Volume 3, Issue1, January 2012
Available Online at www.ijppronline.com
International Journal Of Pharma Professional's Research
Review Article

ISSN NO:0976-6723

GASTRO-RETENTIVE BUOYANT FLOATING DRUG DELIVERY SYSTEM: A REVIEW

Navpreet Kaur*

Chandigarh college of Pharmacy, Landran Chandigarh

Abstract

A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that i) are locally active in the stomach, ii) have an absorption window in the stomach or in the upper small intestine, iii) are unstable in the intestinal or colonic environment, or iv) exhibit low solubility at high pH values. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention.This review covers all the aspects related to gastric retention such as basic GIT (gastrointestinal tract) physiology,factors affecting gastric retention time. This article also covers recent approaches to gastric retention as well as in vivo-in vitro parameters of stomach specific FDDS.

Keywords: - Gastroretentive dosage forms, floating drug delivery system, gastrointestinal tract.

Introduction

Despite tremendous advancements in drug delivery (1), oral route is the most convenient and prefer means of any drug delivery to systemic circulation as it provides improved therapeutic advantages such as ease of administration,patient compliance and flexibility in formulations (2). Effective oral drug delivery process depends upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs (3).Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed (4). However, the short gastric retention time and unpredictable rapid gastric rate can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to decreased therapeutic efficacy of administered dose (5).To increase the GRT of drugs, a gastroretentive dosage form(GRDF) can be developed. Dosage form with a prolonged GRT i.e gastroretentive dosage form will provide us with new and important therapeutic options (6).

Correspondence Address:
Navpreet Kaur
Chandigarh college of Pharmacy, Landran Chandigarh (India)
E-mail: Navpreet27dec@gmail.com
Ph. no.: +91-07837865665

Gastroretentive drug delivery system

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastricresidence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment (7). The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of floating drug delivery system (FDDS), mucoadhesivesystem, sedimentation system, expansion modified shape systems or by the simultaneous administration of pharmacological agent that delay gastric emptying (8). Among these systems, FDDS have been most commonly used. Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability (9).

Basic gastrointestinal tract physiology

Anatomically the stomach is divided into 3 regions fundus, body and antrum (pylorus)(10). The proximal

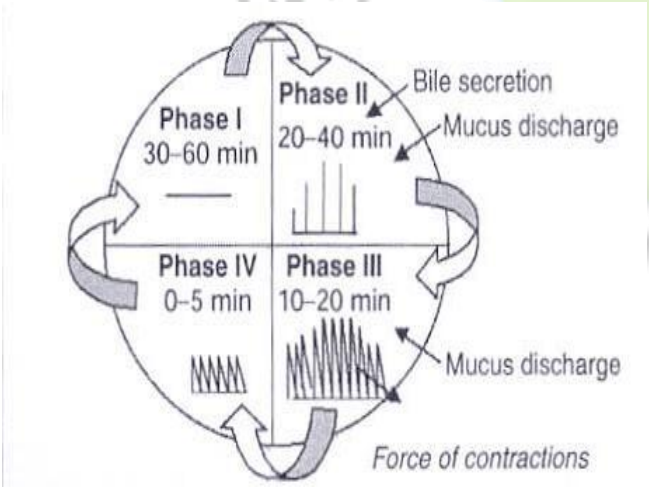
stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying (11). Gastric emptying occurs during fasting as well as fed state (12). During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours(13).This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (14).The concentration of the hormone motilin in the blood controls the duration of the phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions (15).

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually (16).

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 (17).

Phase IV- lasts for 0 to 5 minutes and occurs between phases IIIand I of 2 consecutive cycles (18).



Factors affecting gastric retention time:

Density: GRT is a function of dosage form buoyancy that is dependent on the density of adosage form which affects the gastric emptyingrate (19). A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period (20). A density of $<1.0 gm/cm^3$ is required to exhibit floating property (21).

Size of tablets: The size of the dosage form is another factor that influences gastric retention (22). The mean GRT of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeepingwaves. In most cases, the larger the size of the dosage form, the greater will be the GRT because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine (23). Dosage form units with diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm (24).

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 floating, 90% to 100% retention at 24 hours compared with other shapes (25).

Viscosity grade of polymer: Drug release and floating properties of FDDS are greatly affected by viscosity of polymer and their interaction. Low viscosity polymer (HPMC K100 LV) was found to be more beneficial than high viscosity polymer in improving floating property. In addition, decrease in the release rate was absorbed with increase in polymer viscosity.

Gender: Generally women have slower gastric emptying time than do men. Mean ambulatory gastro retention time (GRT) in meals (3.4±0.4hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight height and body surface (26).

Age: Low gastric emptying time is observed in elderly than so in younger subjects. Elderly peoples, especially those over 70 years have significantly longer GRT (27).

Posture: GRT can vary between supine and upright ambulatory states of the patient (28).

a) Upright position: Upright position floating forms against postprandial emptying because of floating form remains above the gastric contents irrespective of its size.

b) Supine position: This supine position offers no reliable protection against early and erratic emptying.

In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in the GRT compared with upright subjects.

mucoadhesion. These systems are used to localize a

Concomitant intake of drugs: Drugs such as prokinetic agents (metoclopramide and cisapride) anti cholinergics (atropine) opiates (example codeine) may affect the performance of FDDS. The administration of GI motility decreasing drugs can increase gastric emptying time.

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 (29).

Calorie content: GRT can be increased by 4 to 10 hrs with a meal that is high in proteins and fats (30).

Frequency of feed: The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the MMC (31).

Approaches to gastro retentive drug delivery system:

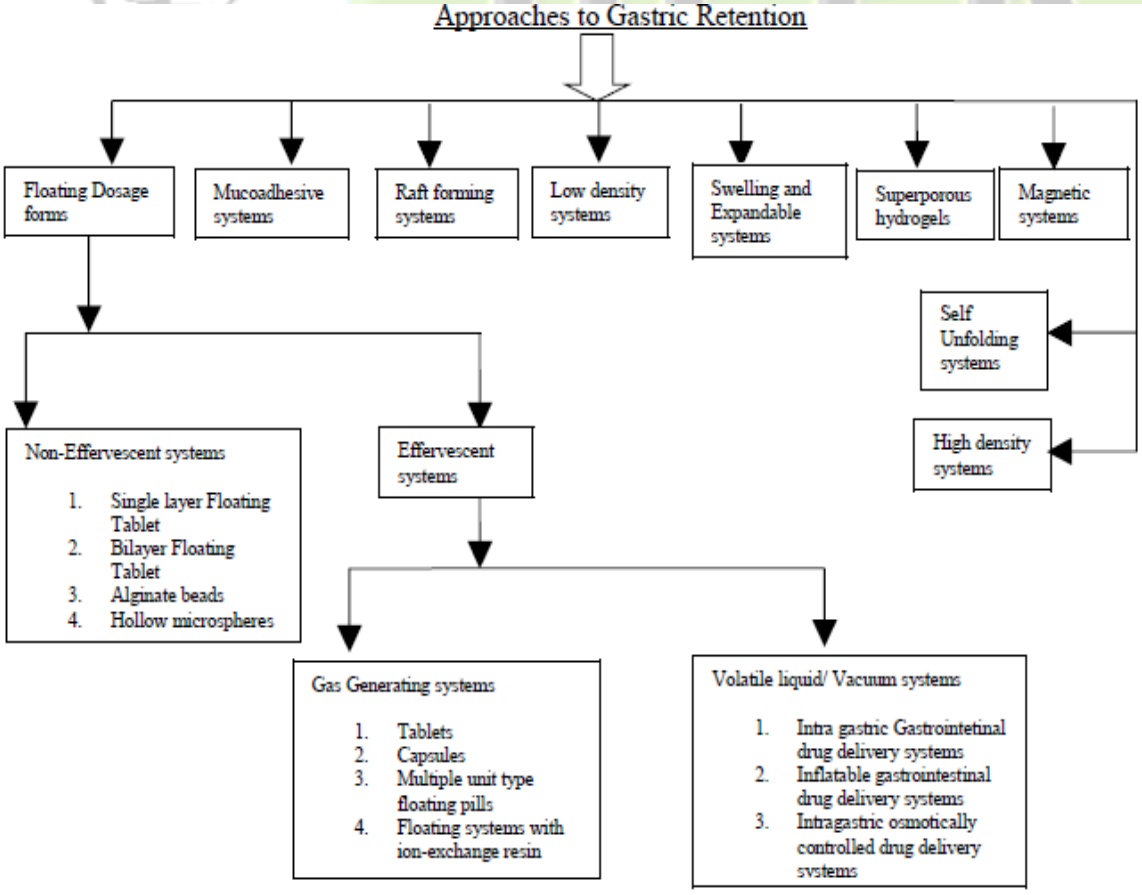
To formulate a successful stomach specific or gastro retentive drug delivery system several techniques are currently used such as:

Bioadhesive or Mucoadhesive systems

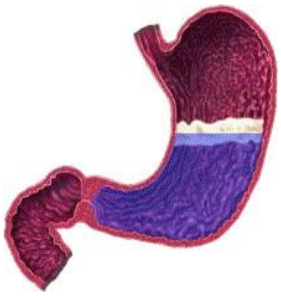
The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as delivery device within the lumen and cavity of the body to increase the drug absorption process in a site-specific manner (32).Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seems to limit the potential of mucoadhesion as a gastroretentive force (33). Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, and CMC, etc

Raft systems incorporating alginate gels

The mechanism involved in the raft formation includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluid because of the low bulk density created by the formation of CO_2 (34).A gel-forming solution (e.g. sodium alginatesolution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid.

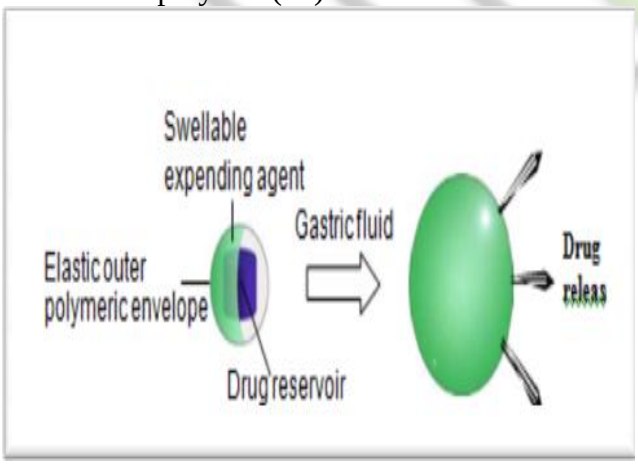


Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.



Swelling type system

These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters (34,35). These polymeric matrices remain in the gastric cavity for several hours even in fed state. By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer (36).



Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10 nm and 10 µm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur.

Superporous hydrogel, average pore size > 100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-Di-Sol (cross carmellose sodium) (32,36).

Magnetic systems

These are the systems which includes external stimuli as magnetic field for site specific delivery. Some magnetically active compounds are incorporated in the dosage form to achieve site specificity (32,35).

Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastro retentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect.

(1) The use of hydrogels swelling in contact with the gastric juice.

(2) Osmotic systems, comprising an osmotic medium in a semipermeable membrane.

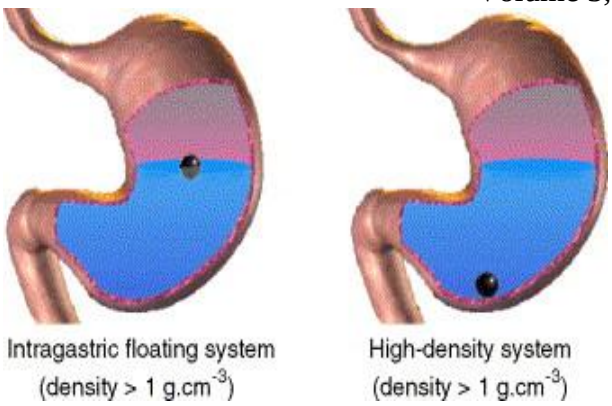
(3) Systems based on low-boiling liquids converting into a gas at the body temperature (36).

Low density approach

Density systems have a density lower than thatof the gastric fluid so they are buoyant (37). In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time.

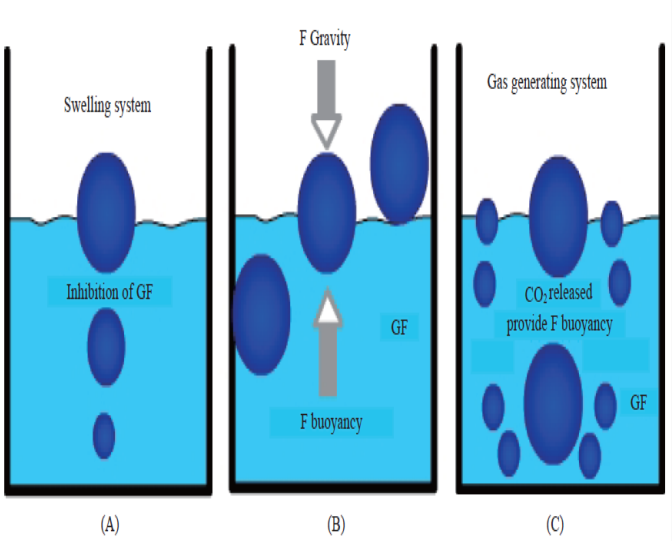
High density systems

This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part of the antrum. They include coated pellets and have density greater than that of the stomach content (1.004 gm/cm3) (35). Commonly used Excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder (26).



Floating drug delivery systems and its mechanism

Floating drug delivery systems or Hydro dynamically controlled systems were first described by Davis in 1968 (38). These systems have a bulk density lower than gastric fluids and thus remain buoyant in thestomach for a prolonged period of time,without affecting the gastric emptying rate of other contents (43,40). While the system is floating on thegastric contents, the drug is releasedslowly at a desired rate from the system.After the release of the drug, the residual system is emptied from the stomach. This results in an increase inthe GRT and a better control offluctuations in the plasma drug concentrations (21).These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. 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.



Composition of floating drug delivery system

1)Drug: Drugs for controlled release gastro retentive dosage forms are molecules that have poor colon absorption but are characterized by better absorption properties at the upper parts of the GIT.

Drugs that can be formulated as FDDS are the one that have narrow absorption window in GIT (eg:L-DOPA,furosemide,riboflavin) that are basically absorbed from stomach and upper part of GIT (eg:cinnarizine and chlordiazepoxide) that are locally active in the stomach (eg: misoprostol and antacids) that exhibit low solubility at high pH values (eg:diazepam,verapamil) those are unstable in the intestinal or colonic environment (eg:captopril, ranitidine HCl, metronidazole) that disturb normal colonic microbes (eg:antibiotics used for eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin) (41).

2) Polymer: Polymer act as a carrier for drug. The property of polymer has a major influence on the dissolution profile of drug.

a)Hydrocolloids- Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gum, modified cellulose derivatives.Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HydroxyPropyl,Methyl Cellulose (HPMC) (K4M, K100M and K15M), Gellangum (Gelrite®), Sodium Carboxy Methyl Cellulose (CMC), MethylCellulose (MC), Hydroxy Propyl Cellulose (HPC) can be used.. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

b)Inert fatty materials-Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Eg. Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used.

c) Release rate accelerants-The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.

d) Release rate retardants-Insoluble substances such as dicalcium phosphate, talc, magnesium strearate decresesd the solubility and hence retard the release of medicaments.

e) Buoyancy increasing agents-Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may beadapted up to 80 % by weight.

3) Gas generating agents: These agents generate gas (CO_2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period

of time and release the drug slowly at a desired rate. Gas generating agents include citric acid, sod bicarbonate and tartaric acid, Di-SGC (DiSodium Glycine Carbonate), CG (Citroglycine) (30).

4) Diluent, Lubricant, Glidant: Diluents are the fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate. Commonly used diluents are lactose, mannitol, sorbitol, microcrystalline cellulose, dextrose. Lubricants are intended to reduce the friction during tablet ejection between the walls of the tablet and the walls of the die cavity in which tablet is formed. Glidants are intended to promote flow of the tablet granulation or powder materials by reducing friction between the particles.

5) Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

Types of FDDS based on mechanism of buoyancy

A) Single unit floating dosage systems
1) Effervescent system
2) Non-effervescent systems
B) Multiple unit floating dosage systems
1) Effervescent system
2) Non-effervescent systems
3) Hollow microspheres

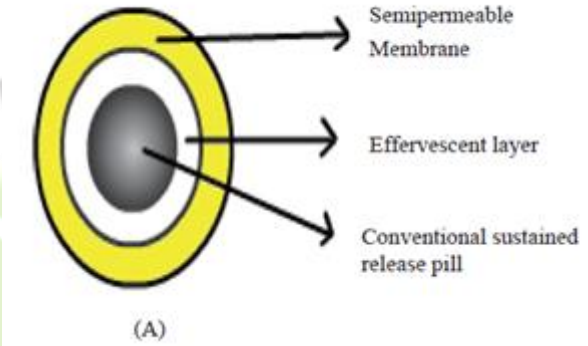
A) Single Unit Floating Dosage Systems or Gas Generating Systems: Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and thus they may cause high variability in BA and local irritation due large amount of drug delivered at a particular site of the GIT.

i) Effervescent System: These systems generate gas (CO_2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at adesired rate. The main ingredients of effervescent system include swellable polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sod. bicarbonate and tartaric acid (42).

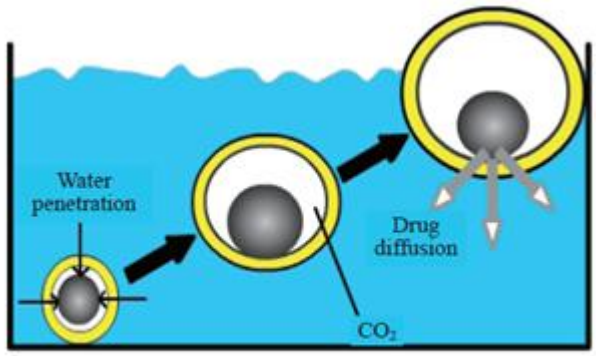
ii) Non-Effervescent Systems: These systems use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrixforming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. After oral administration:

(i) The dosage form swells when it comes in contact with gastric fluids and attains a bulk density less than 1, the air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoirand allows sustained release of drug through the gelatinous mass. eg: Floating capsule.

(ii) The inherent low density of dosage form helps inthe buoyancy of the dosage form.eg: Hollow microspheres or microballoons (43).



(A)



(B)

B) Multiple Unit Floating Dosage Systems

The purpose of designing multiple unit dosage form is to develop a reliable formulation that has all the advantageous of single unit form (44).Single unit formulations are associated with problems such as sticking together or being obstructed in GIT, which may have a potential danger of producing irritation. Multiple unit systems avoid the all or none gastric emptying nature of single unit systems. It reduces the variability in absorption and the probability for dose dumping is lower.

i) Effervescent System: This new multiple type of floating dosage systems is composed of effervescent layers and coated on controlled release pills. The inner layer of effervescent agentscontaining sodium Bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between two agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and Reduced fluctuations of drug concentration:

purified shellac. When this system was immersed in the buffer at 37 ℃, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills with a density less than 1.0g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug was released in a controlled manner (34).

ii) Non-Effervescent System: A little report is found on such systems as compared to effervescent multiple systems.

iii) Floating Microspheres: A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Both natural and synthetic polymers have been used to prepare floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation.

Advantages of FDDS

Treatment of gastrointestinal disorders: The prolonged and controlled administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.

Enhanced bioavailability: The bioavailability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations.

Site specific drug delivery: A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine. Targeting of drug to stomach appears to be useful for all substances intended to produce a lasting local action on the gastro duodenal wall. For instance, the eradication of Helicobacter pylori requires the administration of various medications several times a day resulting in poor patient compliance. A more reliable therapy can be achieved by using FDDS, which allows reduction of dosage and frequency of administration.

Enhanced first-pass biotransformation: In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

Continuous input of the drug following CR GRDF administration produces blood drug concentrations within 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.

Controlled drug delivery/reduced frequency of dosing: The drugs having short biological half life, a controlled and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy.

Improved receptor activation selectivity: FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body: Slow release of the drug into the body minimizes
the counter activity leading to higher drug efficiency.

Extended time over critical (effective) concentration: The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

Minimized adverse activity at the colon: Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon (45).

Disadvantages of FDDS

1.Not suitable for drugs that have solubility or stability problem in GIT

2.These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

3.The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

4.Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.

5. These systems are not advantageous over the conventional dosage forms for those drugs, which are absorbed throughout the gastrointestinal tract.

6. Drugs which are irritant to gastric mucosa are also not suitable.

7. The dosage form should be administered with a full glass of water (200-250 ml) (46).

In Vitro and In Vivo evaluation parameters of stomach specific FDDS.

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behaviour exhibit prolonged gastric residence in vivo. However, it should be noted that good in vitro floating behaviour alone is not sufficient proof of efficient gastric retention in vivo. The effects of the simultaneous presence of food and the complex motility of the stomach are difficult to assess. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained (11).

1) Evaluation of powder blend

a) Angle of Repose
b) Bulk Density
c) Percentage porosity

2) Evaluation of tablets

a) Buoyancy capabilities
b) Floating lag time and total floating time determination
c) Drug release
d) Weight variation
e) Hardness & friability
f) Particle size analysis, surface characterization (for floating microspheres and beads)
f) X-Ray/Gamma Scintiography
g) Pharmacokinetic studies
h) Specific gravity

Evaluation of powder blend

a) Angle of repose: Angle of repose is defined as "the maximum angle possible between the surface of the pile of powder and the horizontal plane." The frictional forces in a loose powder or granules can be measured by angle of repose. Lower the angle of repose, better the flow properties.

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 (14).

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

Where, θ = 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 1

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

b) Bulk density: Bulk density denotes the total density of the material. It includes the true volume of inter particle spaces and intra particle pores. The packing of particles is mainly responsible for bulk .Bulk density is defined as:

Bulk density = (Weight of the powder/ Bulk volume of powder) ---- (2)

When particles are packed, it is possible that a large amount of gaps may be present between the particles. Therefore, trapping of powder allows the particles to shift and remove the voids to minimum volume. The volume occupied by the powder in this condition represents the bulk volume. Substituting this volume for a given weight of powder in equation (2) gives the bulk density.

c) Percentage porosity: Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc (26).

$$\% \text{ porosity, } \epsilon = \frac{\text{void volume}}{\text{bulk volume}} \times 100 \quad \text{----- (3)}$$

$$\% \text{ porosity, } \epsilon = \frac{(\text{bulk volume} - \text{true volume})}{\text{True density}} \times 100 \quad \text{----- (4)}$$

Evaluation of tablets

Buoyancy capabilities of the FDDS: The floating behaviour was evaluated using resultant weight measurements. The experiment was carried out in two different media, deionised water and a simulated meal, in order to monitor possible differences. The results showed that higher molecular weight polymers with a slower rate of hydration exhibit enhanced floating behaviour and this was observed more in a simulated meal medium compared with deionised water.

Floating lag time and total floating time determination: The time between the introduction of the tablet into the medium and its rise to upper one third of the Hardness

dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 mole/lit HCl maintained at 37ºC, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium (46).

Drug release: The test for in vitro measurement is usually performed in stimulated gastric fluid or 0.1 mol/l HCl maintained at 37˚C. It is determined using USP dissolution apparatus containing 900 ml 0.1 mol/l HCl as the dissolution medium at 37˚C. The time taken by the dosage form to float is termed as the floating lag-time and the time for which the dosage form floats is termed as the floating or flotation time. Recently, proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage forms). A 100-ml glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker could hold 70 ml 0.1mol/l 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 2ml/min to mimic the gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with that of USP dissolution Apparatus 2 (Paddle). A problem involving adherence of the tablets to the shaft of the paddle was observed with the USP dissolution apparatus. The tablets did not stick to the agitating device in the proposed dissolution method and the observed drug release followed zero-order kinetics. A similarity in the dissolution curves was observed between the USP method and the proposed method at a 10% difference level (f2 = 57). The proposed test may exhibit a good in vitro-in vivo correlation since an attempt was made to mimic the in vivo conditions, such as the gastric volume, gastric emptying, and gastric acid secretion rate (7).

Weight variation: Ten tablets were selected 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. The following percentage deviation in weight variation was allowed (14)

Average weight of a tablet	Percent deviation
130 mg or less	10
>130mg and <324mg	7.5
324 mg or more	5

and friability:Hardness is defined as the "force required to break a tablet in diametric compression test." Hardness is hence, also termed as the tablet crushing strength. Some devices which are used to test hardness are Monsanto tester, strong Cobb tester, Pfizer tester, etc (15). The laboratory friability tester is known as the Roche Friabilator. This consists of a device which subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm & drop the tablet to a distance of six inches with each revolution. Normally, a pre-weighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. Most of the effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging, that may be required.

X-Ray/Gamma scintiography: X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day. 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 (7). 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 scintiscanner . 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 (27).

Pharmacokinetic studies: Pharmacokinetic studies are an integral part of the in vivo studies and they include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration (Tmax) (11).

Specific Gravity: Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium (1).

Applications 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 GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained drug delivery: HBS (hydro dynamically balanced system) 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. eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) (10).

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, eg, riboflavin and furosemide. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced (19).

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. eg. 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%) (17).

Minimized adverse activity at the colon : Retention of the drug at the stomach (HBS system), minimizes the amount of drug that reaches the colon, that prevents the undesirable activities of the drug in colon. 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 (9).

Recent study indicated that the administration of diltiazem floating tablet twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patient.

Madopar® HBS- containing L-dopa and benserazide- here drug is released and absorbed over a period of 6-8 hour and maintain substantial plasma concentration for parkinson's patients.

Cytotech® -- containing misoprostol, a synthetic prostaglandin- E1 analog, for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDS).As it provides high concentration of drug within gastric mucosa, it is used to eradicate pylori(A causative organism for chronic gastritis and peptic ulcers).

5-Fluorouracil has been successfully evaluated in patients with stomach neoplasm.

Developing HBS dosage form for tacrine provides a better delivery system and reduces its GI side effects in alzheimer's patients.

Alza corporation has developed a gastroretentive platform for the OROS® system, whichshowed prolong residence time in a dog model as the product remain in the canine stomach at 12 hrs post dose and was frequently present at 24 hrs, (25).

Conclusion

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Floating drug delivery system can provide sufficient gastric retention which may help to provide sustained release dosage form with enhanced absorption.

References

1.Chawla G, Gupta P, Koradia V and Bansal A. A Means to Address Regional Variability in Intestinal Drug Absorption. Pharma. Technology.July 2003.50-68.

2.Dahiya A, Rohilla A, Rohilla S, Khan M.U. Gastroretentive Dosage Forms: Review on Floating Drug Delivery System. IRJP 2 (5)2011.72-78.

3.Dahiya A, Rohilla A, Rohilla S, Khan M.U. Gastroretentive Dosage Forms: An Approach to Oral Controlled Drug Delivery Systems. IJPBA.2011; 2(2).615-620.

4.Singh K.D, Gawande A, Soni A, Patida S.An Approach to Oral Controlled Drug Delivery Systems by gastro retentive dosage form.IJPAIM, Issue 1,(2) 2011.1-6.

5.Foda N.H, Ali S.M. Gastroretentive drug delivery systems as a potential tool for enhancing the efficacy of antibiotics: A Review. IJPBS.Vol 2.Issue 2.April-june 2011.94- 104.

6. Sharma S, Nanda A. Use of porous carriers in the development of intragastric floating drug delivery system:Review.IRJP.2(10)2011,16-18.

7. Hardenia S.S, Jain A, Patel R, Anukausha. Floating Drug Delivery Systems: A Review. AJPLS. Vol. 1 (3), July-Sept, 2011,284-293.

8. Shahwal K. V, Upadhyay A. Gastro-retentive floating drug delivery systems. IJBR 2(6)2011.381-390.

9. Kumar V. V. An overview of gastro retentive drug delivery system. June 9, 2011.
10. Jain A. New Concept: Floating Drug Delivery System. IJNDD, 3(3), Jul-Sep, 2011, 162-169.
11.Kumar A, Verma R, Purohit S, Bhandari A. An Overview of gastro-retentive drug delivery system .jonc, Vol.2, Issue 3, May 2011.
12. Parkash V, Jogpal V, Maan S, Sharma V, Deepika and Yadav K.S.A review on gastroretentive drug delivery system. IJPLS, Vol. 2, Issue 5: May: 2011, 773-781.
13.Sharma V, Singh L, Sharma V. A Novel approach to combat regional variability: Floating drug delivery system. Volume 8, Issue 2, May – June 2011.154-159.
14. Sharma N, Agarwal D, Gupta K..M. and. Khinchi P.M . A Comprehensive Review on Floating Drug Delivery System. Vol. 2 (2) Apr – Jun 2011.428-444.
15. Kumar D, Saini S, Seth N, Khullar R and Sharma R. Approaches, Techniques and Evaluation of Gastroretentive Drug Delivery System:AnOverview.IJRAP2(3)2011,767-774.
16. Rajput C.G, Majmudar D.F, Patel K.J, Patel N.K , Thakor S.R and Patel R.R. Floating Drug Delivery System- A Review. Pharm ExtVol 1 Issue 1, September, 2010
17. Mor J. Progress in floating drug delivery systems: A Review. IJPPR .Vol 2, Issue4,December-2011,441-446.
18.Goyal M, Prajapati R, Purohit K.K. and Mehta C.S. Floating Drug Delievery System.JCPR 5(1) 2011,7-18.
19.Jamil F, Kumar S, Sharma S, Vishvakarma P and Singh L. Review on Stomach Specific Drug Delivery Systems: Development and Evaluation. IJRPBS. Vol. 2(4) Oct - Dec 2011,1427-1433.
20. Ganesh N. S, Suraj Mahadev Ambale, Ramesh B, Kiran B and Deshpande.An Overview on limitations of gastroretentive drug delivery System. International JPSRR.Vol 8, Issue 2, May – June 2011,133-139.
21. Gopalakrishnan S. and Chenthilnaa A. Floating Drug Delivery Systems: A Review.JPhrmaST Vol. 3 (2), 2011, 548-554.
22. Mayavanshi A.V and Gajjar S.S. Floating drug delivery systems to increase gastric retention of drugs: A Review. Oct.-Dec. 2010, 345-348.
23. Garg R and Gupta G.D. Progress in controlled gastroretentive delivery. September 2008; 7 (3):1055-1066.
24. Vinod K.R, Vasa S, Anbuazaghan S, Banji D, Padmasri A and Sandhya S. Approaches for gastrotentive drug delivery systems. IJABPT, Vol-1. Aug-Oct 2010,589-60.
25. Thakur N, Gupta P.B, Patel D, Chaturvedi K .S, Jain P. N and Banweer J. A. Comprehensive review on floating oral drug delivery system .DIT 2(7)2010, 328-330.
26. Bhowmik D, Chiranjib B, Margret C, Jayakar B and Sampath K.P. Floating drug delivery system: A Review, Der Pharmacia Lettre, 2009, 1 (2) 199-218.
27. Shahaa S.H, Patel J.K, Pundarikakshudua K and Patel N.V. An overview of a gastro retentive floating drug delivery system. Asian Journal of Pharmaceutical Sciences 2009, 4 (1): 65-80.2009, 4 (1): 65-80.
28. Narang N. An updated review on: Floating Drug Delivery System (FDDS).Int J App Pharm, Vol 3 Iissue 1, 2011, 1-7.
29. Garg S and Sharma S. Gastroretentive Drug Delivery Systems, Business briefing :pharmatech 2003,160-166.
30. Katakam V.K, Somagoni J.M, Reddy S, Eaga C.M, Rallabandi B.R.C and Yamsani MR. Floating Drug Delivery Systems: A Review. Vol. 4 (2) April 2010, 610-647.
31. M. Uddin, P. B. Rathi, A. R. Siddiqui, A. R. Sonawane and D. D. Gadade. Recent Development in Floating Delivery Systems for Gastric Retention of Drugs An Overview. Asian Journal of Biomedical and Pharmaceutical Sciences 1 (3) 2011, 26-42.
32. Mathur P, Saroha K, Syan N, Verma S and Kumar V. Floating drug delivery system: An innovative acceptable approach in gastroretentive drug delivery. 2010, 2 (2): 257-270.
33. Dhiman S, Thakur S. G, Kumar A, Rehni K.S, Sood S and Arora S. Gastroretentive: A Controlled Release Drug Delivery System, Asian J Pharm Clin Res, vol 4, suppl 1, 2011, 5-13.
34. Nasa P, Mahant S and Sharma D. Floating Systems: A novel approach towards gastroretentive drug delivery system. 2010, Vol-2, 1-7.
35. Mathur P, Saroha K, Syan N, Verma S, Nanda S and Valecha V. An overview on recent advancements and developments in gastroretentive buoyant drug delivery system 2011, 2 (1): 161-169.
36.Ramdas TD, Hosmani A, Bhandari A, Kumar B and Somvanshi S. Novel sustained release gastroretentive drug delivery system:A review. Vol-2,Issue-11,Jan 2004, 26-41.
37. Rocca G J, Omidian H and Shah K. Progresses in Gastroretentive Drug Delivery Systems. Business briefing: pharmatech 2003,152-156.
38. Sheth S.N and Mistry B. R. Formulation and

Evaluation of Floating Drug Delivery System. IJPBS.Vol 2,Issue1,Jan-March 2011,571-580.

39. Punitha S, Sabitha G, Kala V and Rajasekar S. Floating Drug Delivery System: Chronotherapeutic Approach. IRJP 2(4),2011,38-45.

40.Shakti Dwivedi and Vikash Kumar. Floating Drug Delivery Systems- A Concept of Gastroretention Dosages Form. Ijrpbs, Vol. 2(4) Oct - Dec 201,1413-1426.

41.Lahoti S.R, Iftequar S, Sabina M, Dehglan M.H, Shoaib S and Mohiuddin S. An Overview of Floating Drug Delivery System Research.IRJP 2(11) 2011,50-57.

42.Dr Latha D C, Dr Nagaveni G and Dr Vijayalakshmi G. Floating Drug Delivery System - A Review. IJCPR, Vol 3, Issue 4, 2-4.

43. Nadigoti J and Shayeda. Floating Drug Delivery Systems.IntJPSN Vol-2 Issue 3,October - December 2009,595-604.

44.Viswanatha Reddy M, Jayashankar Reddy V , Ramesh Y, Venkateswarlu L, Kumar S A and Rao S M G. A Review of Gastroretentive Drug Delivery System on Different Absorption Windows.RJPBCS.Vol 2 Issue 3 July – September 2011,720-732.

45. Klausner A E, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms.J.Control.Release 90 (2003),143-162.

46.SinghP.L, Dr Rajesh K.S, Umalkar G.D, Chauhan K.V, Rana K V and Vasava S K. Floating effervescent tablet: A Review.JPBMS 5(11) 2011,1-6.