

REVIEW ON- GASTRORETENTIVE DRUG DELIVERY SYSTEM

Ganesh Kankal^{*1}, Mahale N.B¹, Salunkhe K.S¹, Chaudhari S.R¹

¹Amrutvahini College of Pharmacy, Sangamner, Dist – Ahmednagar, Maharashtra, India.

*Corresponding Author Email: ganesh.kankal@gmail.com

ABSTRACT

It is a new drug delivery system to maximize effectiveness and compliance. The advantage of floating drug delivery system is, to prolongs the release of the drug, increases gastric residency time, and enhances bioavailability by superior technology of floatation to achieve gastric retention technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, It including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract).

KEY WORDS

Floating drug delivery, bioavailability, and bioadhesive.

INTRODUCTION

Gastro retentive drug delivery system belongs to oral controlled drug delivery system group that are capable to retain in the stomach by passing the gastric transit. These dosage forms are also defined as floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug.

The real challenge in the development of a gastro retentive drug delivery system is not just sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper part of the GIT until all the drug is completely released. This can be accomplished by floating drug delivery system which helps to retain dosage form in the stomach and releases the drug in controlled manner for longer period of time.

GRDDS is retained for longer periods of time in the stomach e.g. Hydrophilic matrix tablets, floating capsules and bioadhesive tablet. Thus the longer period of gastric retention as compared to other oral controlled drug delivery system can be attributed. The floating results in release of the drug in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drugs by changing the concentrations of polymers.

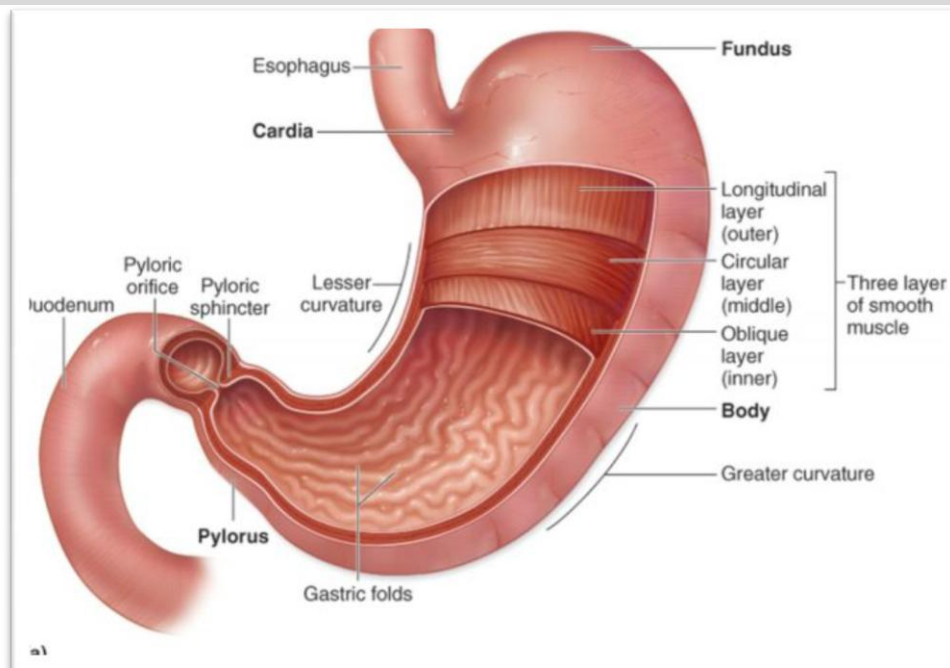
BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

The stomach is a muscular, hollow, dilated part of the alimentary canal. The main function of the stomach is to store food temporarily, grind it, and then release it slowly in to the duodenum. The stomach is an important site of enzyme production. Due to its small surface

The excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded. Area, very little absorption takes place from the

stomach. It provides a barrier to the delivery of drugs to the small intestine. The stomach is located below the diaphragm. Various factors such as volume ingested, posture and skeletal build affect the exact position of the stomach.

Figure 1: Anatomy of the gastrointestinal tract



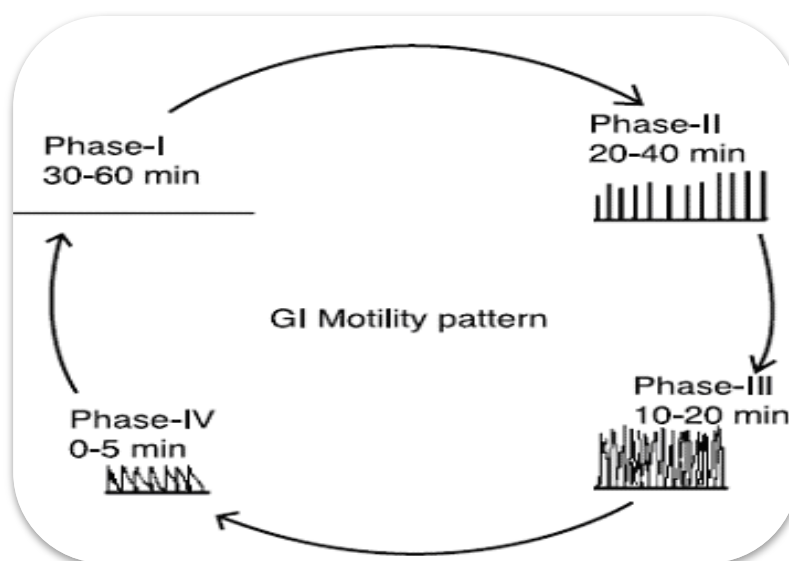
Anatomically the stomach is divided into 3 regions: **fundus, body, and antrum (pylorus)**. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric 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 interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into 4 phases.

Gastrointestinal motility and gastric emptying:

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1– 3) and air. The mucus spreads and covers the mucosal

surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes, interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The interdigestive motility pattern is commonly called as Migrating Motor Complex (MMC) and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motility in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower esophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum.

Figure 2: Four phases of GI motility



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

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.

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 occur 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. 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.

FACTORS AFFECTING GASTRIC RETENTION

- i. **Density:** Density of the dosage form should be less than the gastric contents (1.004gm/ml).
- ii. **Size:** dosage forms with the diameter more than 7.5 mm are reported to have greater gastric retention time (GRT).
- iii. **Fed or Unfed State:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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.
- iv. **Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.
- v. **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.
- vi. **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.

- vii. *Gender*: Gastric residence time in males (3.4 ± 0.4 hours) is less as compare to female (4.6 ± 1.2 hours), regardless of the weight, height and body surface. So dosage form does not retain in male for longer duration of time in stomach as compared to female.
- viii. *Age*: Elderly people, especially those over 70 years have a significantly longer GRT.
- ix. *Posture*: GRT can vary between supine and upright ambulatory states of the patients.
- x. *Concomitant drug administration*: Anticholinergic like atropine and propantheline opiates like codeine and prokinetic agents like metoclopramide and cisapride decrease gastric motility and increase gastric residence time if dosage forms.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- i. *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.
- ii. *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.
- iii. *Sustained drug delivery*: Reduced frequency of dosing for drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.
- iv. *Targeted therapy for local ailments in the upper GIT*: The prolonged and sustained

administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

- v. *Reduced fluctuations of drug concentration*: Continuous input of the drug following CRGRDF 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.
- vi. *Improved selectivity in receptor activation*: Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
- vii. *Reduced counter-activity of the body*: In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
- viii. *Extended time over critical (effective) concentration*: For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic 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.
- ix. *Minimized adverse activity at the colon*: Retention of the drug in the GRDF 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.

- x. *Site specific drug delivery:* A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper

small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

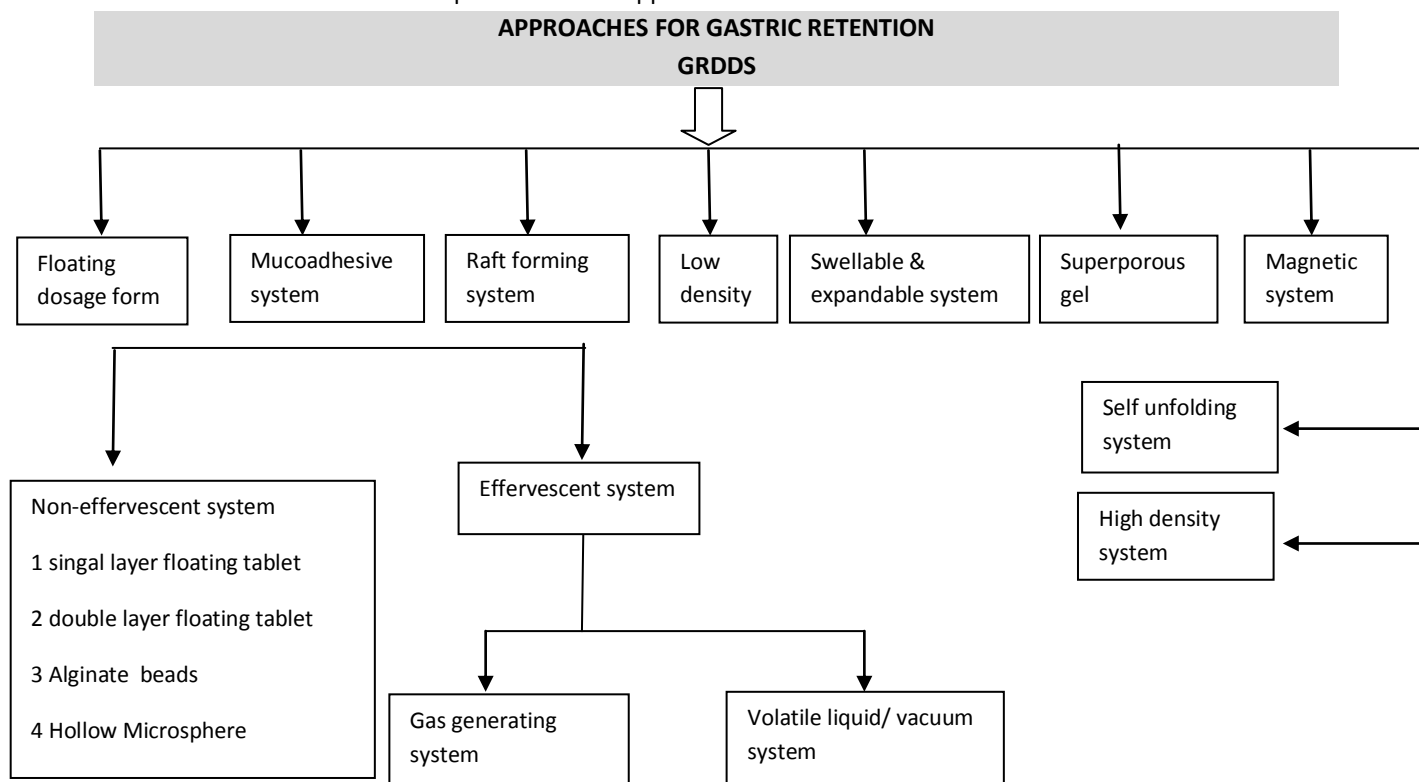
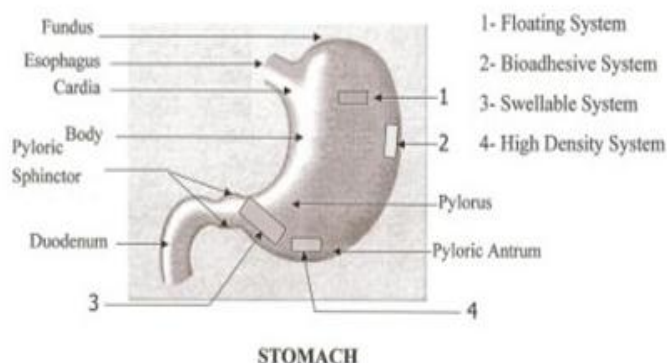


Figure 3: Schematic presentation of various approaches for gastric retention:



Different types of FDSS

Based on the mechanism of buoyancy, floating systems can be classified into two distinct categories viz. non-effervescent and effervescent systems

A. Non-Effervescent systems:

A. Colloidal gel barrier systems:

Hydro dynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose

type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. hydroxyethyl cellulose (HEC) hydroxypropyl cellulose (HPC) hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) incorporated either in tablets or capsules. When such a system comes in contact with the gastric fluid, the hydrochloride in the system hydrates and forms a colloidal gel barrier around its surface. This gel barrier controls the rate of the fluid penetration into the device and consequent release of drug from it. As the exterior surface of the dosage form goes in to the solution, the adjacent hydrochloride layer becomes hydrated and thus maintains the gel layer. The air trapped inside the swollen polymer maintains the density less than unity and confers buoyancy to these dosage forms. The HBS must comply with following three major criteria:

1. It must have sufficient structure to form cohesive gel barrier.
2. It must maintain an overall specific density lower than that of gastric contents.
3. It should dissolve slowly enough to serve as reservoir for the delivery system¹³.

A bilayer tablet can also be prepared to contain one immediate release and other sustained release layer. Immediate release layer delivers the initial dose whereas sustained release layer

absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in system with bulk density lesser than that of gastric fluid and allows it to remain buoyant in the stomach for an extended period of time. A multi-layer, flexible, sheath-like device buoyant in gastric juice showing sustained release characteristics have also been developed. The device consists of at least one dry self-supporting carrier film made up of water insoluble polymer matrix having a drug dispersed/dissolved therein, and a barrier film overlaying the carrier film. Both carrier and barrier films are sealed together along their periphery and in such a way as to entrap a plurality of small air

pockets, which bring about the buoyancy to the laminated films¹⁴.

B. Micro porous compartment system:

This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. 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. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption¹⁵.

C. Alginate beads:

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at – 40°C for 24 hrs, leading to formation of porous system that maintained floating force for over 12 hrs. They were compared with non-floating solid beads of same material. The latter gave a short residence time of 1 hr, while floating beads gave a prolonged residence time of more than 5.5 hrs¹⁰. Floating systems comprising of calcium alginate core separated by an air compartment from a membrane of calcium alginate or a calcium alginate/polyvinyl alcohol (PVA) have also been developed. The porous structure generated by leaching of PVA (water soluble additive in coating composition) was found to increase membrane permeability and thus preventing the collapse of air compartment

D. Hollow Microspheres:

Microspheres (micro balloons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an

internal cavity in microsphere of polymer with drug. The micro balloons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours¹⁷.

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. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts¹⁸.

1. Volatile liquid containing systems:

These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period. A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber

contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach¹⁹.

2. Gas generating systems:

These buoyant delivery systems utilize effervescent reaction between carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO₂ which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity less than 1 and making it to float. These tablets may be either single layered wherein the CO₂ generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect.

Figure 4: Gas-generating systems, Schematic monolayer drug delivery system
(a) Bilayer gas-generating systems, with (c) or without (b) semi permeable membrane:

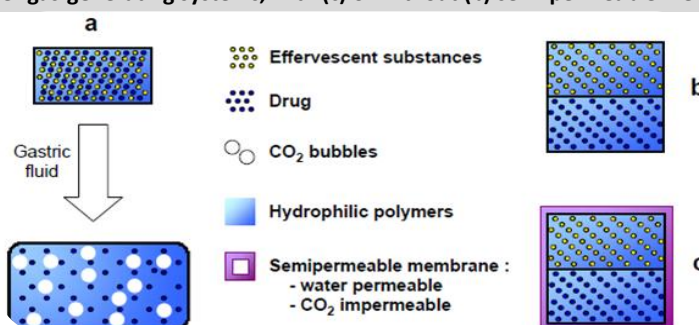
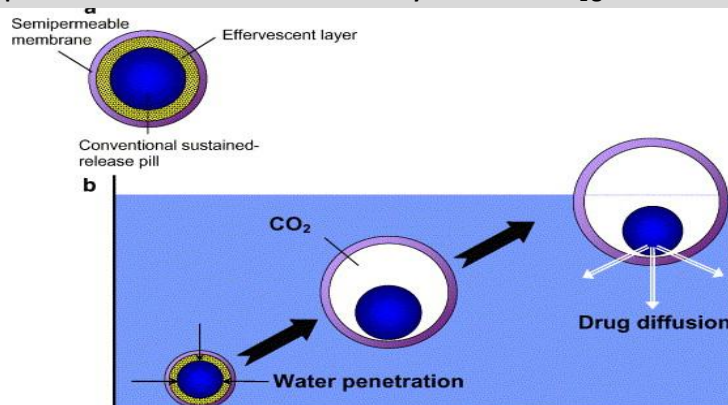


Figure 5: Schematic representation of "floating pill" proposed by Ichikawa
(a). The penetration of water into effervescent layer leads to a CO₂ generation and makes the system float (b).

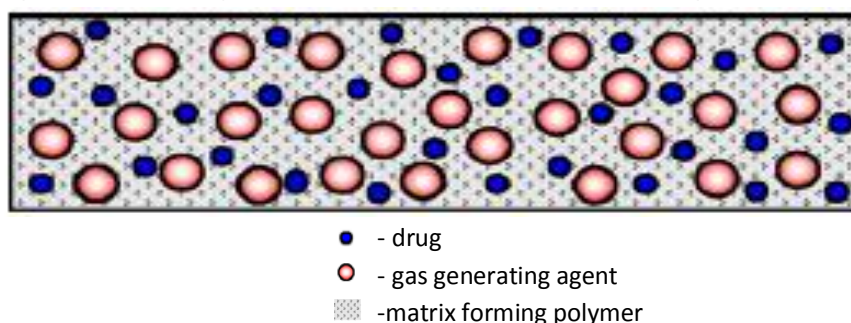


3. Matrix Tablets:

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug. Bilayer tablet can also be prepared by gas generating matrix in one layer and second layer with drug for its sustain release effect. Floating capsules also prepared by incorporating such mixtures. Triple

layer tablet also prepared having first swellable floating layer, second sustained release layer of 2 drugs (Metronidazole and Tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for Triple Therapy of H.Pylori²¹.

Figure 6: Schematic presentation of the structure of the floating matrix tablet:



C. BIOADHESIVE DRUG DELIVERY SYSTEM

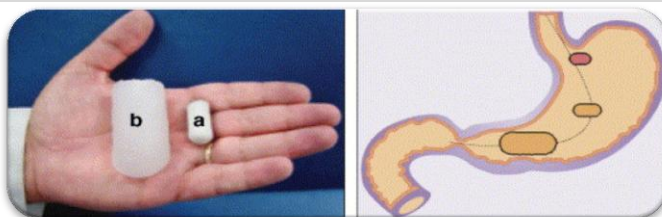
Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used. The mucosal layer is presenting indifferent of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose and eye. These represent potential sites for attachment of bioadhesive system and hence, the mucoadhesive drug delivery systems could be designed for buccal, oral, vaginal, rectal, nasal and ocular routes of administration. Examples

of Materials commonly used for bioadhesion are poly (acrylic acid) (Carbopol®, polycarbophil), chitosan, cholestyramine, tragacanth, sodium alginate.

D. SWELLING AND EXPANDING SYSTEMS

These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time. These systems may be named as "plug type systems", since they exhibit the tendency to remain lodged at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and hence maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period. On the other hand, a low degree of cross-linking results in the extensive swelling of the system, succeeded by the rapid dissolution of the polymer²⁷.

Figure 7: swelling and expanding systems

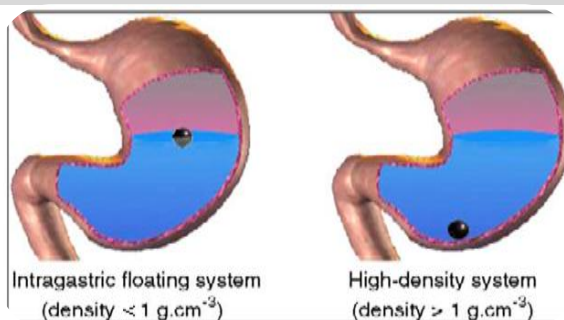


E. HIGH DENSITY SYSTEMS

These dosage forms have a density (3 g/ml) far exceeding that of normal stomach contents (1 g/ml) and thus retained in rugae of the stomach and are capable of withstanding its peristaltic movements.

The density of these systems should at least be 1.004 g/ml. This is accomplished by coating the drug with heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Figure 8: Schematic representation of high density system:



F. MODIFIED- SHAPE SYSTEMS

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on size, shape and flexural modulus of the drug delivery system.

G. COMBINATION OF FLOATING, MUCOADHESION AND SWELLABLE SYTEMS

These systems combine floating, mucoadhesion and swelling mechanism for gastric retention of dosage forms. A preferred formulation comprises a mixture of a high or medium viscosity (HPMC) and a high or medium viscosity (HEC). The formulations optionally may comprise a low viscosity HPMC. It also includes a salt being capable of releasing gaseous carbon dioxide alkaline metal carbonates can be used, an acid may be added, such as citric acid and maleic acid. These systems mainly act by three different mechanisms such as swelling, floating due to gas and mucoadhesion.

H. MAGNETIC SYSTEMS

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet

placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesive granules containing ultrafine ferrite (g-Fe₂O₃). They guided them to the esophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h. although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

I. RAFT-FORMING SYSTEMS

This system is used for delivery of antacids and drug delivery for treatment of gastrointestinal infections and disorders. The mechanism involved in this system 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 raft.

This raft floats in gastric fluids because of the low bulk density created by the formation of CO₂. Usually the system contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and to float on the gastric fluids.

Figure 9: Schematic illustration of the barrier formed by a raft-forming system:



Table 1: Drugs used in the gastro retentive formulations

TYPE	EXAMPLE
FLOATING MICROSPHERES	Aspirin, Griseofulvin, ciprofloxacin hydrochloride, P-nitro aniline, Indomethasone, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, orlistat, Cholestyramine, Theophylline, Nifedipine, Nicardipine, captorlil, cimetidine, Dipyridamol, Tranilast and Terfenadine
FLOATING GRANULES	Diclofenac sodium, Indomethacin and Prednisolone, Ranitidine Hydrochloride-Gelucire.
FILMS	Cinnarizine, Albendazole
FLOATING TABLETS AND PILLS	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Cephalexin, Cefuroxime, Fluorouracil, Isosorbide mononitrate, Isoniazide, Para-amino benzoic acid, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, Pentoxifylline and Diltiazem hydrochloride.
FLOATING CAPSULES	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Theophylline, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid, Pepstatin and Propranolol

Table 2: Other Excipients (Excipients used in (GRDDS)

TYPE	EXAMPLE
POLYMERS	
Hydrocolloids	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxy Propyl Methyl Cellulose (HPMC) (K4M, K100M and K15M), Gellan gum(Gelrite®), Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC).
Inert fatty materials	Bees wax, Fatty acids, Long chain fatty alcohols, Gelucires® 39/01 and 43/01.
EFFERVESCENT AGENTS	Sodium bicarbonate, Citric acid, Tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine).
RELEASE RATE ACCELERANTS	Lactose, Mannitol
BUOYANCY INCREASING AGENTS- LOW DENSITY MATERIAL	Ethyl cellulose. Polypropylene foam powder (Accurel MP 1000®).

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM

- 1) Evaluation of powder blend for-
 - a) Angle of Repose
 - b) Bulk Density
 - c) Percentage porosity
- 2) Evaluation of tablets for-
 - a) Buoyancy capabilities
 - b) In vitro floating and dissolution behaviour
- c) Weight variation
- d) Hardness & friability
- e) Particle size analysis, surface characterization (for floating microspheres and beads):
 - f) X-Ray/Gamma Scintigraphy
 - g) Pharmacokinetic studies

➤ 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.” Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base (r) with ruler.

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

b) Bulk density

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk. Bulk density is defined as:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}}$$

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.

$$\% \text{ porosity} = \frac{\text{void volume}}{\text{Bulk volume}} \times 100$$

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

➤ Evaluation of floating tablets

a) Measurement of buoyancy capabilities of the FDS

The floating behavior is evaluated with resultant weight measurements. The experiment is carried out in two different media, deionised water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water.

b) In Vitro floating and dissolution behaviour

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states “the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started”. A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of in vitro performance of floating dosage forms.

c) Weight variation

In practice, composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10, however provides an average weight but contains a problem of averaged value. To help alleviate this problem, the United States pharmacopeia (USP) provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample. The USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit, and if no tablet differs by more than 2 times the percentage limit.

d) Hardness & 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. The laboratory friability tester is known as the Roche Friabilator. This consists of a device which subjects a number of tablets to the 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 revolution. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weights are generally considered acceptable. Most of the effervescent tablet undergoes high friability losses, which accounts for the special stack packaging that may be required for this type of tablet.

e)

Particle size analysis, surface characterization (for floating microspheres and beads)

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 (SEM).

f) X-Ray/gamma scintigraphy

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), 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 radionuclide in a formulation allows indirect external observation using a γ -camera or scintiscanner. 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 GIT.

g) Pharmacokinetic studies

Pharmacokinetic studies are an integral part of the in vivo studies and several works have been reported on these. 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 364.65ng/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 mg/ml-1h).

Table 3: Some of the marketed formulations available as GRDDS

Brand name	Delivery system	Drug	Category	Company name
Topalkan®	Floating liquid alginate preparation	Al - Mg	Antacid	Pierre Fabre Drug, France
Convion®	colloidal gel forming FDDS	Ferrous sulphate	Antianemic	Ranbaxy, India
Cifran OD®	Gas-generating floating form	Ciprofloxacin	Antibiotic	Ranbaxy, India
Valrelease®	Floating capsule	Diazepam	CNS depressant	Hoffmann-LaRoche, USA
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide and L-Dopa	Antiparkinsons	Roche Products, USA

REFERENCES

- 1) Modi SA. Sustained release drug delivery system: a review. International Journal of Pharma Research and Development. 2011; 2:147-158.
- 2) Chien, Y 1992, Novel Drug Delivery Systems., 2nd edi., Marcel Dekker, New York.
- 3) Bansal A, Chawla G, Gupta P & Koradia V, 'Gastroretention a means to address regional variability in intestinal drug absorption', Pharmaceutical technology, 2003, pp. 50-68.
- 4) Talukder R & Fassihi R, 'Gastroretentive delivery systems: A mini review', Drug Dev Ind Pharm, 2004, vol. 30, pp. 10191028

- 5) Vishal Cristian. A review on floating drug delivery system as a part of grdds., International Journal of Pharma Research and Development(IJPRD), 2011; Vol 3(6): August 2011 (233 – 241)
- 6) N. K. Jain; "Controlled & novel drug delivery system"; Pharmaceutical product development ; 434-437
- 7) C. Deepa latha, G. Nagaveni, G. Vijaya lakshmi., A review on Floating Drug Delivery System., International Journal of Current Pharmaceutical Research., Vol 3, Issue 4, 2011
- 8) Shiv Shankar Hardenia, Ankit Jain, Ritesh Patel, Anu kaushal., A review on Floating Drug Delivery Systems., Asian Journal of Pharmacy and Life Science Vol. 1 (3), July-Sept, 2011
- 9) Shah S.H, Patel J.K and Patel N.V., Stomach specific drug delivery systems: A review International Journal of PharmTech ResearchVol.1, No.3. 2009; 623-633.
- 10) Joseph NJ, Laxmi S, Jayakrishnan A. A floating type oral dosage form for piroxicam based on hollow microspheres: in vitro and in vivo evaluation in rabbits. J Control Release. 2002;79:71-79.
- 11) Brahma N. Singh, Kwon H. Kim., A review on Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention., Journal Of Controlled Release 63 (2000) 235–259
- 12) Praveen Nasa, Sheefali Mahant, Deepika Sharma., Floating Systems: A Novel Approach towards Gastroretentive Drug Delivery Systems., International Journal of Pharmacy and Pharmaceutical Sciences Vol 2, Suppl 3, 2010
- 13) Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm. Res. 1997; 14:815-819.
- 14) Arora S, Ali J, Ahuja A, Khar K R, Baboota S., Floating Drug Delivery Systems: A Review. AAPS Pharm.Sci.Tech. 2005; 6(3) Article 47.
- 15) Rajnikanth P, Mishra B., Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H.pylori. J. Cont. Rel. 2008; 25:33-41.
- 16) P.L. Bardonnnet, V. Faivre, W.J. Pugh, J.C. Piffaretti, F. Falson., Gastroretentive dosage forms: Overview and special case of Helicobacter pylori., Journal of Controlled Release 111 (2006) 1 – 18
- 17) S. Garg, S. Sharma, Gastroretentive drug delivery systems, Business Briefing: PharmaTech, 2003, pp. 160– 166.
- 18) B.N. Singh, K.H. Kim, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. Control. Release 63(3) (2000) 235– 259.
- 19) L.H. Reddy, R.S. Murthy, Floating dosage systems in drug delivery, Crit. Rev. Ther. Drug Carr. Syst. 19 (6) (2002) 553–585.
- 20) S. Kockisch, G.D. Rees, S.A. Young, J. Tsibouklis, J.D. Smart, Polymeric microspheres for drug delivery to the oral cavity: an in vitro evaluation of mucoadhesive potential, J. Pharm. Sci. 92 (8) (2003) 1614– 1623.
- 21) Gourav Joshi, Seema Saini, Sandeep Arora, Arvind Sharma, Vikas Kumar., Innovation In Gastroretentive Drug Delivery Systems: Formulations And Techniques For Anti-Diabetic., IJAPR / April 2011/ Vol. 2 / Issue. 4 / 147- 156
- 22) Kavitha K, Puneeth K.P, Tamizh Mani., Development and Evaluation of Rosiglitazone Maleate Floating Tablets using Natural Gums. Int.J. PharmTech Res. 2010, 2(3), 1662-1669.
- 23) V.H.K. Li, J.R. Robinson, V.H.L. Lee. Influence of drug properties and routes of drug administration of the design of sustained and controlled release systems. Controlled Drug Delivery 1987, 29(2), 4-94
- 24) Ramdas T. Dolas., Novel Sustained Release Gastroretentive Drug Delivery System: A Review ., IJPRD/2011/PUB/ARTI/VOV-2/ISSUE-11/JAN/004
- 25) Soppimath KS, Kulkarni AR, Rudzinski W E, Aminabhavi TM. Microspheres as floating drug delivery system to increase the gastric residence of drugs. Drug Metab Rev. 2001;33:149-160.
- 26) Singh B, Ahuja N 2004. Response surface optimization of drug delivery system. In Jain NK, editor. Progress in Controlled and Novel Drug Delivery System. New Delhi, India: CBS Publishers and Distributors, p. 76-97, 470-509.



***Corresponding Author:**

Ganesh Kankal*

Amrutvahini College of Pharmacy, Sangamner,
Dist – Ahmednagar , Maharashtra, India.