FLOATING DRUG DELIVERY SYSTEM A NOVEL APPROACH FOR GASTRO RETENTIVE DRUG DELIVERY

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ABSTRACT

In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. It is known that differences in gastric physiology (such as, gastric pH, motility) exhibit both intra- as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. The methodologies used in the development of FDDS by formulating effervescent and non effervescent floating tablets based on buoyancy mechanism. By utilizing above feasible approaches it is possible to deliver drugs which have narrow therapeutic window. Our review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, preparation, factors affecting on FDDS, advantages, applications, limitations and the future potential of FDDS.

KEYWORDS: Floating Drug Delivery System, Gastric Residence Time, Effervescent, Non effervescent, and Gastro Retentive Dosage Form.
INTRODUCTION
Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.\cite{1, 2} Drugs with short half-lives and drugs that easily absorbed from gastrointestinal tract development of oral sustained-controlled release formulations is an attempt to release (GIT) are eliminated quickly from the systemic circulation. For these types of drugs the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. Floating drug delivery system is an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. This drug delivery system not only prolongs GI residence time but does so in an area of the GI tract that could maximize drug reaching its absorption site in solution and hence ready for absorption. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 min and 2 h. In the fasted state the electrical activity in the stomach, the inter-digestive myoelectric cycle or migrating myoelectriccomplex (MMC) governs the activity and hence the transit of dosage forms. It is characterized by four phases: Phase I–period of no contraction (40–60 min), phase II–period of intermittent contractions (20–40 min), phase III–period of regular contractions at the maximal frequency that travel distally also known as house keeper wave (10–20 min), and phase IV–period of transition between phase III and phase I (0–5 min). Oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. 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. There are many difficulties faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. 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. Controlled gastric retention of solid dosage form may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape system or by simultaneous administration of pharmacological agents which delay gastric emptying.
Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to 2 complications.

I. Short gastric residence time.

II. Unpredictable gastric emptying rate.[5]

Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. 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. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed.[5]

BASIC OF GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[6]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine. Every 2 to 3 hours.[7] This is called the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Wilson and Washington-ton, 1989).[8]

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (pre-burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.\textsuperscript{[9]} Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

**Stomach Physiology**

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.\textsuperscript{[10]}

There are images to four major types of secretory epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands

- Mucous cells: secrete alkaline mucus that protects the epithelium against shear stress and acid.
- Parietal cells: secrete hydrochloric acid.
- Chief cells: secrete pepsin, a proteolytic enzyme.
- G cells: secrete the hormone gastrin. The contraction of gastric smooth muscle serves two basic functions
  - Ingested food is crushed, ground, mixed and liquefying to form Chyme.
  - Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.
Physiology of Gastrointestinal Tract

Fig. No. 1: Physiology of stomach

Gastric Motility

Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility- for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility likely are a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals. Liquid readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing pyloric gatekeeper. The gastric volume is important for dissolution of the dosage form in vivo. The resting volume of the stomach is 25-50 ml. There is a large difference in gastric secretion of normal and achlorhydric individuals. Gastric pH also has pronounced effect of absorption of drug from delivery system. The pH of fasting stomach is 1.2-.2.0 and in fed condition 2.0-6.0.
Gastric Empty Rate

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. The intimate contact of the drug delivery system 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 intestine.[11]

CLASSIFICATION OF DRUG DELIVERY

A. Single Unit Floating Dosage Systems
a) Effervescent Systems (Gas-generating Systems)
b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems
a) Non-effervescent Systems
b) Effervescent Systems (Gas-generating Systems)
c) Hollow Microspheres

C. Raft Forming Systems
A. Single Unit Floating Dosage Systems
a) Effervescent Systems (Gas-generating Systems)

These buoyant systems utilized matrices prepared with swellable polymers like HPMC, 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 12. Excipients used most commonly in these
systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

b) Non-Effervescent Systems
This type of system, after swallowing, swells unrestrained via imbibition 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. Examples of this type of FDDS include colloidal gelbarrier,[12] micro porous compartment system[13], alginate beads[14], and hollow microspheres.[15] Another type is a Fluid- filled floating chamber[16] which includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior.

![Diagram of Gas Filled Floating Chamber](image)

**Fig. No. 2: Gas filled floatation chamber**

The device is of swallowable size, remains afloat within the stomach for a prolonged time and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. A newer self-correcting floatable asymmetric configuration drug delivery system has a 3-layer matrix to control the drug release. This 3-layer principle has been improved by
development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process.

B. Multiple Unit Floating Systems

In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose-dumping. Reports have been found on the development of both non-effervescent and effervescent multiple unit systems.\textsuperscript{[17]} Much research has been focused and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties.

a) Non-effervescent Systems

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported.\textsuperscript{[18]} A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug–polymer ratio.

b) Effervescent Systems (Gas-generating Systems)

There are reports of sustained release floating granules containing tetracycline hydrochloride.\textsuperscript{[19]} The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h. Floating mini capsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa.\textsuperscript{[20]} These mini capsules contain a central core and a
coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO2 release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. A multiple unit system was prepared \(^{21}\) comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system.

Figure 3: (a) Different layers-Semi permeable membrane, Effervescent Layer, Core pill layer

A new multiple type of floating dosage system had developed having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in figure ). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub layers to avoid direct contact between the 2 agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.\(^{[22]}\)
c) Hollow Microspheres

Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® Sand cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. Sustained release floating microspheres using polycarbonate were developed\(^{[23]}\), employing solvent evaporation technique. Aspirin, griseofulvin and p-nitroaniline were used as model drugs. Dispersed phase containing polycarbonate solution in dichloromethane, and micronized drug, was added to the dispersion medium containing sodium chloride, polyvinyl alcohol and methanol. The dispersion was stirred for 3-4h to assure the complete solvent evaporation, and the microspheres obtained were filtered, washed with coldwater and dried. The spherical and hollow nature of the microspheres was confirmed by Scanning electron microscopic studies. The microspheres showed a drug payload of more than 50%, and the amount of drug incorporated is found to influence the particle size distribution and drug release. The larger proportion of bigger particles was seen at high drug loading, which can be attributed to the increased viscosity of the dispersed phase.
C. Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.\(^{[24]}\) (a), 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 has been reported in the literature. The 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 \(F\) is on the higher positive side (Figure 3(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra gastric buoyancy capability variations.\(^{[25]}\)

\[ F = F_{buoyancy} - F_{gravity} = (Df - Ds) gv \]

Where,
MECHANISM OF ACTION

There are various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems, mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (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 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 has been reported in the literature. The 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 F 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.\[25\]

\[
F = F_{buoyancy} - F_{gravity} = (D_f - D_s) \cdot g \cdot v
\]

Where,

F= total vertical force
Df = fluid density
Ds = object density v = volume and
g = acceleration due to gravity
Fig. No. 6: Mechanism of floating system, Gastric Fluid.

**Drug Candidates Suitable for Floating Drug Delivery**

Drugs which have site-specific absorption in the stomach or upper parts of the small intestine (furosemide, riboflavine-5-phosphate), drugs required to exert local therapeutic action in the stomach (antacids, anti-H.pylori agents, misoprostol), drugs unstable in the lower part of Gastro-intestinal tract (captopril), drugs insoluble in intestinal fluids (quinidine, diazepam), drugs with variable bioavailability (satolol HCl).\[^{26, 27}\]

**APPROACHES TO DESIGN FLOATING DRUG DELIVERY SYSTEM**

**Practical approaches in designing FDDS**

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm\(^3\), so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system.\[^{28}\]

**Approaches to Design Single and Multiple Unit Dosage Form**

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.\[^{29}\]

1. **For Single Unit Dosage Forms (Eg: tablets)**
   a) **Floating lag time**
   It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.
b) **In vitro drug release and duration of floating**

This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °C in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the drug content. The time (hrs.) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.

c) **In vivo evaluation for gastro-retention:**

This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc. In low density approaches\[^{30}\] the globular shells apparently having lower density than that of gastric fluid can be used as a carrier like popcorn, poprice, polystrol for the drug for its controlled release. The polymer of choice can be either Ethyl cellulose or HPMC. Depending on type of release desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid filled floating chamber type of dosage forms includes incorporation of a gas filled floatation chamber in to a micro porous component that houses as a reservoir having apertures present at top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug.

2) **Hydro Dynamically Balanced 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.\[^{31}\]

3) **For Multiple Unit Dosage Forms (Eg: microspheres)**

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the multiple unit dosage forms a real so evaluated for

(i) Morphological and dimensional analysis with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.
(ii) In vitro floating ability (Buoyancy %): A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a desiccators and weighed. The buoyancy is calculated from the following formula.

Buoyancy (%) = \( \frac{W_f}{W_f + W_s} \times 100 \)

Where,

Wf andWs are the weights of floating and settled microspheres respectively.

Drug-excipient (DE) interactions: This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicates the DE interaction. Apart from the above mentioned evaluation parameters, granules are also evaluated for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy.

METHOD OF PREPARATION OF FLOATING EFFERVESCENT TABLET

- By direct compression
- By wet granulation
- Dry Granulation

**Wet Granulation**

This technique is most widely used and most general method for preparation of tablets. The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (Crystal water of citric acid, liquid water, or water vapour) ethanol (Possibly diluted with water), isopropanol, or other solvents. When granulating either with solvents containing water or pure water, the effervescent reaction will start. Care must be taken to maintain adequate control of the process. Vacuum processing is often beneficial due to the ability to control the effervescent reaction and the drying process.

**Dry Granulation**

When ingredients used in tablet formulation is sensitive to moisture then slugging may use. Slugging of the material is done by using heavy-duty tableting equipment or with roller compaction.
Direct Compression

In Direct compression vehicles can be used which are having good free-flowing properties no segregating and are having compressible mixture. Direct compression technique buoyancy gravity is mainly used in the formulation of floating effervescent tablet and for all moisture sensitive products.

FACTORS AFFECTING THE FLOATING DRUG DELIVERY SYSTEM

a) **Nature of Meal:** Motility pattern of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and because of this the gastric emptying rate is decreased and drug release is prolonged.\(^\text{31}\).

b) **Frequency of Feed:** when successive meals are given, the GRT can increase by over 40 minutes compared with a single meal because of the low frequency of migrating myoelectric complex.

c) **Gender:** Mean GRT of a male in meals (3.4±0.4 hours) is less compared to the female of the same age and race (4.6±1.2 hours), regardless of the height, weight and body surface of the two.

d) **Age:** Elderly people have a significantly longer GRT, especially those who are over 70 years of age.

e) **Fed and Unfed State:** Under fasting conditions, the GI motility is characterised by periods of strong motors activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweep sun digested material from the stomach and, if the timing of the 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.

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

g) **Size** – Dosage form unit with a diameter of more than 7.5mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm.
h) **Shape of dosage form** – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

i) **Single or multiple unit formulation** – Multiple unit formulations show a more predictable 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 form.

j) **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

k) **Posture** – GRT can vary between supine and upright ambulatory states of the patient (Well LJ et.al. 1998).

l) **Concomitant drug administration** – Anticholinergic like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.

m) **Biological factors** – Diabetes and Crohn’s disease.

The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. The author studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process in vivo using gamma scintigraphy (51). To perform the studies, floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated. On comparison of floating and non-floating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling and retro pelling waves of the digestive phase. It was also observed that of the floating and non-floating units, the floating units were had a
longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms.

![Stomach Diagram](image)

**Fig. No. 7: In vivo picturisation of various gastro retentive formulations**

When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention. A comparison was made to study the affect of fed and non-fed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

**MARKETED PRODUCTS OF FLOATING DRUG DELIVERY SYSTEM**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Products</th>
<th>Active Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Madapar</td>
<td>Levodopa and benserzide</td>
</tr>
<tr>
<td>2</td>
<td>Valrelease</td>
<td>Diazepam</td>
</tr>
<tr>
<td>3</td>
<td>Topalkan</td>
<td>Aluminum Magnesium Antacid</td>
</tr>
<tr>
<td>4</td>
<td>Almagate</td>
<td>Flatcoat Antacid</td>
</tr>
<tr>
<td>5</td>
<td>Liquid gavison</td>
<td>Alginic acid and sodium Bicarbonate</td>
</tr>
<tr>
<td>6</td>
<td>Cytotec</td>
<td>Misoprostol</td>
</tr>
<tr>
<td>7</td>
<td>Conviron</td>
<td>Ferrous sulphate</td>
</tr>
</tbody>
</table>

**MARKETED PRODUCTS OF FLOATING DRUG DELIVERY SYSTEM TABLE NO.1**

**EVALUATION OF FLOATING DRUG DELIVERY SYSTEM**

There are different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behaviour show prolonged gastric residence in
vivo. However, it has to be pointed out that good in vitro floating behaviour alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

**In-vitro evaluation of floating tablets**
Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

**I. Pre-compression parameters**

**a) Angle of Repose**
The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Shown in fig -

![Angle of Repose](image)

*Fig. No.8: Angle of repose*

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

\[
\tan = \frac{h}{r}
\]

\[\theta = \tan^{-1} \left(\frac{h}{r}\right)\]

\[\theta = \text{angle of repose}\]

h = height of the heap

r = radius of the heap
The relationship between Angle of repose and powder flow is as follows in table - 2.

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Powder flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

b) Compressibility Index

The bulk volume and tapped volume was measured and compressibility index was calculated using the formula (Aulton, 2003).

Compressibility index = 100 \((V_o-V_f)/V_o\) Equation IV

Where,

\(V_o\) = Bulk volume
\(V_f\) = Tapped volume

II. Post-Compression Parameter

a) Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.\(^{[32]}\)

d) Friability test

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The % friability was then calculated by\(^{[33]}\) – \(\%\) of Friability = 100 \((1-W_0/W)\)
e) **Tablet Density**

Tablet density was an important parameter for floating tablets. The tablet would float only when its density was less than that of gastric fluid (1.004). The density was determined using the following relationship:\[^{[34]}\]

\[
V = \pi r^2 h \quad d = \frac{m}{v}
\]

\(v\) = volume of tablet (cc)

\(r\) = radius of tablet (cm)

\(h\) = crown thickness of tablet (g/cc)

\(m\) = mass of tablet

f) **Weight Variation Test**: Ten tablets were elected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia.

<table>
<thead>
<tr>
<th>Average weight of a tablet</th>
<th>Percent deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 mg or less</td>
<td>10</td>
</tr>
<tr>
<td>&gt;130mg and &lt;324mg</td>
<td>7.5</td>
</tr>
<tr>
<td>324 or more</td>
<td>5</td>
</tr>
</tbody>
</table>

The following percentage deviation in weight variation was allowed as shown in table-3.

g) **Buoyancy / Floating Test**

The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time. It is determined by using USP dissolution apparatus containing 900 ml of 0.1mole/lit HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.\[^{[34]}\]

h) **Swelling Study**

The floating tablets were weighed individually (Designated as W0) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C ± 1°C at a regular 1hr intervals till 24 hrs. The floating tablets are removed from beaker and the excess surface liquid is removed carefully using the tissue paper. The swollen floating tablets were then reweighed (Wt.) and % swelling index (SI) was calculated using the following formula:\[^{[34,35]}\]

\[
\text{Swelling index} \% (SI) = \left(\frac{\text{Wt.} - \text{W0}}{\text{W0}}\right) \times 100
\]

Where,
S.I. = Swelling index  
Wt. = Weight of tablet at time t  
Wo = Weight of tablet before placing in the beaker.

i) In vitro Dissolution Studies
The In vitro dissolution study was performing by using a United States Pharmacopeia (USP) type II (Paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl is used as the dissolution medium and the temperature was maintained at 37°C ± 0.5°C. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 hrs and the same volume was replaced with pre-warmed fresh dissolution media. The samples were filtered through a Whatman filter paper and diluted to a suitable concentration of 0.1 N HCl.

j) Drug Release
Dissolution test were performed using dissolution test apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analysed for their drug content after an appropriate dilution.\(^{37,38}\)

k) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads)
Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight and simulated meal, total beads or microspheres. The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope.\(^{38}\)

l) X-Ray/Gamma scintigraphy
X-Ray/Gamma scintigraphy is a very popular evaluation parameter for floating dosage form now a day (Fell and Digenis, 1984). It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a $\gamma$-emitting radionuclide in a formulation
allows indirect external observation using a γ-camera or scinti-scanner (Harries and Sharma, 1990). In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

m) Pharmacokinetic studies
Pharmacokinetic studies are the integral part of the in vivo studies and several works has been on that. The pharmacokinetics studies of verapamil, from the loading pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0–infinity) values (3.75h and 364.65 mg/ml, respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets (tmax value 1.21h, and AUC value 224.22ng/mlh). No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

n) Fourier transform infrared analysis
Fourier transform infrared spectroscopy (FTIR, Shimadzu, Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug loaded polymer formulations were obtained on FTIR. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm²; the spectra were scanned over the wave number range of 3600 to 400 cm⁻¹ at the ambient temperature.[39]

o) Differential Scanning Calorimetry (DSC)
DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25°C – 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min.[39]
p) Surface topography
The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profile meter.[40]

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

- Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids
- FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
- Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro esophageal reflux.
- Ease of administration and better patient compliance.
- Site-specific drug delivery.
- Enhanced absorption of drugs which solubilize only in stomach
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- FDDS improves patient compliance by decreasing dosing frequency.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
- Better therapeutic effect of short half-life drugs can be achieved.
LIMITATION OF FLOATING DRUG DELIVERY SYSTEM

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
- 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.
- These systems also require the presence of food to delay their gastric emptying.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosal not suitable to be formulated as floating drug delivery systems.
- Gastric emptying of Floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.\(^{[41]}\)
- The dose should be taken with a full glass of water.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

APPLICATION OF FDDS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

a) Sustained Drug Delivery

HBS systems 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 CR formulation hence can be overcome with these systems. These systems have a bulk
density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

b) Site-Specific Drug Delivery
These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and Furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was in-creased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional Furosemide tablets.

Absorption Enhancement
Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. E.g. A significantly increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).[42]

Enhanced Bioavailability
The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.[43]

Minimized adverse activity at the colon
Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for beta lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism’s resistance. Reduced fluctuations of drug concentration: Continuous input of the drug following CRGRDF administration produces blood drug concentrations With in a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent
adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.\textsuperscript{[44]}

**Future Potential**

Gastro-retentive floating drug delivery system offers various future potential as evident from several recent publications. Drug absorption in the gastrointestinal tract is highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Among the recently used clinical drugs several narrow absorption window drugs may benefit from compounding into a FDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment. It may be believed that it can be possible with FDDS. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. Buoyant delivery system is also considered as a beneficial strategy for the treatment of gastric and duodenal cancers. The floating concept can be utilized in the development of various anti-reflux formulations. Developing a controlled release system for drugs which are potential to treat the Parkinson’s disease, is also an important area of consideration.

**CONCLUSION**

GRDDS (FDDS) offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper GIT and they can be delivered efficiently thereby maximizing their absorption and enhancing bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, swelling and expanding systems, bioadhesive systems, ion exchange systems, high density systems and other delayed gastric emptying excipient. Floating tablets provide a dosage form which is stable and provides a sustained release drug delivery. Now a day’s lot of work is running to develop different types of gastroretentive delivery systems of various drugs. Day by day the FDDS shows more promise for a bright future.

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