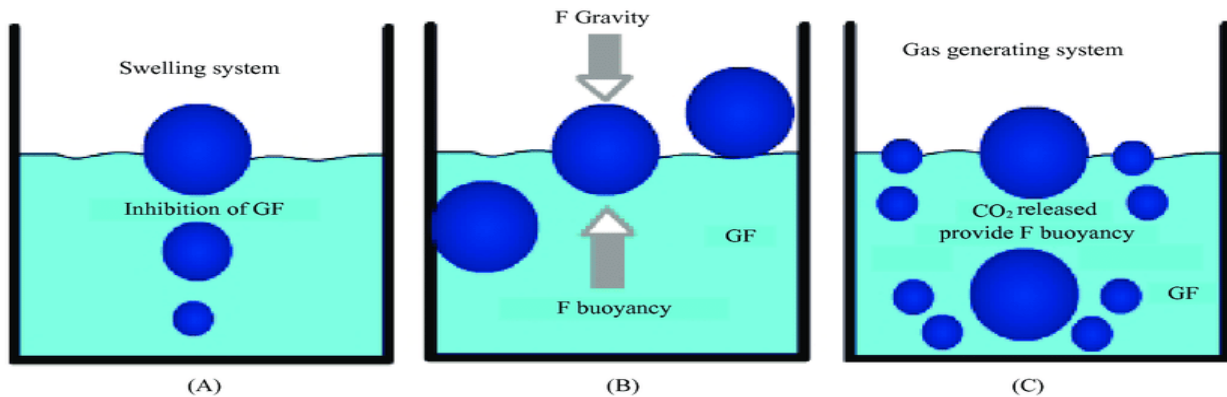


FIGURE3: Mechanism of FDDS, GF- Gastric Fluid, CO₂- Carbon Dioxide

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM¹⁰

Based on the buoyancy mechanism, two significantly different technologies have been used to construct FDDS (11)

Types of Floating system:

- 1) Effervescent system
 - a) Gas generating system
 - b) Volatile liquid / vacuum containing system
- 2) Non- Effervescent system
 - a) Colloidal gel barrier system
 - b) Microballons
 - c) Alginate beds
 - d) Microporous compartment system
 - e) Layered tablets
 - f) Single layered floating tablets
 - g) Double layered floating tablets

Effervescent floating drug delivery system:^{12,13}

The incorporation of a floating chamber filled with vacuum, air, or a noble gas is frequently used to develop floating medication delivery systems inside the stomach. The volatilization of an organic solvent, such as ether or cyclopentane, or the carbon dioxide produced by an effervescent reaction between organic acids, such as citric acid and tartaric acid, and carbonates, such as sodium bicarbonate, are two common ways that gas are introduced into the floating chamber. The following types of effervescent systems were added to the classification.

- a) Gas generating system
- b) Volatile liquid / vacuum containing system
- a) Gas generating system-^{14,15,16,17}

The creation of gas bubbles aids in achieving floatability. Methylcellulose and chitosan, two swellable polymers, as well as a variety of effervescent substances such sodium bicarbonate, tartaric acid, and citric acid make it easier to create the matrix form of these systems. The ideal stoichiometric mixture of sodium bicarbonate and citric acid is thought to be 0.76:1. This mixture is made in such a way that when it comes into contact with stomach acid, carbonic acid gas is released and eventually entraps in swollen hydrocolloids, making dosage forms buoyant. Systems for producing gas include-

1. Intra gastric single layer floating tablets.
2. Intra gastric bi-layer floating tablets.
3. Multiple unit type floating pills.

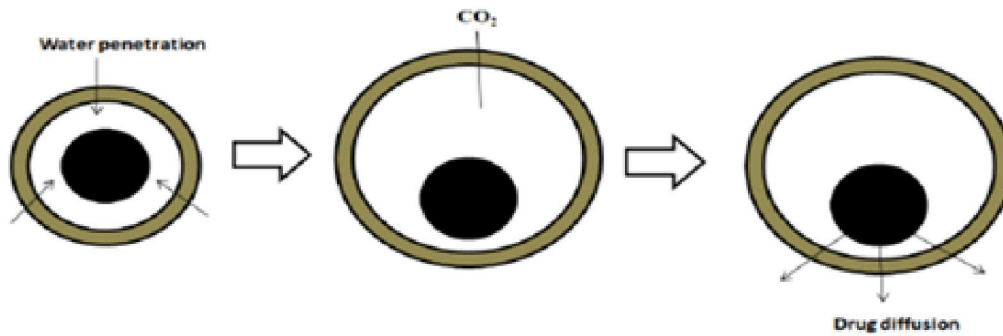


FIGURE 4: Gas generating system.

b) Volatile liquid containing system^{18,19}:

These feature an inflatable chamber with a liquid such as ether or cyclopentane that, when heated by the blood, gasifies and causes the chamber to inflate. These systems have a hollow deformable unit and are osmotically controlled floating devices. The system has two chambers, the first of which holds the medicine and the second of which has the volatile liquid. These systems are also divided into-

1. Intra-gastric floating gastrointestinal drug system.
2. Inflatable gastrointestinal delivery system
3. Intra-gastric-osmotically controlled drug delivery system

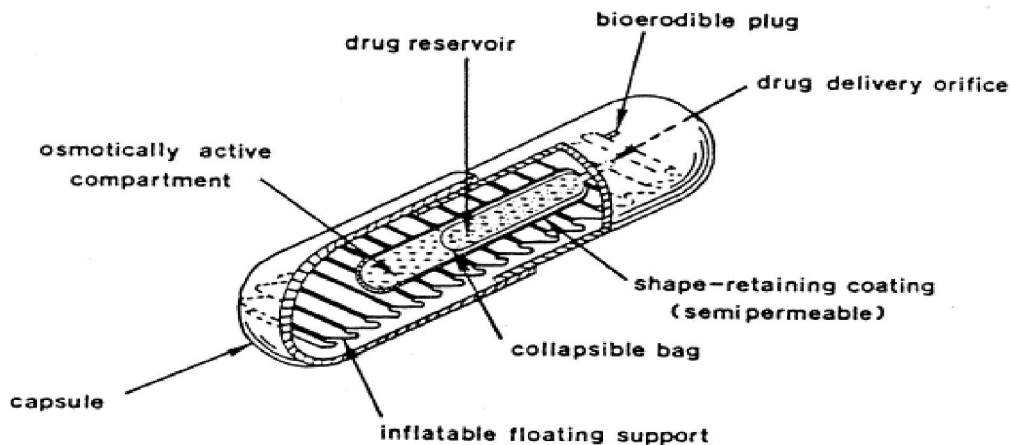


FIGURE 4: Volatile liquid containing system

Non- Effervescent floating drug delivery system^{20,21,16}

These systems expand up after consumption due to the ingestion of gastric fluid, delaying their escape from the stomach. In the formulation of these systems, a gel that expands when in contact with stomach fluid is typically utilised, which aids in preserving relative integrity and a bulk density of 1 within the outer gelatinous barrier. These systems buoyancy relies on the air that the polymer has captured. The most popular polymers employed in the creation of these systems are HPMC, carbopol, polyacrylate polymers, etc. These systems are also divided into-

1. Colloidal gel barrier system / Hydrodynamically balanced systems (HBS)
2. Microballoons / Hollow microspheres
3. Alginate beads
4. Microporous compartment systems
5. Layered tablets
 - a. Single layered floating tablets
 - b. Double layered floating tablets

DRUG CANDIDATES SUITABLE AND UNSUITABLE FOR FLOATING DRUG DELIVERY SYSTEMS^[14,18,22]

The suitable and unsuitable medication candidates for FDDS are listed in Table 1 and Table 2 severally.

TABLE 1: Drug candidates suitable for floating Drug Delivery system.

S No	Suitable Drug Candidates	Examples
1	Medication with narrow absorption window in GIT.	Methotrexate, Levodopa, Repaglinidine, Riboflavin, Furosemide, Cyclosporine, Atenolol, Theophyllin, Para-aminobenzoic Acid.
2	Medication acting regionally within the stomach.	Antacids, Anti-ulcer medication, Misoprostol
3	Medication having low solubility at high nucleon concentration values.	Diazepam, chlordiazepoxide, verapamil HCL, Furosemide
4	Medication having unstable properties within the enteral or colonic atmosphere.	Captopril, ranitidine HCL, metronidazole, Metformin HCL.
5	Medication caused imbalance of normal colonic microbes.	Antibiotics against H. Pylori, Amoxil Trihydrate, Tetracycline, Clarithromycin

TABLE 2: Drug candidates unsuitable for floating Drug Delivery System.

S No	Unsuitable Drug Candidates	Examples
1.	Medication having terribly restricted acid solubility.	Diphenylhydantoin
2.	Medication that suffers instability among the gastric environment.	Erythromycin
3.	Medication that are used for selective release in the colon.	Mesalamine and Corticosteroids

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

1. Determination of hardness of tablet:-

Twenty randomly selected tablets from each batch of formulations should be used to determine the hardness using a hardness tester similar to that made by Monsanto.[23]

2. Determination of weight variation:-

Twenty randomly chosen pills are carefully weighed, and the average weight of the tablets is computed. The individual weight divergence from the average weight is then determined.

3. Determination of thickness of the tablet:-

Slide callipers are used to measure the tentablets' specific crown to crown thickness for each batch.[24]

4. Floating lag time:-

It is measured in seconds or minutes and refers to how long it takes the tablet to surface on the dissolve media.[25]

5. Measurement of Floating Capacity:

Three separate tablets are placed in each flask, which contains 400ml of 0.1(N) HCL solutions. The time it takes for each tablet to float continuously on the water's surface is then measured, as well as the time it takes for each tablet to go from the bottom of the flask to the top. After that, the sample mean and standard deviation are computed.[26]

6. Angle of repose:

Angle of repose measurements can be used to determine the frictional forces present in loose powder or grains. This is the greatest angle that may be formed between a pile of powder or grains' surface and the horizontal plane. Granules were permitted to pass through a funnel that was mounted to a stand at a specific height (h). The height and radius of the granule heap created were then measured to determine the angle of repose.[27]

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

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

θ = angle of repose

h = height of the heap

r = radius of the heap

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM:

1. Enhanced Bioavailability:

When compared to the administration of riboflavin CR polymeric formulations without GRDF, the bioavailability of riboflavin CR-GRDF is significantly increased. The amount of medication absorption is influenced by a number of simultaneous mechanisms linked to drug absorption and transit in the gastrointestinal system. (1990, Cook JD et al.)[28]

2. Sustained drug delivery:

Problems with oral CR formulations include gastric residence duration in the GIT. The HBS systems, which can stay in the stomach for extended periods of time and have a bulk density of 1, can solve these issues by allowing them to float on the contents of the stomach. These systems aren't allowed to pass through the pyloric opening because they are relatively larger in size. (2003) (Moursy NM et al.)[28]

3. Site specific drug delivery system:

For medications that are selectively absorbed from the stomach or the closest region of the small intestine, these systems are very beneficial. The medication is delivered to the stomach in a regulated, gradual manner, resulting in adequate local therapeutic levels while limiting systemic exposure. This lessens the drug's adverse effects on the blood circulation. Additionally, a site-directed delivery system may reduce the dosing frequency due to the prolonged gastric availability. Such as riboflavin and furosemide. (1994; Menon A et al.)[28]

4. Absorption Enhancement:

Potential candidates for formulation as floating drug delivery systems include medications with low bioavailability caused by site-specific absorption from the upper section of the GIT. This would maximise their absorption. (2000) Rouge N et al.)[28]

5. Maximize the bioavailability:

Gastro retentive floating drug delivery system is applied for extended the activity of the dosage type, drug to extended action bioavailability is maximized.[29]

6. Minimize the absorption:

The dosage types have less bioavailability specific site absorption from the upper part of GIT, enhancing the absorption of the dosage type.[29]

V. CONCLUSION:

Medication absorption in the gastrointestinal system is a very variable process, and lengthening the dosage form's gastric retention increases the amount of time it takes for the medication to be absorbed. The process of a medicine being absorbed in the gastrointestinal system varies greatly, and the longer the dosage form is retained in the stomach, the longer it will take for the drug to be absorbed. Consequently, gastro retentive dosage forms offer an additional benefit for medications that are absorbed primarily in the upper gastrointestinal tract.

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