

Floating Drug Delivery System – An Approach To Oral Controlled Drug Delivery

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Abstract: The design of oral controlled drug delivery systems (CDDS) should primarily aimed at achieving more predictable and increased bioavailability of drugs. Placing of DDS in specific region of the GIT offers numerous advantages, specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon. Recent scientific and patent literature has shown increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. GRDFs are designed on the basis of one of the several approaches like formulating low density dosage form that remain buoyant above gastric fluid (Floating Dosage Form) or high density dosage form that is retained at bottom of the stomach, imparting bio-adhesion to the stomach mucosa, reducing motility of the GIT by concomitant administration of drugs or pharmaceutical excipients, expanding the dosage form by swelling or unfolding to a large size which limits the emptying of the dosage form through the polymeric sphincter, utilizing ion – exchange resin which adheres to mucosa, or using modified shape system. This review article focuses on the current technological development in FDDS with special emphasis on its potential for oral controlled drug delivery.

Keywords: Bioavailability, absorption window, floating, bio-adhesion, ion–exchange, modified shape.

INTRODUCTION^[1, 2]

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. The design of oral controlled drug delivery systems (CDDS) should primarily aimed at achieving more predictable and increased bioavailability of drugs. However the developmental process is precluded by several physiological difficulties such as inability to restrain & locate the CDDS within the desired regions of GIT due to various gastric emptying & motility. The gastric emptying process can vary from a few minutes to 12 hrs. This

mainly lead to unpredictable time for peak plasma levels & bioavailability, therefore CRDFs not suitable for various important drugs and is characterized by a narrow absorption window in the upper part of GIT which is a relatively short transit time of DFs in this anatomical segments in period of less than 6 hrs. Such drugs leave the upper part of GIT and reaches non-absorbing distal segment.

Furthermore, the relative gastric emptying time (GET) which is normally 2 to 3 hrs. Through the major absorption zone (stomach or upper part of intestine), and can result in incomplete drug released from the DDS leading to diminished efficacy of the administered dose. Therefore

placing of DDS in specific region of the GIT offers numerous advantages, specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon^[1].

Recent scientific and patent literature has shown increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for this in the GIT is to control gastric residence time (GRT) using gastroretentive dosage forms (GRDFs) that will provide us with new and important therapeutic options. GRDFs are designed on the basis of one of the several approaches like formulating low density dosage form that remain buoyant above gastric fluid (Floating Dosage Form) or high density dosage form that is retained at bottom of the stomach, imparting bio-adhesion to the stomach mucosa, reducing motility of the GIT by concomitant administration of drugs or pharmaceutical excipients, expanding the dosage form by swelling or unfolding to a large size which limits the emptying of the dosage form through the polymeric sphincter, utilizing ion – exchange resin which adheres to mucosa, or using modified shape system.

From the formulation and technological point of view, floating drug delivery system (FDDS) is considerably easy and logical approach in development of GRDFs. Hence, this review article focuses on the current technological

development in FDDS with special emphasis on its potential for oral controlled drug delivery.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY^[3,4]:-

Anatomically the stomach is divided in to three regions: Fundus, Body and Antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs which is called as interdigestive myoelectric cycle or migrating myoelectric cycle (MMC) which is further divided in to four phases. 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.

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 also known as housekeeper wave.
4. Phase 4-last for 0-5 minutes and occurs between phase 3 and phase 1 of 2 consecutive cycles.(Period of transition).

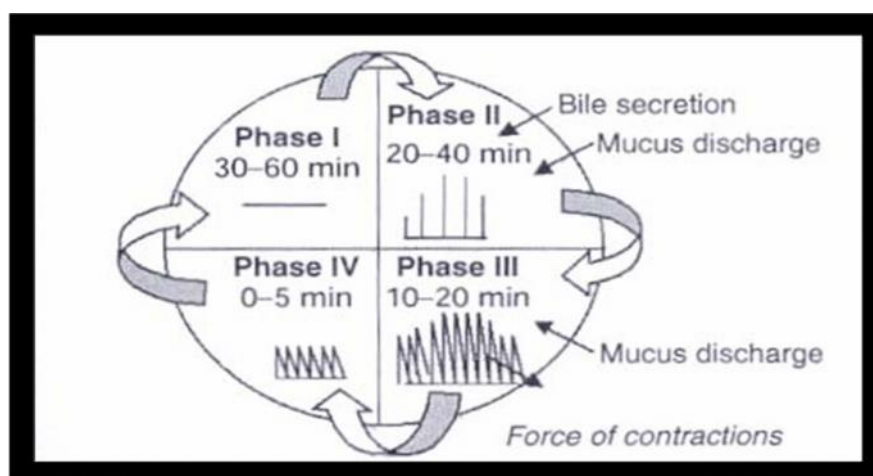


Fig. 1: Motility pattern in GIT

FACTORS AFFECTING THE GASTRORETENTIVE SYSTEM^[5,6]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of 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. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system.

- **Density** – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- **Size** – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape of dosage form** – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. (Caldwell et al., 1998; Murthy et al., 2000).
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content** – GRT can be increased by 4 to 10 hours with a meal that is high in proteins

and fats (Marvola et al., 1989) (Mojaverian et al., 1988).

- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.
- **Biological factors** – Diabetes and Crohn's disease, etc.

APPROACHES TO DESIGN FLOATING DOSAGE FORMS^[7]:-

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

❖ Single-Unit Dosage Forms:-

In Low-density approach the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells 24 popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugarpolymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture.

The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the 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 into a microporous 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. 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.

Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlorthalidone hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlorthalidone hydrochloride is 150 mg/mL and is ~0.1 mg/mL at neutral pH).

The 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. The system was designed in such a manner that it floated to prolong gastric residence time in vivo, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

❖ **Multiple-Unit Dosage Forms^[7,8]**

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the disadvantages of single-unit formulations. Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of prodanger of producing irritation. Multiple unit systems avoid the “all-or-none” gastric emptying nature of single unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lower. In pursuit of this endeavour many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microspheres, also referred to as “microballoons,” have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide-generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

(A) Non-effervescent systems

i. Colloidal gel barrier systems^[9]

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20-75% w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

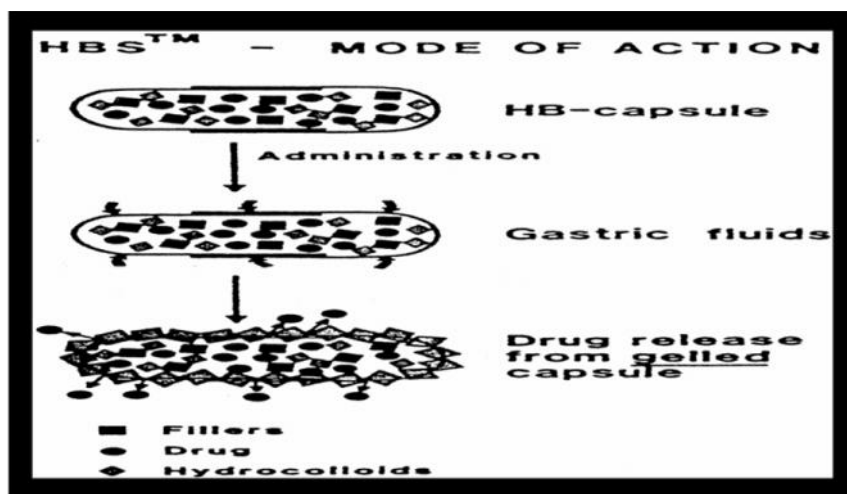


Fig.2: Hydrodynamically balanced system (HBS).

ii. Micro porous compartment systems^[10]:-

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.

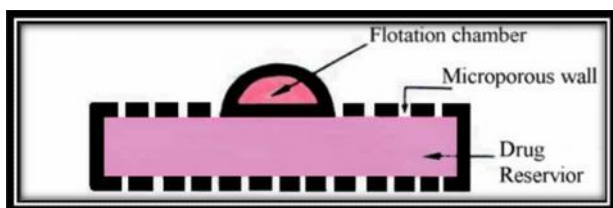


Fig.3: Gas filled floatation chamber

iii. Multiparticulate system: Floating Beads^[10]

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi- particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet.

iv. Microballoons^[10]:-

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric microballoons as carrier for drugs. Hollow microspheres are known as the microballoons. Microballoons were floatable in

vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movements.

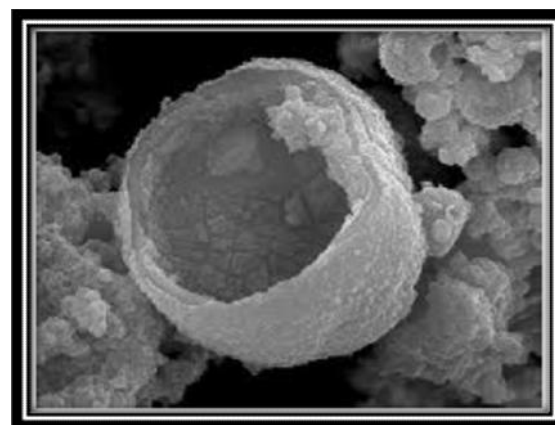


Fig.4: Floating hollow microsphere or microballoon

(B) Effervescent systems:

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

i. Volatile liquid containing systems^[9]:-

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

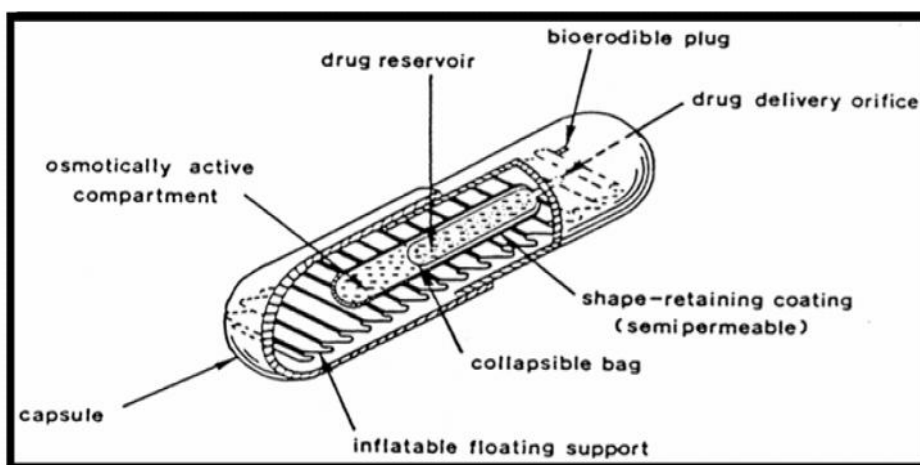


Fig.5: Intragastric osmotic controlled drug delivery system

ii. Gas generating systems^[9, 10]:-

These buoyant delivery systems utilize an effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over time. These are formulated by intimately mixing the CO₂ generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

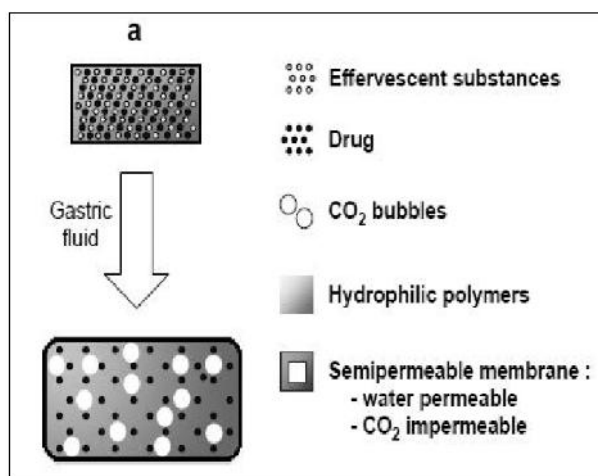


Figure 6: Gas generating system: schematic monolayer drug delivery system

RECENT WORK ON FLOATING DRUG DELIVERY SYSTEM:-

- ❖ **Sandra Strubing** et al studied the mechanism of floating and drug release behaviour of poly(vinyl acetate)-based floating tablets with membrane controlled drug delivery of Propranolol HCl containing tablets with Kollidon SR as an excipient for direct compression and different Kollicoat SR 30 D/Kollicoat IR coats. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics and remained afloat until the end of the monitored 24 h time interval.
- ❖ **Srisagul S** et al developed a multiple-unit floating drug delivery system based on gas formation technique in order to prolong the gastric residence time and to increase the overall bioavailability of the dosage form of anhydrous theophylline. Drug-containing core pellets prepared by extrusion-spheronization processes, which are coated with double layers of an inner effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of an aqueous colloidal polymer dispersion (Eudragit® RL 30D, RS 30D, NE 30D). The optimum system floated completely within 3 min and maintained the buoyancy over a period of 24 h.
- ❖ **P.S. Rajinikanth** et al developed a new intra-gastric floating **in situ gelling system** for controlled delivery of amoxicillin for the treatment of peptic ulcer disease caused by Helicobacter pylori (H. pylori). Gellan based amoxicillin floating in situ gelling systems (AFIG) were prepared by dissolving varying concentrations of gellan gum in deionized water. The results substantiated that the prepared AFIG has feasibility of forming rigid

gels in the gastric environment and eradicated *H. pylori* from the gastrointestinal tract more effectively than amoxicillin suspension because of the prolonged gastrointestinal residence time of the formulation. The in situ gelling system floated completely within 2 min and maintained the buoyancy over a period of >24 h.

- ❖ **Praneeth Kumar Siripuram** et al formulated floating sustained-release matrices of metoprolol succinate using Gelucire 43/01 and Gelucire 44/14 by a melt-solidification technique. The in vitro and in vivo characteristics of the prepared matrices were evaluated. The in vitro drug release studies performed in 0.1 N HCl revealed a proportional increase in drug release pattern with increased concentration of Gelucire 44/14. The in vitro floating characteristics of Gelucire matrices were greater than 12 h with good in vivo gastric retention
- ❖ **J Josephine LJ** et al prepared and evaluated the floating **microspheres** of stavudine as a model drug by emulsion solvent diffusion method using Eudragit RS 100 as a rate controlling polymer for prolongation of gastric retention time for oral delivery. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 12 hrs.
- ❖ **Frances Stops** et al studied was the in vivo behavior of the radio-labelled **calcium alginate beads** when they were administered under fasting conditions with either water or an aqueous solution of citric acid, a potential gut transit delaying substance. The study was performed in healthy male volunteers who swallowed the radio-labelled calcium alginate beads after a 10 h overnight fast. Gamma scintigraphy monitored the movement of the calcium alginate beads. Prolonged gastric retention was achieved when the dosage form was administered with the citric acid solution when compared to retention in the absence of citric acid.
- ❖ **Mahalaxmi Rathnanand** et al formulated and evaluated (in vitro) **floating-pulsatile tablets** of Nizatidine, a H₂ receptor antagonist, which conceptualizes a specific technology, based on combining principles of both the floating and pulsatile principles to deliver a

programmed dose of drug from the developed delivery system anticipated for chronotherapy of excessively secreted gastric acid and for promoting healing of duodenal ulcers. The floating behavior of optimized formulation which was found to be floating for more than five hours.

- ❖ **Mukhopadhyay S** et al formulated **floating-bioadhesive tablets** to increase the stay period of drug in its absorption area of Ciprofloxacin hydrochloride. The effervescent base was prepared by using 1:1 ratio of sodium bicarbonate and citric acid. Increasing the effervescent base of tablets from 5% to 10% significantly lower the lag time of floating as well as floating duration. Floating-bioadhesive tablets of ciprofloxacin hydrochloride increased the gastric residence time as well as bioavailability.
- ❖ **J. Goole** et al developed and the in vitro evaluated **sustained-release minitablets (MT)**, prepared by melt granulation and subsequent compression, which were designed to float over an extended period of time. The importance of the composition and manufacturing parameters of the MT on their floating and dissolution properties was examined. The investigation showed that MT composition and MT diameter had the greatest influence on drug release, which was sustained for more than 8 h.

ADVANTAGES OF FLOATING DRUG DELIVERY^[11]:-

- ❖ Enhanced bioavailability
- ❖ Sustained drug delivery/reduced frequency of dosing
- ❖ Targeted therapy for local ailments in the upper GIT
- ❖ Reduced fluctuations of drug concentration
- ❖ Improved receptor activation selectivity
- ❖ Reduced counter-activity of the body
- ❖ Extended time over critical (effective) concentration
- ❖ Minimized adverse activity at the colon
- ❖ Site specific drug delivery

LIMITATIONS^[12]

- ❖ These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- ❖ Not suitable for drugs that have solubility or stability problem in GIT.
- ❖ Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- ❖ Drugs which are irritant to gastric mucosa are also not suitable.
- ❖ The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- ❖ The dosage form should be administered with a full glass of water (200-250 ml).
- ❖ These systems are not advantageous over the conventional dosage forms for those drugs, which are absorbed throughout the gastrointestinal tract.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS:-

Various parameters that need to be evaluated in gastroretentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

1. Buoyancy / Floating Test^[13,14]:-

The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaCl with 0.02% Tween 80, pH 1.2) or intestinal fluids (KH₂PO₄/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 37°C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m²). The amount of time the dosage form floats is termed the floating time. In the case of floating microparticles, the number of floating particles and the time during which they remain buoyant on the test solution can be determined. The floating process depends on the balance between the weight and volume of the dosage form. An increase in the buoyancy force caused by the increased volume causes a resultant weight increase and leads to dosage-form flotation.

2. Swelling Study^[13,14]:-

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet

diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{(W1 - W0) \times 100}{W0}$$

W0

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form

3. In Vitro Drug Release Studies^[13,14,15]:-

The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900 mL of 0.1 HCl as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time.

Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug content after an appropriate dilution.

Recently Gohel et al proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 mL of 0.1 mole/lit HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 mL/min to mimic gastric acid secretion rate.

The performance of the modified dissolution apparatus was compared with USP dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level. The proposed test may show good in vitro-in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

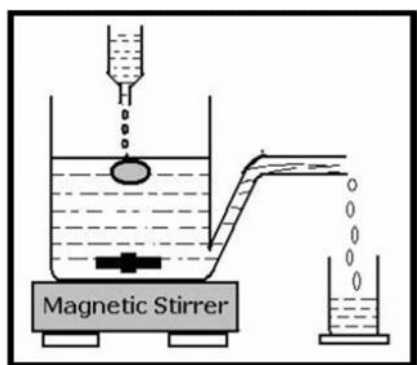


Fig.7: In vitro dissolution method

4. Resultant weight test^[13,14]:-

An in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid.

This force determines the resultant weight of the object when immersed and may be used to quantify its floating or non-floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the object as shown in the equation

$$F = F_{\text{buoy}} - F_{\text{grav}}$$

$$F = d_f g V - d_s g V = (d_f - d_s) g V$$

$$F = (d_f - M/V) g V$$

in which F is the total vertical force (resultant weight of the object), g is acceleration due to gravity, d_f is the fluid density, d_s is the object density, M is the object mass, and V is the volume of the object.

By convention, a positive resultant weight signifies that the force F is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force F acts downward and that the object sinks.

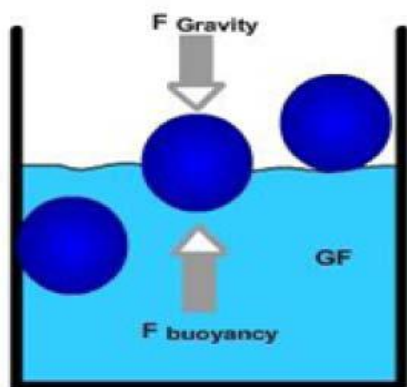


Fig.8: Effect of various forces on floating system

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the

multiple unit dosage forms are also evaluated for^[16]:-

(i) **Morphological and dimensional analysis** with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

(ii) **% yield of microspheres:**

$$\frac{\text{Weight of microspheres obtained} \times 100}{\text{Total weight of drug and polymer}}$$

(iii) **Entrapment efficiency:**

$$\frac{\text{Practical amount of drug present} \times 100}{\text{Theoretical drug content}}$$

In vivo methods:-

1) X-Ray method/gamma-Scintigraphy^[15, 16]:-

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day⁴⁰. It helps to locate dosage form in the g.i.t. 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 γ -emitting radio-nuclide in a formulation allows indirect external observation using a γ -camera or scintiscanner⁴¹. In case of γ -scintigraphy, the γ -rays emitted by the radio-nuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

2) Pharmacokinetic studies^[17]:

Pharmacokinetic studies are the integral part of the in vivo studies and several works have been on that. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The t_{max} and AUC (0-infinity) values (3.75 h and 364.65 ng.ml-1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (t_{max} value 1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the C_{max} 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.

APPLICATIONS^[9]:-

1. 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.

2. 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.

3. 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.

RECENT ADVANCEMENT IN FDDS:-

1. Osmotic Regulated systems^[9]

It is comprised of osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastricosmotically controlled drug delivery device. The inflatable support inside from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to be inflates the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotic ally active compartment

2. PVA-PVP Spray Dried Tablets^[16]

These tablets shows immediate floating with almost no lag time, floating for 24 hr and do not sink. No swelling and erosion takes place in the GIT, so the release does not depend upon osmolarity of the medium. Buoyancy in such system is due to high porosity in the tablet. The exceptionally good compressibility of spray dried PVA-PVP combination makes it possible to

produce mechanically stable oral DF, even with extremely low pressure

3. Ion exchange resins Beads^[19]

A coated ion exchange resin bead formulation has been shown to have gastric retention properties which were loaded with bicarbonates. Ion exchange resins were loaded with bicarbonate and a negatively charged drug is bound to the resin. The resulted beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to uncoated beads, which will sink quickly.

4. Micro particles^[20]

This approach is based on low-density foam powder. This system is advantageous because of its zero to negligible lag time before starting of floatation. These floating microcapsules prepared by emulsion solvent evaporation technique, contain polypropylene foam powder, polymers and model drug. Drug release increases rate significantly increases with different types of polymers.

5. Lipid based sustained release matrix systems^[21,22]

Floating glycerol monooleate single-unit lipid matrix containing high drug: excipients ratio achieved sustained drug release. Hydrophobic lipid, gelucire 43/01 can be considered as an effective carrier for design of multiple –unit FDDS of highly water-soluble drugs.

6. Chitosan granules/Microcapsules^[23]

These are prepared by de-acidification process. When added to acidic and neutral media these granules were immediately buoyant and provide a controlled release of the drug. Laminated preparations can be prepared by coating with chitosan granule layer with chitosan membrane. These preparations buoyant and provide sustained release.

7. Floating Rafts^[4, 24]

Floating Rafts are used in the treatment of gastric oesophageal reflux. This raft formulation based on an alginate biopolymer. On ingestion, this formulation reacts with gastric acid to form floating raft structure, which impedes the reflux of acid and food by acting as a physical barrier. The raft has a pH value higher than that of the stomach

contents so that in the event of gastric reflux, the wall of the oesophagus is not subjected to irritation by HCl. Such formulation on entering the stomach forms a colloidal gel. Sodium alginate solution reacting with gastric acid and this gel floats on the surface of the gastric contents due to CO₂ generation by gas generating excipients impeding reflux of acid into the oesophagus.

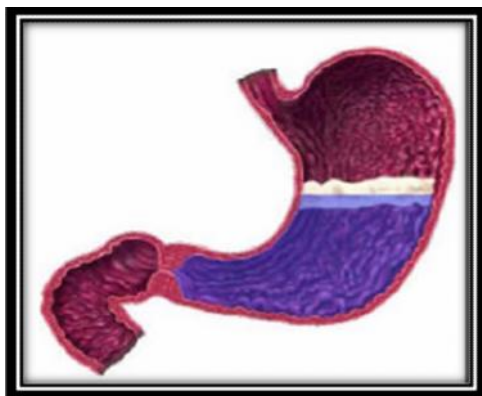


Fig.9: Barrier formed by a raft-forming system

7. Multiple unit floating pill^[25]

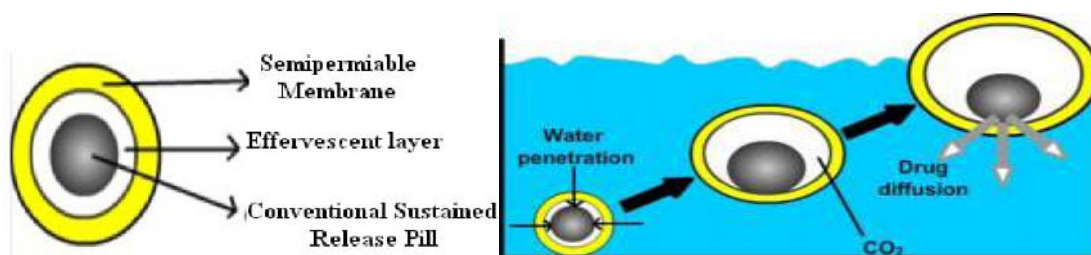


Figure 10: A) Multiple unit floating pill B) Mechanism of floatation via CO₂ generation

Table.1 Patents on GRDDS^[13]

Sr.No.	US Patent NO	YEAR	Patent Title
1	20100015224	2010	Programmable buoyant delivery technology.
2	20100286660	2010	Gastroretentive duodenal pill
4	20090324694	2009	GRDDS comprising an extruded hydratable Polymer
5	20080220060	2008	Gastroretentive formulations & manufacturing process
6	20060013876	2006	Novel floating dosage form

The system consisted of sustained- release pills as seeds surrounded by double layers. The inner layer was an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided and finally air-dried. The results into two sublayers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sublayer and of tartaric acid was in the outer layer. When the system was immersed in a buffer solution at 37°C, it sank at once in the solution and formed swollen pills, like balloons, with a density much lower than 1 g/ ml. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layers with the diffusion of water through the outer swellable membrane layers. The system float completely within 10 min and approximately 80% remained floating over a period of 5hr.

Marketed Products of FDDS^[13]**Table 2: Generally Manufactured Marketed Product**

S.No	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	REMARKS
1.	Modapar®	Levodopa(100mg), Benserazide(25 mg)	Roche Products, USA	Floating CR capsule
2	CifranOD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas generating Floating tablet
3	Valrelease®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating Capsule
5	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent floating Liquid alginate preparation
6	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
7	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid Alginate preparation

Table 3. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems^[33]

Tablets	<ul style="list-style-type: none"> • Chlorpheniramine maleate • Theophylline • Furosemide • Ciprofolxacin • Pentoxifyllin • Captopril • Acetylsalicylic acid • Nimodipine • Amoxycillintrihydrate • Verapamil HCl • Isosorbide dinitrate • Sotalol • Atenolol • Isosorbide mononitrate • Acetaminophen • Ampicillin • Cinnarazine • Diltiazem • Florouracil • Piretanide • Prednisolone • Riboflavin- 5' Phosphate
Capsules	<ul style="list-style-type: none"> • Nicardipine • L-Dopaandbenserazide • Chlordiazepoxide HCl • Furosemide • Misoprostal • Diazepam • Propranolol • Urodeoxycholic acid
Microspheres	<ul style="list-style-type: none"> • Verapamil

	<ul style="list-style-type: none"> • Aspirin, griseofulvin, and p-nitroaniline • Ketoprofen • Tranilast • Ibuprofen • Terfenadine •
Granules	<ul style="list-style-type: none"> • Indomethacin • Diclofenac sodium
Films	Cinnarizine

CONCLUSION:

Floating drug delivery systems have plenty of advantages over the other drug delivery system. As floating drug delivery system provides a dosage form which is stable and provides a sustained release. The principle of hydrodynamically balanced systems preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The most important criteria which has to be looked into for the productions of a floating drug delivery system

is that the density of the dosage form should be less than that of gastric fluid and so, it was seen that FDDS serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. Day after day the FDDS shows more promise for a bright future.

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