

GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

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INTRODUCTION:

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bioadhesive system, swelling system and expanding system and floating system.

In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. Unfortunately floating devices administered in a single unit form (Hydrodynamically balanced system) HBS are unreliable in prolonging the GRT owing to their 'all-or-nothing' emptying process and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract.

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached.

Although some important applications, including oral administration of peptide and protein drugs, can be used to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route. More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability.

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.

Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorised as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

Certain types of drugs can benefit from using gastric retentive devices. These include:

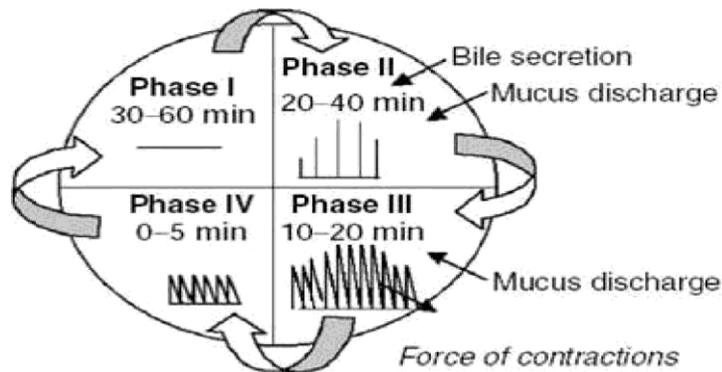
- Acting locally in the stomach.
 - Primarily absorbed in the stomach.
 - Poorly soluble at an alkaline pH.
 - Narrow window of absorption.
 - Absorbed rapidly from the GI tract.
 - Degrade in the colon.
- Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and major draw-back is non-site specificity.
- Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- Pharmaceutical field is now focusing towards such drugs which require site specificity.
- Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine.

MERITS OF GRDDS:

- Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.
- Patient compliance by making a once a day therapy.
- Improved therapeutic efficacy.

PHYSIOLOGY OF STOMACH:

- The main function of stomach is to store food temporarily, grind it and then release it to duodenum.
- The end portion of stomach and starting of intestine means duodenum is joined by Pyloric sphincter, which a valve type unit and it can open maximum upto **12.8±7 mm**. So dosage forms having higher size are retained more time in stomach.
- Gastric fluid volume in stomach is minimum of **25-50 ml** at resting stage
- pH of gastric fluid is generally **1.5–2** in fasted state and may raised upto 2–6 in fed condition but it come back down soon by secretion of more gastric acid.
- Gastric Retention Time of any dosage form is generally **1-2.5 hours** in fasted state but in fed condition GRT is increased, especially with fatty food.
- Food is passed out from stomach to intestine by gastric motility. There is specific motility pattern in **fasted condition** called as **Migrating Myoelectric Complex (MMC) cycle**. MMC is subdivided into four phases.



Phase I is basal phase, which is silent period of 30-60 minutes and characterized by lack of secretory, electrical and contractile activity and there is no contractions.

Phase II is pre-burst phase, which exhibit intermittent action for 20-40 minutes. Some bile secretion started and contractile motions increases frequency. Mucus discharge is started during later part of phase II.

Phase III is burst phase, which is characterized by intense and large regular contractions termed as "**house keeper waves**". These waves sweep off undigested food by maximizing the pyloric opening and lasts for 10-20 minutes. Thus, these phase enables efficient evacuation of the stomach contents.

Phase IV is transition period up to 5 minute, between phase III & I.

- The whole MMC cycle is repeated every 2-3 hours.
- The motor activity in the **fed condition** is induced 5-10 min after the ingestion of the meal and persists as long as food remains in the stomach.
- The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 hrs and more typically 3-4 hrs. Its phasic contractions are similar to those seen during phase II of the MMC.

Salient Features Of Upper Gastrointestinal Tract: TableNo.1

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m ²)	Absorption pathway
Stomach	0.2	Variable	1-4	<10 ³	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	10 ³ – 10 ¹⁰	120-200	P, C, A, F, I, E, CM

P – Passive diffusion

C – Aqueous channel transport

A – Active transport

F – Facilitated transport

I – Ion-pair transport

E – Entero-or pinocytosis

CM – Carrier mediated transport

Different Features Of Stomach

Gastric pH: Fasted healthy subject 1.1 ± 0.15

Fed healthy subject 3.6 ± 0.4

Volume : Resting volume is about 25-50 ml

Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.

Effect of food on Gastric secretion: About 3 liters of secretions are added to the food. Gastro intestinal transit time Figure No.1

Requirements For Gastric Retention:

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Need For Gastro Retention:⁷

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal Small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections

DRUGS WHICH REQUIRE GASTRIC RETENTION

- Drugs acting locally in the stomach E.g. Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach E.g. Amoxycillin
- Drugs that are poorly soluble at alkaline pH E.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption E.g. Cyclosporin, Methotrexate, Levodopa, etc.
- Drugs which are absorbed rapidly from the GI tract. E.g. Metonidazole, tetracycline.
- Drugs that degrade in the colon. E.g. Ranitidine, Metformin HCl.

Advantages Of Gastroretentive Delivery Systems:⁸

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. b-lactam antibiotics (penicillins and cephalosporins)
- Retention of drug delivery systems in the stomach prolongs overall.
- Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacin

Limitations Of The Techniques Of Gastroretention:

1. More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.
2. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
3. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
4. Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti-inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs, that are absorbed throughout the gastrointestinal tract.
5. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
6. In all the above systems the physical integrity of the system is very important and
7. Primary requirement for the success of these systems.

FACTORS AFFECTING GASTRIC RETENTION TIME OF THE DOSAGE FORM

1.Density: GRT is a function of dosage form buoyancy that is dependent on the density.

2.Size: Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.

3. 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. ≈

4.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.

5.Fed or unfed state: under fasting conditions: 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.

6. 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.

7. Caloric content: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

8. 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.

9. 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.

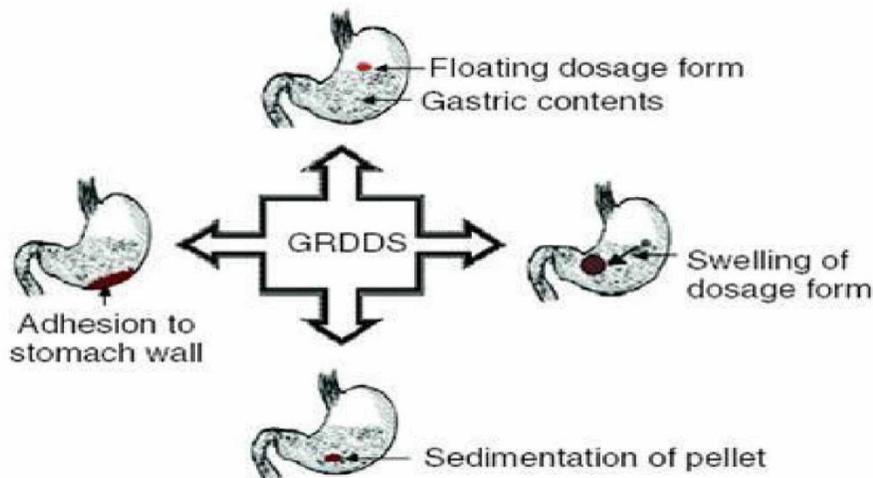
10. Age: Elderly people, especially those over 70, have a significantly longer GRT.

11. Posture: GRT can vary between supine and upright ambulatory states of the patient.

12. Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

13. Biological factors: Diabetes and Crohn's disease.

GRDDS TECHNOLOGIES



A) FLOATING – A LOW DENSITY APPROACH

- Floating drug delivery systems(FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.
- While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.

Floating Drug Delivery:

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcelluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy.^{13,14}

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realised either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favourable incidence of this prolonged gastric residence time.¹⁵

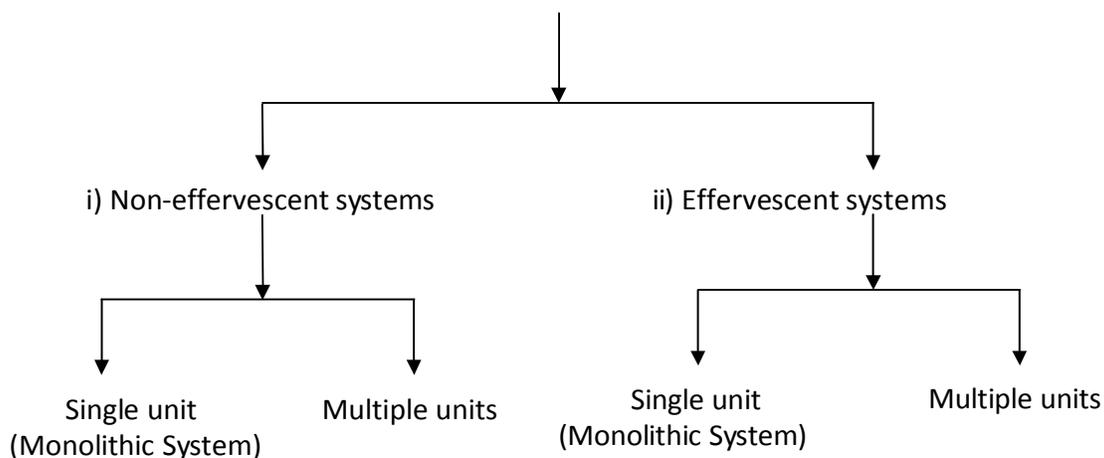
Gas-Generating Systems:

These buoyant systems utilised matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable,

allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.

Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion exchange resin technology, etc.¹⁶

CLASSIFICATION OF THE FLOATING SYSTEMS:



i) Non-Effervescent systems

- In this type of FDDS, most commonly used Excipients are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.
- The approach involves intimate mixing of the drug with gel forming hydrocolloids, which swell in contact with the gastric fluid after oral administration and maintains a relative integrity, shape and bulk density of less than a unity. Within the outer gelatinous barrier, the air entrapped by the swollen polymers confers to the buoyancy of these dosage forms.

SINGLE UNIT SYSTEMS

a) Floating tablet

It's a matrix tablet with single layered or bi-layered.

Matrix tablet were prepared by incorporating gel forming hydrocolloids like HPMC, which the most commonly used polymer for floating. Out of various grades of HPMC, low viscosity grade are use for floating purpose. Mixture of alginate and HPMC also prepared for floating tablet.

Bilayer matrix tablet are prepared by providing polymers responsible for floating in one layer and drug loaded in other layer and so whole unit will float and will remain in the stomach. The other type of bilayer tablet is prepared by incorporating a loading dose of drug in one layer and remaining drug in other layer along with hydrocolloid for its sustained release effect.

b) Floating capsule

HBS™ CAPSULES

- ❑ It is Hydrodynamically Balanced System. It is a hard gelatin capsule containing drug with high level of one or more highly swellable gel forming hydrocolloids (20-75%) like HPMC, HPC, HEC, Na-CMC etc.
- ❑ Capsule shell dissolves in gastric fluids and hydrocolloids are hydrated to form colloidal gel barrier around its surface and maintains shape.
- ❑ Thus, the increase in volume leads to decrease the overall bulk density and imparts buoyancy. Gel structure controls rate of diffusion of fluid-in and drug- out making "**Receding Boundary**".
- ❑ After exterior surface dissolves/erodes, the immediate adjacent hydrocolloid layer is hydrated and process continues to give floating for extended period of time.

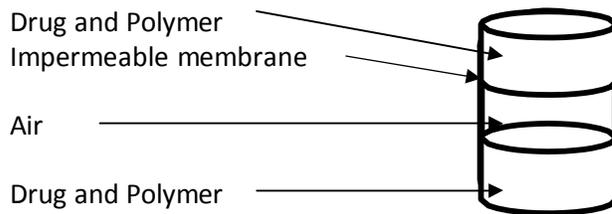
The success of HBS capsule as a better system is exemplified with Chlordiazepoxide HCl. The drug is a classical example of solubility problem wherein it exhibits a 4000 fold difference in solubility going from pH 3-6.

BILAYER CAPSULE

- ❑ Capsule is filled with non compressed bilayer formulation. One layer is drug releasing layer and other is floating layer. Both the layer consists of hydrocolloid gelling layer such as HPMC, gums, polysaccharides and gelatin.

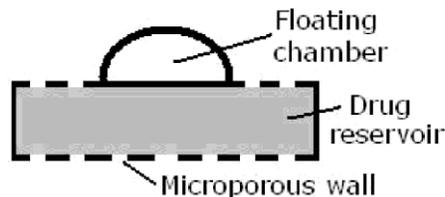
Upon coming in contact of gastric fluid capsule dissolves and bilayer mixture forms gelatinous mass with sufficient cohesive binding of two layers.

c) Tablets with hollow cylinder



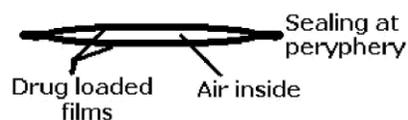
- ❑ The device consisting of two drug-loaded HPMC matrix tablets, which are placed within an impermeable, hollow polypropylene cylinder (open at both ends). Each matrix tablet closed one of the cylinder's ends so that an air-filled space was created in between, providing a low total system density. The device remained **floating until at least one of the tablets is dissolved**.

d) Micro-porous reservoir



- ❑ This device comprised of a drug reservoir encapsulated in microporous compartment having pores on its surface.
- ❑ A floating chamber was attached at one surface which gives buoyancy to entire device. Drug is slowly dissolves out via micro pores.

e) Multi-layer flexible film:



- ❑ The device consist of two films which are **sealed together along their**

periphery and in such a way as to entrap some air between two films and so make air pocket which imparts buoyancy.

- ❑ Out of two films, one is carrier film made up of water insoluble polymer matrix having a drug dispersed or dissolved therein and other is barrier film overlaying the carrier film. Barrier film consists of copolymer of water insoluble and water- and drug-permeable polymer. Floating time and drug release rate can be modulated by appropriate selection of polymer matrix.

MULTIPLE UNIT SYSTEMS

- ❑ Single unit dosage forms are associated with problems such as sticking together or being obstructed in the GIT, which may have a potential danger of producing irritation. Also there are chances of unreliability and incapability for producing results in prolonging residence time in the stomach when orally administered owing to their **fortuitous** (all or none) emptying process.
- ❑ On the other hand, multiple unit dosage forms appear to be better suited as they claim to reduce the inter subject variability in absorption and lower the probability of dose dumping.
- ❑ These dosage forms are available as powders, granules, beads, micro-spheres, micro-capsules, micro-balloons, etc.

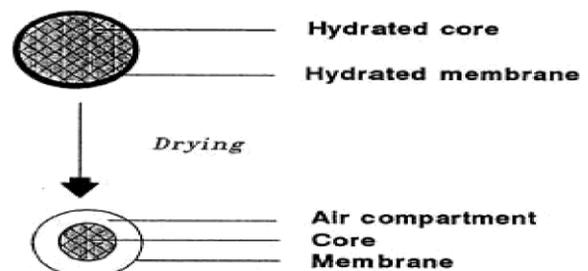
a) Bead system

1. CALCIUM ALGINATE/ PECTINATE BEADS

- ❑ Freeze dried calcium alginate beads are produced by dropping sodium alginate solution into aqueous solution of calcium chloride. So due to chemical reaction named as **ionotropic gelation**, gelation takes place and forms solid spherical gel beads, which are separated from solution and they are freeze dried at -40°C for 24 hours. The resultant weight of beads is less giving buoyancy up to 12 hours.
- ❑ Similar to alginate, pectin can also be used for preparing gel beads. Combination of both means calcium-alginate-pectinate gel bead also tried, which gives faster drug release as compared to only calcium pectinate beads.
- ❑ Calcium alginate beads also prepared with incorporation of Chitosan polymer so that it can incorporate air in beads.

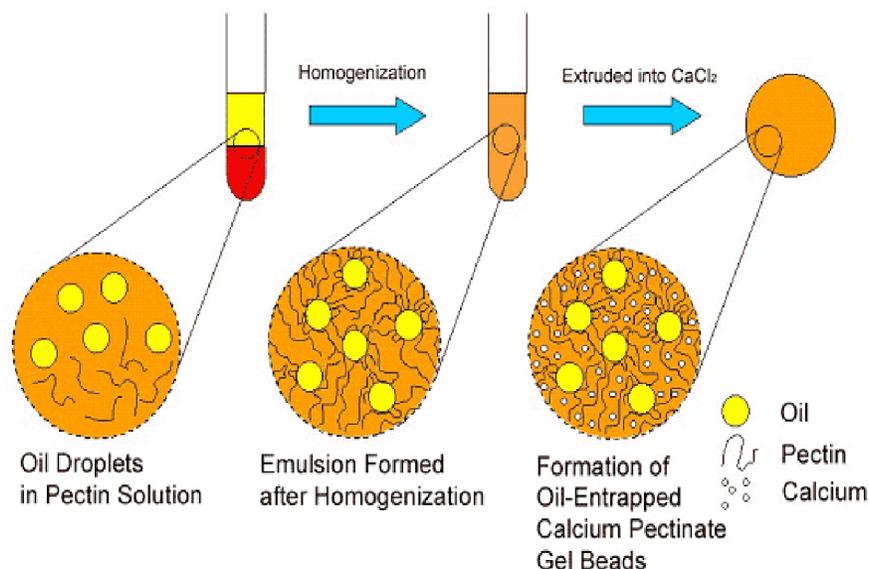
2. ALGINATE BEADS WITH AIR COMPARTMENT

- ❑ These are also calcium alginate beads but the difference is that the calcium alginate core is separated by air compartment from a coating membrane calcium alginate or mixture of calcium alginate and PVA.



- During the preparation of calcium alginate beads before drying process the beads are coated with the coating solution which may be calcium alginate or mixture of calcium alginate and PVA, and then they are dried.
- So that due to shrinkage of internal core bead during drying it produces the air compartment which imparts buoyancy. PVA is incorporated in coating mixture for improving membrane permeability as PVA is water soluble additive cause the leaching from membrane and making pores in membrane.

3. OIL ENTRAPPED GEL BEADS



- Vegetable oil is used as a floating carrier as they are **light weight and hydrophobic** used for floating by incorporating it into gel matrix of beads. Oil entrapped beads are prepared by both calcium alginate bead and calcium pectinate beads.
- *Pectin has some emulsification property*, so aqueous solution of pectin is mixed with edible oil. Emulsion is obtained by homogenization. And this emulsion is extruded into calcium chloride solution to form beads which are separated, washed and dried.

4. CASEIN-GELATIN FLOATING BEADS

- *Casein has emulsifying property and thus cause air bubble incorporation* that act as air reservoir for floating system. Beads are prepared by adding solution of casein and gelatin in deionized water at 60°C to the preheated mineral oil. The dispersion is stirred to obtain emulsion and temperature is reduced to 5°C by rapid cooling and previously cooled acetone is added to get solid beads which are dried under vacuum.
- **Floating is due to air entrapment** is proved by preparing non floating beads which are prepared similarly from a solution mixture of casein and gelatin previously treated at reduced pressure to completely remove air bubbles.

b) Microspheres

Development of Floating Microspheres

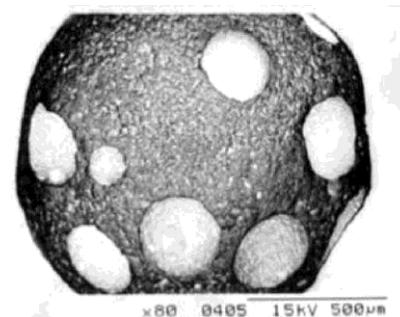
Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs.

Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of Acrylic resins, Eudragit, PMAA, Polyethylene oxide, and Cellulose acetate; Polystyrene floatable shells; Polycarbonate floating balloons and Gelucire floating granules are the recent developments.

1. HOLLOW MICROSPHERES

- Hollow (porous) microsphere using polymers like polycarbonates have been prepared using solvent evaporation technique. After preparation of microsphere, organic solvent evaporates from it creating holes inside microsphere. A high (50%) drug loading can be achieved.



The advantages of hollow microspheres include:

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Better therapeutic effect of short half-life drugs can be achieved.
4. Gastric retention time is increased because of buoyancy.
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Enhanced absorption of drugs which solubilise only in stomach.

8. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
9. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

Characterization of Floating Microspheres

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose. The particle size is determined by optical microscopy; true density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy.

Floating behavior of hollow microspheres is studied in a dissolution test apparatus by spreading the microspheres on a simulated gastric fluid (pH 1.2) containing tween 80 as a surfactant; the media is stirred and a temperature of 37°C is maintained throughout the study. After specific intervals of time, both the fractions of the microspheres floating and settled are collected; the buoyancy of the floating microspheres can be calculated using the data.

The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs). The in-vitro and in-vivo data can be correlated.

Applications of Floating Microspheres

Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can also be delivered efficiently thereby maximizing their absorption and improving the bioavailability.

Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis²¹. The development of such systems allow administration of non-systemic, controlled release antacid formulations containing calcium carbonate and also locally acting anti-ulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

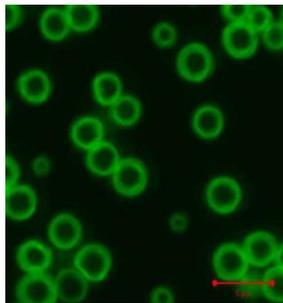
The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only

from very specific sites of the GI mucosa. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms may allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin, low-molecular-weight Heparin, and LHRH.

Hollow microspheres of non-steroidal anti-inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quite beneficial for rheumatic patients.

The drugs recently reported to be entrapped in hollow microspheres include Aspirin, Griseofulvin, Ibuprofen, Terfenadine, Diclofenac sodium, Indomethacin, Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin.

MICROBALLOONS



- Microballoons are the hollow microspheres which are completely hollow from inside forming cavity inside and drug loaded in their outer shells are prepared by an emulsion solvent diffusion method. Organic phase of drug and polymer in ethanol/dichloromethane is poured on to aqueous solution of PVA maintained at 40°C. So gas phase of organic solvent is generated in dispersed polymer droplet, goes out by creating internal cavity which is responsible for floating

c) Floating powder

- Floating powder which can be filled in capsule or compress to tablet was made up of drug, pH dependent polymer - which was a water soluble salt of alginic acid (such as a **sodium or potassium alginate**) and a pH independent hydrocolloid gelling agent (such as **HPMC, HPC, MC**) and binder.
- The uniqueness of this formulation is it release drug at controlled rate regardless of pH of environment and free

d) Carrier systems

1. CALCIUM SILICATE AS FLOATING CARRIER

- Sustain release granules were prepared using drug, polymer (HPC) and **calcium silicate as a floating carrier**, which has a characteristically porous structure with numerous pores and a large individual pore volume. The coated granules acquired floatability from the air trapped in the pores of calcium silicate when they were coated with polymer.

2. GELUCIRE® GRANULES:

- ☐ Gelucire® is hydrophobic lipid which is available in various grades according to its HLB value and melting points. **Gelucire® 39/01 and 43/01 has been used as floating carriers.** Granules are prepared by melt granulation technique. It imparts buoyancy due to its hydrophobicity and low density. It is good carrier for controlled release of highly water soluble drugs.

ii) Effervescent systems

- ☐ These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

a) 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 SR 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.Pylori.

b) Matrix tablets with carbopol

Carbopol is polymer which has pH dependent gelling property. It gels only at alkaline pH, so generally not gives gelling in acidic pH of gastric fluid and therefore not used as a swelling or matrixing polymer as HPMC and other used in GRDDS.

- ☐ But when gas generating bicarbonates are incorporated in it, due to *generation of alkaline micro-environment by carbonate*, Carbopol gives swelling and gelling. But this system not remains intact for long time; it can be coated with permeable elastic polymer like Eudragit to support integrity of core.

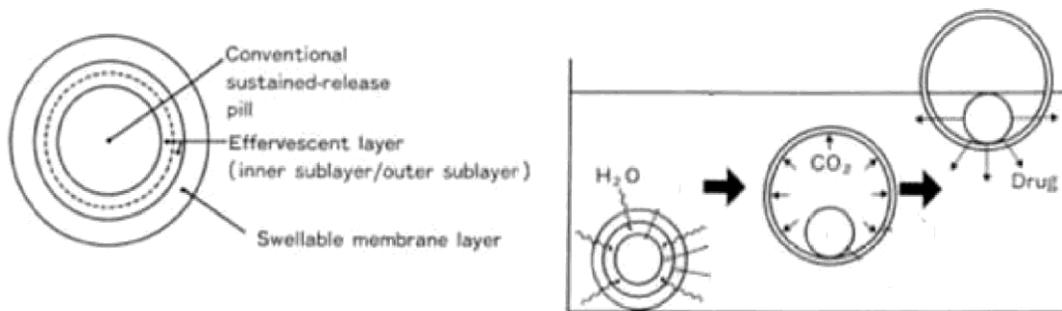
c) Coated effervescent core

- ☐ Tablet is prepared with drug and effervescent material and then coated by polymeric coating of polymer like Eudragit RS with some plasticizer. Coating has higher elongation value and high water and low CO₂ gas permeability. So CO₂ gas generation makes floating system in gastric fluid.
- ☐ By using similar system, pulsatile system is also developed by using semipermeable coat which ruptures after predetermined time and release

all drug.

d) Floating pills

- ❑ Floating pill system is consisting of SR drug pill surrounded by double layers coat. The inner layer is an effervescent layer containing two sub-layers to avoid direct contact of NaHCO_3 and tartaric acid. Outer layer is swellable permeable layer which is made up of PVA and shellac.
- ❑ When system comes in contact with water or gastric fluid which penetrate inside through swellable membrane and CO_2 gas is generated by reaction of inner effervescent mixture. As CO_2 gas not goes out from outer membrane makes a balloon like system which can float. This system is floats completely within 10 minutes and remains buoyant up to 5 hours irrespective of pH and viscosity of medium.



a) Structural characteristics of floating pill

b) Floating mechanism of the pill

e) Floating based on ion-exchange resin

- ❑ This system comprised of ion exchange resin beads loaded with bicarbonate and a negatively charged drug tagged to resin. The beads were further encapsulated in a semi permeable membrane.
- ❑ Upon coming in contact with gastric fluid, chloride ion of HCl acid is exchange with bicarbonate and produce CO_2 gas, which can not escape due to semi permeable membrane. So CO_2 generation makes floating system. Uncoated beads don't show floating due to escape of CO_2 .

f) Programmable drug delivery

- ❑ Programmable drug delivery is system consist of drug compact, rubber disc, spring, valve, bicarbonate containing balloon in non-digestible body of HGC.
- ❑ As shown in figure when system enters in gastric fluid, fluid enters via non returning rubber valve. By reaction with bicarbonate generates CO_2 gas. As the valve is non returning type, CO_2 gas can't escape out of system and so it swells balloon which is attached to system in such a way that cannot detach from it.

- ❑ Thus the whole system is now floating. Drug is released slowly from the drug compact made by high compression or by matrixing with polymer. As drug releases, size of compact decreases and rubber disc is coming down due to pressure of spring.
- ❑ When all drug is removed, rubber disc came down to lowest position and a horizontal-vertical orifice of disc matches with minipore made in side of the wall of HGC, CO₂ gas removes out of system via orifice and minipore and system sink down and goes out of stomach and then out of body.

g) Porous alginate beads

- ❑ Porous alginate beads are prepared by incorporating CO₂ gas generating agents like NaHCO₃ and CaCO₃. Bicarbonates are added with stirring into aqueous solution of sodium alginate and then mixture is added to solution of Calcium chloride with 10% acetic acid.
- ❑ So due to acetic acid and bicarbonate, CO₂ gas is generated and simultaneously gelling of beads by calcium ions are occurring producing the beads CO₂ which goes out during stirring and creating porous structures in calcium alginate beads.

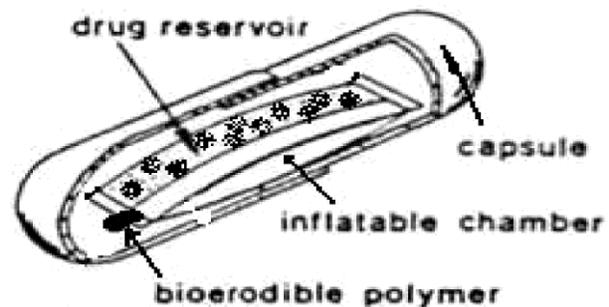
h) Multiple films for floating

- ❑ Two release controlling films(bigger than other films), one drug containing film and one effervescent film are prepared separately and assembled in such way that small sized drug and effervescent films are sandwiched between two bigger rate controlling films, and the periphery is sealed with small amount of polymer solution. So CO₂ gas generation inside assembly cause floating in gastric fluid.

i) Deformable unit with inflatable chamber

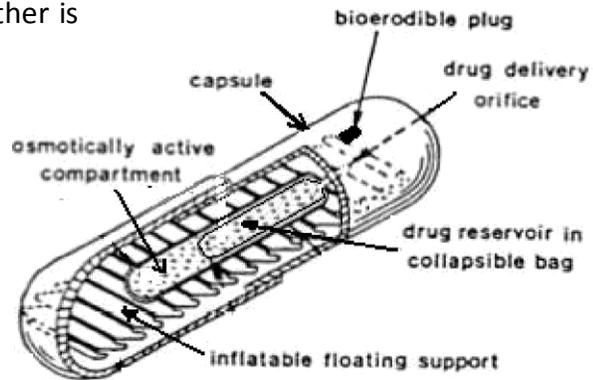
- ❑ The system is kept in HGC which degrades in stomach to release system.
- ❑ This system is hollow deformable unit consists of two chambers separated by an impermeable, pressure responsive movable bladder. First chamber contains drug reservoir and second chamber contains volatile liquid like ether, cyclopentane, etc. which gasifies at body temperature to cause inflation of chamber in stomach.

Inflation makes unit of lower density and gives buoyancy and also gives pressure on bladder to move and release drug from reservoir. The device may also consist of bioerodible plug that gradually dissolved, and after predetermined time (when all drug released), it unplugs system and gas release from system and system is then expelled out of body.



i) Osmotically controlled DDS

- ❑ The system is kept in HGC which degrades in stomach to release system.
- ❑ This system consists of mainly two different part attached with each other, one is floating part and other is osmotic controlled part.
- ❑ Floating part made up of deformable polymeric bag containing liquid that gasify at body temperature. Osmotic pressure controlling part consists of two part, drug reservoir & osmotically active compartment.
- ❑ Inner drug reservoir is in impermeable collapsible bag along with drug delivery orifice and outer osmotically active compartment made up of semipermeable membrane containing osmotically active salts.
- ❑ When system comes in gastric fluids, inflation of floating part gives buoyancy and osmotic pressure generated in outer compartment due to fluid intake and drug is release due via orifice under osmotic pressure.
- ❑ Floating part also contains biodegradable plug that gradually dissolved/erodes, and after predetermined time (when all drug released), it unplugs system and gas release from floating part and system is then expelled out of body.



B) EXPANDABLE APPROACH

- ❑ Expandable systems are also called as **plug type systems**. They achieve larger size in stomach and size of whole system goes beyond the size of pyloric sphincter and thus the system retains in stomach.
- ❑ The expandable GRDFs are usually based on three configurations:
 - o A small collapsed configuration which enables sufficient oral intake
 - o Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.
 - o A smaller form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.
- ❑ The expansion can be achieved by i) *Swelling system* ii) *Unfolding system*

i) Swelling systems

- ❑ Swelling system are generally matrix system containing hydrocolloids which by action of hydration and osmosis get swelled. Swelling index means how

much fold it can increase in volume and swelling time are the important factor for such systems.

☐ In every swellable hydrogel, **there are mainly 3 layers: 1st swelling, 2nd diffusion and 3rd erosion layer**. So along with swelling, erosion process also started. To develop dosage form having good strength to maintain integrity, it should have more cross linking of polymer chain. But higher cross linking is associated with poor swelling property and slower dissolution/diffusion of drug from hydrogel.

☐ So, there should be optimum amount of cross linking is require to maintain balance between swelling and dissolution of hydrogel.

a) Polymeric envelope

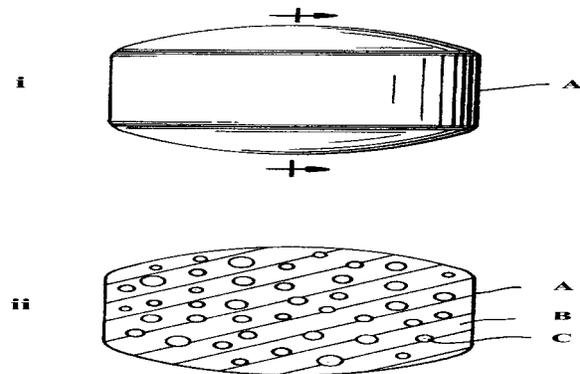
☐ This system comprise of drug reservoir (A) in center surrounded by swellable material (B) are placed in elastic polymeric envelope type system (C).

☐ The polymeric envelope is permeable to drug and fluids. This system gets swollen in gastric fluid and integrity is retained by elastic polymeric envelope and drug is released in controlled manner.

b) Tiny pills in the matrix

☐ Urquhart and Theeuwes developed a dosage form with a very high swelling ratio, exhibiting a 2-50 fold volume increase.

☐ In this system tiny pills containing drug are incorporated into hydrogel matrix and coated with wax to give strength to wall. Mechanism is not only by plug in pylorus sphincter, but it also keeps the stomach in fed state and thus delays house keeper waves which comes in fasted state.



i) The dosage from side-view

ii) The cross-sectional view which comprises of

A) Waxy wall

B) Hydrogel Matrix

C) Tiny pills

☐ After administration, system achieves high volume and tiny pills are released slowly out from matrix and gives GR to drug.

ii) Unfolding systems

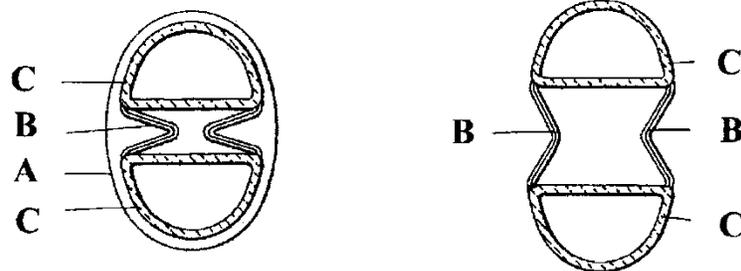
☐ Unfolding systems are systems which are actually of larger size but they are folded to decrease size and kept in capsules. In stomach these systems comes out of capsules and unfolds to larger size.

- ❑ The important factor for unfolding system is **shape memory**. They should have sufficient shape memory such that they retain their unfolded (expanded) shape in stomach against gastric motility and not get folded again and escape out till the desired time interval.

a) Obstructing means

- ❑ The 1st unfolding system developed for veterinary purpose and termed as “obstructing means” as they create obstruction in passage of food by plugging sphincter.
- ❑ It is capsule (A) containing 2 reservoirs (C) attached together with hydrophilic/hydrophobic strips (B).
- ❑ The flexible strips get enlarge and get sufficient strength and becomes rigid to achieve gastro retention.

Prior to administration Post-administration



A - gelatin capsule

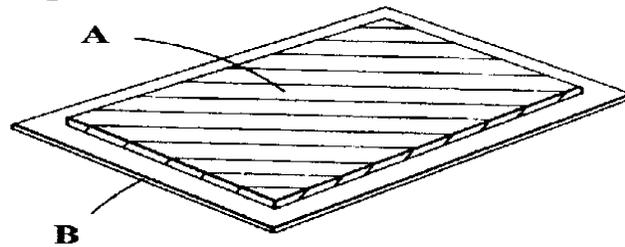
B - hydrophobic/hydrophilic strip

C - permeable material

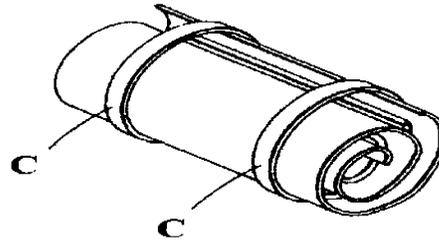
b) Multi-layer polymeric sheets

- ❑ This system has one erodible polymeric film containing drug (A) is adhere on another non-erodible carrier polymeric film (B).
- ❑ This bilayer sheet is folded and gelatin bands/strips (C) are used to maintain folded and system is placed in capsule. So in stomach capsule and gelatin band dissolves to give unfolded system.

Prior to folding

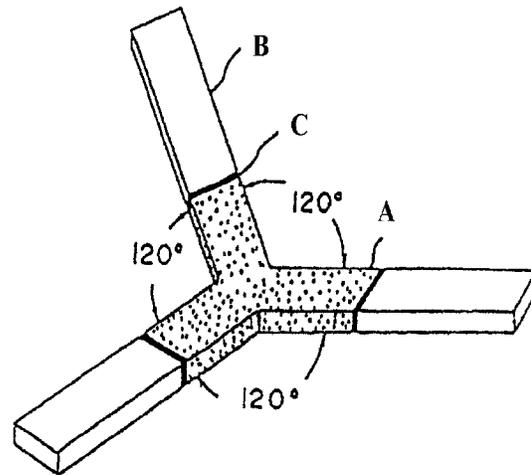


Folded, administration form



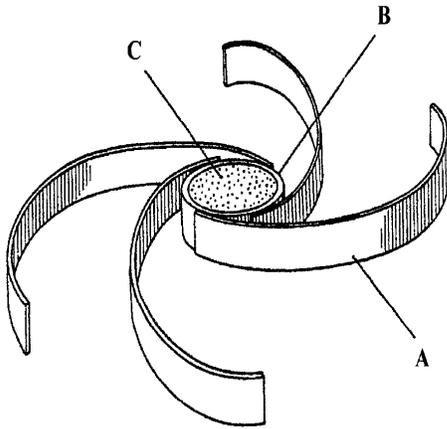
c) Geometrical configurations

□ Various geometric configurations tried are stick, ring, tetrahedron, planar disc, planar multilobe and ring. These devices had various properties like, sufficient resistance to forces applied by the stomach, thus preventing rapid passage through the pylorus; allowance of free passage of food while in residence in the stomach; and desired in vivo circumference larger than 5 cm, to ensure gastro-retentivity.



- Although various configurations tried, only tetrahedron shape gives good positive results and however other failed with some negative results in vivo. Then after other configurations tried, made by configurations with at least three coplanar limbs extending from a center, e.g. cylindrical-shape, cross-shape or Y-shape.
- They contain central shape memory material (A) assuring unfolding for prolonged time and outer erodible part containing drug reservoir (B).

c) Receptacle means



- ❑ This unfolding system is spiral or coil configuration. It is designed as a 'receptacle means' (A) that holds a drug reservoir formed as a tablet (B) or capsule, and one or more retention arms (C) attached to it.
- ❑ The retention arms, in the form of fibers or ribbons, are characterized by unfolding or uncoiling in the stomach to reach a circumference of more than 3 cm and gives gastro retention.

C) BIO MUCO-ADHESIVE APPROACH

- ❑ Adhesive systems may **adhere to mucin**, which is cytoprotective gel layer on membrane of stomach wall or adhere to epithelial cells. And thus due to adhesiveness in stomach wall, retain in stomach.
- ❑ The reason why **this approach is less used for GRDDS** can be answered by knowing fact that mucus layer is turning over continuously and mucus is not only at surface of lumen but also found within lumen as soluble mucus. Hence it can show wide variability and unpredictability.
- ❑ Although attempts has been done to use this advantage by preparing dosage form with combination of GRDDS technology like floating + bioadhesive.

D) HIGH DENSITY APPROACH

- ❑ The bottom part of stomach has curved shape (Rugae) and it is horizontally lower than the position of pyloric sphincter. Advantage of such geometry can be taken by preparing dosage form **having higher density around more than 1.004 g/cm³** (density of normal stomach content) and also capable to withstand peristaltic movement of stomach.
- ❑ These type of formulations having high density around 2-3 can be prepared by coating drug or mixing drug with heavy inert material like Iron powder, Zinc oxide, TiO₂ or BaSO₄ (Density = 4.9).

E) RAFT FORMING SYSTEMS

- ❑ Raft forming systems have received much attention for the delivery of

antacids and drug delivery for treatment of gastrointestinal infection and disorders.

- ❑ The mechanism involved in this system included the **formation of viscous gel** in contact with gastric fluids, wherein each portion of the liquid swells, forming a continuous layer called **RAFT**.

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

EVALUATION OF GRDDS

A) IN-VITRO EVALUATION

i) Floating systems

a) Buoyancy Lag Time

- ❑ It is determined in order to assess the **time taken** by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time

- ❑ Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37⁰C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

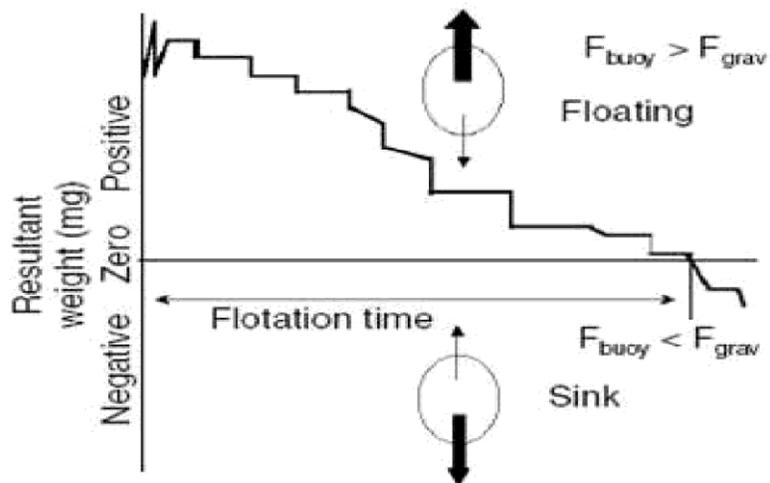
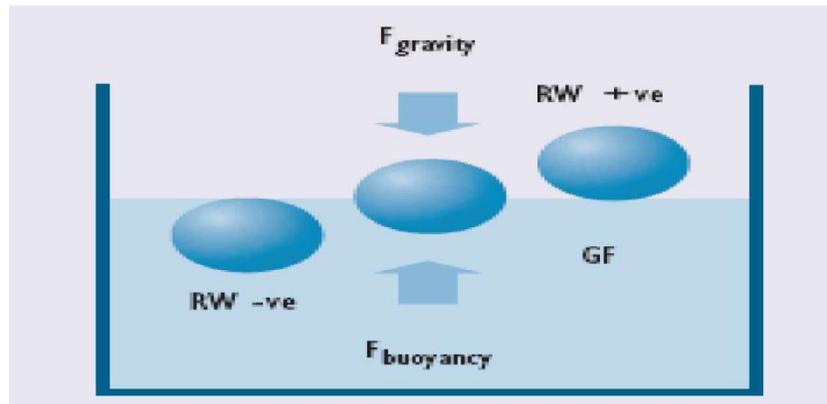
c) Specific Gravity / Density

- ❑ Density can be determined by the displacement method using **Benzene** as displacement medium.

d) Resultant Weight

- ❑ Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form.

- The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (F_{buoy}) and gravity force (F_{grav}) acting on dosage form



$$F = F_{buoy} - F_{grav} \quad F = D_f g V - D_s g V \quad F = (D_f - D_s) g V$$

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

Where,

- F** = resultant weight of object
- D_f** = Density of Fluid
- D_s** = Density of Solid object
- g** = Gravitational force
- M** = Mass of dosage form
- V** = Volume of dosage form

- So when D_s , density of dosage form is lower, F force is positive gives buoyancy and when it is D_s is higher, F will negative shows sinking.
- Plot of F vs. Time is drawn and floating time is time when F approaches to zero from positive values.

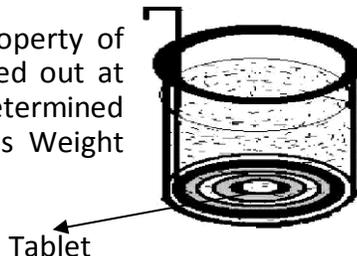
ii) Swelling systems

a) Swelling Index

- After immersion of swelling dosage form into SGF at 37°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

b) Water Uptake

- It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as Weight Gain.



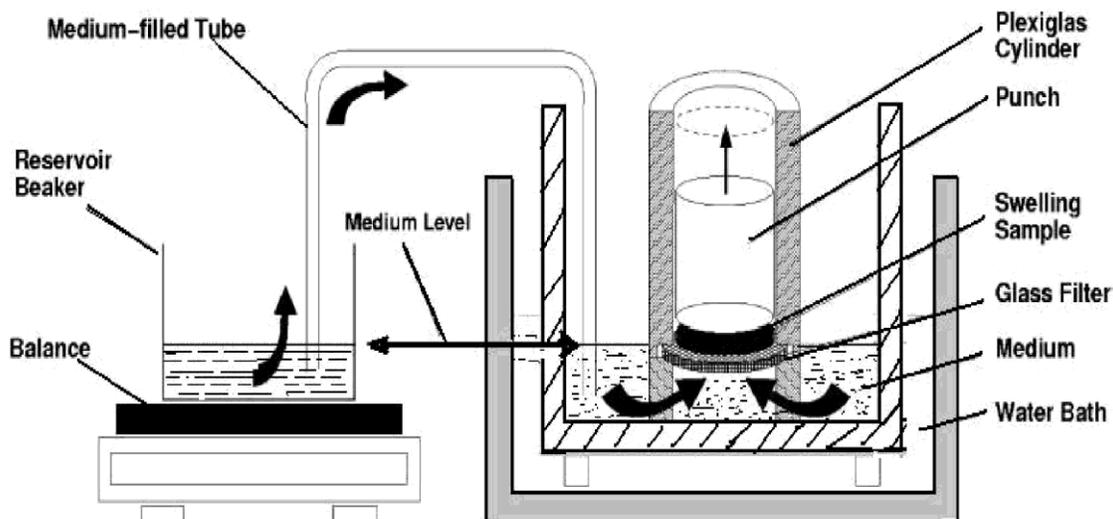
- Water uptake = $WU = (W_t - W_o) * 100 / W_o$
Where, W_t = weight of dosage form at time t
 W_o = initial weight of dosage form
- While we remove dosage form out and measure dimensions, the outer gel layer is disturbed which can create a problem. So new idea came into picture by which swelling index and water uptake can be measured without disturbing tablet.
- In this assembly concentric circles with various diameters are drawn in computer and print out is laminated to make hydrophobic. This laminated piece is attached with some system which can facilitate up and down movement of assembly.
- This assembly is placed in beaker and tablet is placed exactly at center and then there is no disturbance given to tablet.
- Tablet is allowed to swell on laminated paper and diameter can be easily noted without removing out.
- To determine water uptake/weight gain, whole assembly can bring out. Weighing of assembly done after wiping off water droplets adhered at surface of assembly and then can be placed back as it is without touching to tablet.
- Rate of water penetration is also important parameter for swelling matrix, that how fast swelling occurs is determined by equation:

$$\text{Penetration Rate} = \left(\frac{\text{Water uptake}}{\text{per Unit Time}} \right) \times \left(\frac{2 \times \text{Area of tablet}}{\text{Water Density}} \right)$$

c) Continuous monitoring of water uptake

- Although previous method has advantage of un-disturbance of swollen tablet, but for measuring water uptake one has to remove whole assembly out of beaker, so process is not continuous.

- ☐ Continuous monitoring of water uptake is possible by following apparatus.



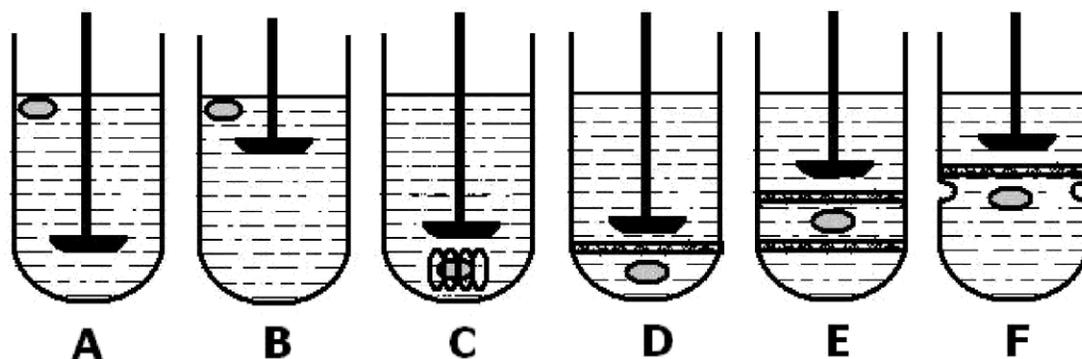
- ☐ In this apparatus, swelling tablet is placed on glass filter as support in one hollow cylinder with smooth surface inside, and one light weight punch is placed on it to prevent floating. This cylinder is placed pre-heated in dissolution medium.
- ☐ Another dissolution medium reservoir beaker is placed on digital balance and both are connected with media filled U tube as shown in figure and medium level is kept equal.
- ☐ As swelling of tablet started, it absorbs water and water level in outer part of cylinder is goes down. The decrease in water level is maintained by importing extra medium via U tube from reservoir beaker.
- ☐ As medium is transfer from reservoir, amount of water transfer can be determined by observing loss in weight by digital balance.

B) IN-VITRO DISSOLUTION TESTS

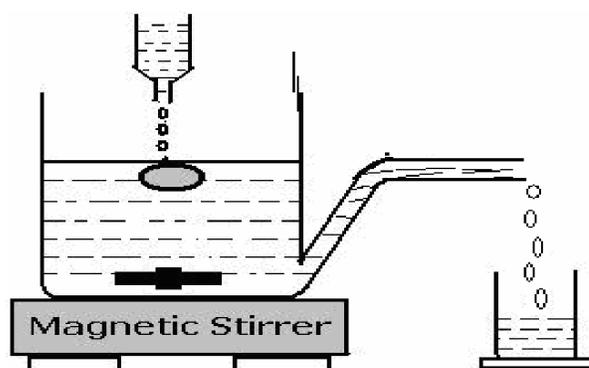
- A. In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results.

In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

- B. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.



- C. Floating unit can be made fully submerged, by attaching some small, loose, non-reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.
- D. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.
- E. Other method suggests placing dosage form between 2 ring/meshes.
- F. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.
- G. In spite of the various modifications done to get the reproducible results, none of them showed co-relation with the in-vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.



- ❑ Rossett-Rice test is used for predicting in-vitro evaluation of directly acting antacid (action by chemical neutralization of acid), where HCl is added gradually to mimic the secretion rate of acid from the stomach.
- ❑ In this modified apparatus as shown in figure, it has side arm from bottom of beaker such that it maintains volume of 70ml in beaker and fresh SGF is added from burette at 2 ml/min rate. Thus sink condition is maintained

along with easy sampling. Stirring is done by magnetic stirrer at 70-75 RPM. Thus this apparatus mimics in-vivo condition for GRDDS.

C) IN-VIVO EVALUATION

a) Radiology

- ☐ X-ray is widely used for examination of internal body systems.. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO₄ is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

b) γ -Scintigraphy

- ☐ Similar to X-ray, γ -emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used γ -emitting material is ⁹⁹Tc.

c) Gastroscopy

- ☐ Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) Magnetic Marker Monitoring

- ☐ In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e) Ultrasonography

- ☐ Used sometimes, not used generally because it is not traceable at intestine.

f) ¹³C Octanoic Acid Breath Test

- ☐ ¹³C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO₂ gas which comes out in breath. The important Carbon atom which will come in CO₂ is replaced with ¹³C isotope. So time upto which ¹³CO₂ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO₂ release. So this method is cheaper than other.

OTHER PARAMETERS:

Apart from the above evaluation, the multiple-unit systems should be evaluated for the micromeritic properties (particle size, size distribution, and density and flow property), surface morphology and physical state of the drug in the dosage form. The evaluation is important to avoid the problems encountered during filling

of these systems or compression into final dosage form.

DEMERITS OF GRDDS

- ❑ Floating systems has limitation, that they **require high level of fluids in stomach** for floating and working efficiently. So more water intake is prescribed with such dosage form.
- ❑ In supine posture (like sleeping), **floating dosage form may swept away** (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- ❑ **Food is also an important factor.** Presence of food delays emptying time of food and dosage form. So presence of food is preferable.
- ❑ **Drugs having stability problem** in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa can not be incorporated into GRDDS.
- ❑ Bio/mucoadhesives systems have problem of **high turn over rate of mucus layer**, thick mucus layer & soluble mucus related limitations.
- ❑ Swellable dosage form **must be capable to swell fast before its exit from stomach** & achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

Drugs Reported To Be Used In The Formulation Of Floating Dosage Forms: Table No.2

Sr.No.	Dosage forms	Drugs
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Terfinadine and Tranilast
2.	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
3.	Films	Cinnarizine
4.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin
5.	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid, Piretamide, Theophylline and Verapamil hydrochloride

Marketed preparation:

- Valrelease® Floating capsule *Diazepam* (15mg) Hoffmann-LaRoche, USA
- Madopar® HBS(Prolopa® HBS) Floating, CR capsule *Benserazide* (25mg) and *LDopa*(100mg) Roche Products, USA
- Liquid Gaviscon® Effervescent Floating liquid alginate preparations Al hydroxide (95 mg), MgCarbonate (358 mg) GlaxoSmithkline, India
- Topalkan® Floating liquid alginate preparation *Al – Mg antacid* Pierre Faber Drug, France
- Almagate Flotcoat® Floating dosage form *Al – Mg antacid –*
- Conviron® Colloidal gel forming FDDS *Ferrous sulphate* Ranbaxy, India
- Cytotech® Bilayer floating capsule *Misoprostol* (100µg/200µg) Pharmacia, USA
- Cifran OD® Gas-generating floating form *Ciprofloxacin* (1gm) Ranbaxy, India

■ Future Prospects:

While the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called 'once-a-day' formulations may be replaced by novel gastroretentive products with release and absorption phases of approximately 24 hours.