Introduction to GRDDS

- Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects.
- Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.
- Gastro retentive Drug Delivery Systems are oral dosage forms which have the ability to be retained in the GI tract and resist rapid gastric emptying.
- This system is a promising approach for drugs having a narrow absorption window.

Introduction to GRDDS

- Oral drug delivery is widely used in pharmaceutical field to treat the diseases.
- Some drugs are absorbed at specific site only, these require release at that specific site.
- Gastro retentive drug delivery(GRDDS) is one of the site specific drug delivery for the delivery of the drugs at stomach.
- It is obtained by retaining dosage form into stomach and drug is being released at controlled manner at specific site.

Suitable candidate drugs for GRDDS

- Drugs acting locally in the stomach.
  - Example: Antacids and drugs for H. Pylori viz., Misoprostol.
- Drugs that are primarily absorbed in the stomach.
  - Example: Amoxicillin
- Drugs that is poorly soluble at alkaline pH.
  - Example: Furosamide, Diazepam, Verapamil, etc.
- Drugs with a narrow absorption window.
  - Example: Cyclosporine, , Levodopa, Methotrexate etc.

- Drugs which are absorbed rapidly from the GI tract.
  - Example: Metronidazole, tetracycline.
- Drugs that degrade in the colon.
  - Example: Ranitidine, Metformin.
- Drugs that disturb normal colonic microbes
  - Example: antibiotics against Helicobacter pylori.

Unsuitable drug candidates for GRDDS

- Drugs having very limited acid solubility
  - Example: Phenytoin
- Drugs that exhibits instability in the gastric environment
  - Example: Erythromycin
- Drugs that are used for selective release in the colon
  - Example: 5- amino salicylic acid and corticosteroids

Advantages of GRDDS

- Enhanced bioavailability,
- Sustained drug delivery/reduced frequency of Dosing,
- Targeted therapy for local ailments in the upper GIT,
- Reduced fluctuations of drug concentration,
- Improved selectivity in receptor activation,
- Reduced counter-activity of the body,
- Extended effective concentration,
- Minimized adverse activity at the colon.

Disadvantages of GRDDS

- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs which are irritant to gastric mucosa are also not suitable.
- These systems do not offer significant

Factors Controlling the Gastric residence time of dosage forms

	Formulation Factors: Dosage Form Related Factors		Food Intake and Its Nature		Patient Related Factors
1	Density of Dosage Form	1	Fed or Unfed State	1	Gender
2	Size of Dosage Form	2	Nature of Meal	2	Age
3	Shape of Dosage Form	3	Caloric Content	3	Disease State
4	Viscosity Grade of Polymer	4	Frequency of Food	4	Emotional State of Subject
5	Single or Multiple Unit Formulation			5	Posture - Upright Position/ Supine Position

Factors Controlling the Gastric residence time of dosage forms

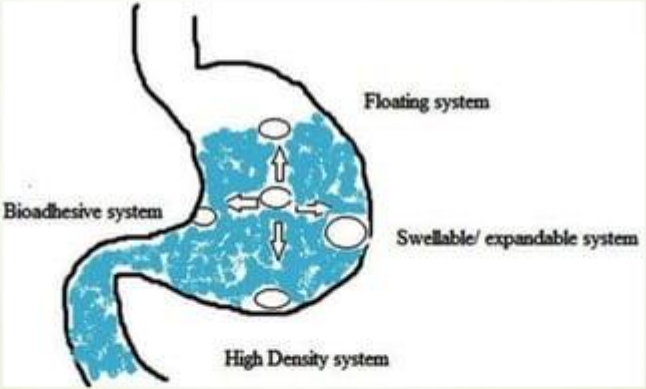
- **Density:** Dosage form with lower density in the gastric content can float to the surface while high density sink to the bottom of the stomach. Suitable density required for floating property is less than 1.0 gm/ cm^3.
- **Size:** Size should be more than 7.5 mm in diameter.
- **Shape:** Either round or spherical shaped dosage form exhibit better property related to other shapes.
- **Single or multiple unit formulation:** Multiple units are desirable due to foretell release profile.
- **Fed or Unfed State:** Gastric retention time is less during fasting condition due to rise in gastric motility.
- **Nature of Meal:** High amount of fatty acid and other indigestible polymers slow down the gastric retention time due to variation in gastric motility.

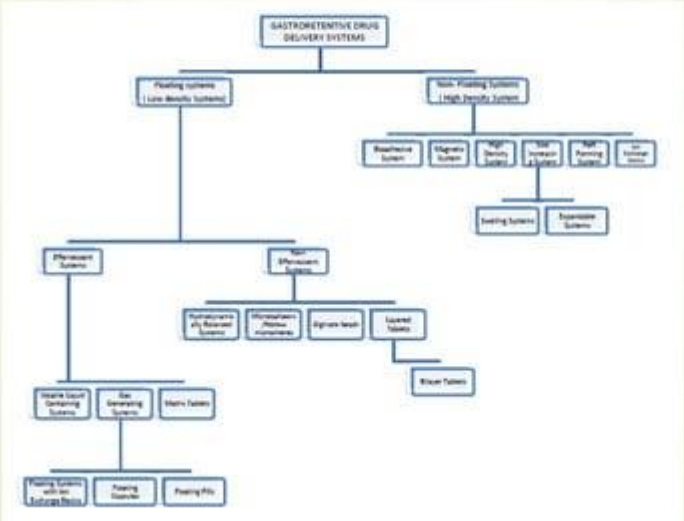
Factors Controlling the Gastric residence time of dosage forms

- **Frequency of Feed:** Low frequency of migrating myoelectric complex (MMC) contributes to GRT upto 400 times which inturn depends on the frequency of food intake.
- **Caloric Content:** A high protein and fat rich diet can increase GRT by 4 to 10h.
- **Gender:** Males have greater GRT than females.
- **Age:** GRT is more in geriatric patients and less in neonates and children. Age above 70 (>70) exhibit longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Disease State:** Gastric disease such as diabetes, Chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc. fluctuates the GRT.
- **Concomitant Intake of Drug:** Combination of some drugs along with gastric motility enhancers or depressants, affect GRT

Rationale for the use of GRDDS

Approaches for prolonging the gastric residence time




GASTRORETENTIVE DRUG DELIVERY SYSTEMS
Floating systems
Non-Floating Systems
Bioadhesive System
Magnetic System
High Density System
High Swelling System
High Porosity System
Swelling Systems
Expandable Systems
Effervescent Systems
Non-Effervescent Systems
Sucrose Tablets
Floating Capsules
Floating Pills

Floating System

- Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability.
- Low density/floating systems are the most practical and extensively studied gastro retentive dosage forms.
- This system is classified into two types; based on the mechanism of buoyancy.
  - Non-effervescent floating and effervescent floating systems.
- This property allows the system to remain buoyant in the stomach for a prolonged period of time.
- The major requirements for floating drug delivery system are:
  - It should release contents slowly to serve as a reservoir.
  - It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm^3).
  - It must form a cohesive gel barrier.

Non-Effervescent Floating Systems

- Highly swellable cellulose derivatives or gel-forming polymers are used in non-effervescent systems.
- The formulation technique involves mixing of drug with a gel-forming polymer.
- Various non-effervescent systems include hydro dynamically balanced systems, micro balloons/ microspheres, Alginate beads, layered tablets.
- Various gel-forming hydrophilic polymers such as HPMC, HPC, Sodium CMC, carrageenan, agar, alginic acid etc. are used to design hydrodynamically balanced system.
- In this system, the drug and polymer is mixed and filled in the gelatine capsule.
- By simple solvent evaporation or solvent diffusion technique, drug-loaded micro balloons/hollow microspheres are formulated.
- Polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar are polymers commonly used to design micro balloons.
- In alginate beads approach, a solution of sodium alginate is dropped into an aqueous solution of calcium chloride and caused the precipitation of calcium alginate.
- These beads can prolong the GRT for more than 5.5 hrs.

Effervescent Floating Systems

- This system includes a gas generating system and volatile liquids.
- This can be applied for single and multiple-unit systems.
- Effervescent agents such as sodium bicarbonate, calcium carbonate, tartaric acid, citric acid are used in combination with hydrophilic polymers are used in the gas generating floating systems.
- When this system comes in contact with gastric fluid, CO_2 is liberated due to the reaction of the effervescent agent with gastric fluid.
- The liberated CO_2 will provide the tablet buoyancy and influence the drug release properties.
- This type of floating systems can be classified into single and double layer floating tablets or multiple unit effervescent floating system.
- Low-Density systems are usually associated with problems such as sticking or being obstructed in the GIT, which can cause gastric irritation.
- Drugs which cause irritation to gastric mucosa are not suitable candidates for low-density systems.
- Volatile liquid containing systems consist of dual chambers having an impermeable, pressure responsive movable bladder separation.
- The floating bases on the incorporation of volatile liquid as Ether or cyclopentane, introduced inflatable chamber which volatilizes at body temperature allowing the system to increase in size and float over the gastric fluids.

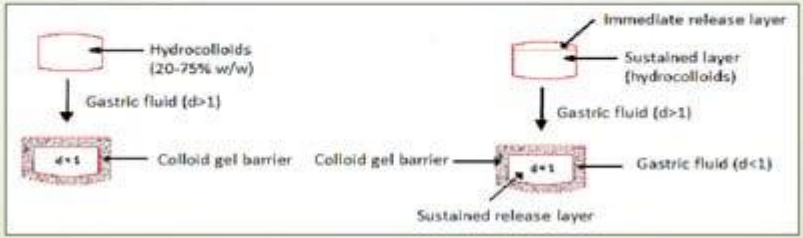
Effervescent Floating Systems

- The effervescent systems can be further classified into two types:
  - Gas Generating systems and
  - Volatile Liquid/Vacuum Systems

- **Gas-generating Systems:** 3 types-
  - HBS,
  - Intra Gastric Bilayer Floating Tablets or
  - Multiple Unit type floating pills

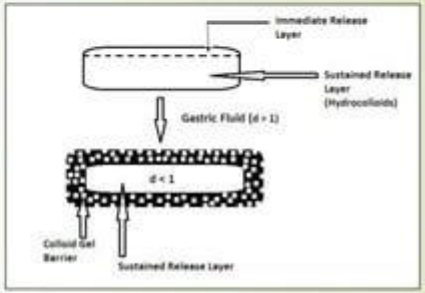
Effervescent Floating Systems

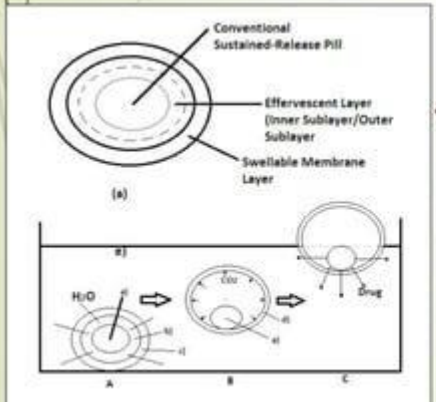
- **Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):**
  - These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet.
  - These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period.
  - The drug is slowly released at a desired rate for a prolonged period.
  - The drug is slowly released at a desired rate from the system and is expelled from the stomach.
  - This leads to an increase in the gastro retentive time and a better control over fluctuation in plasma drug concentration.



Effervescent Floating Systems

- **Intra Gastric Bilayer Floating Tablets:** These are also compressed tablet as and contain two layers i.e. Immediate release layer and Sustained release layer.





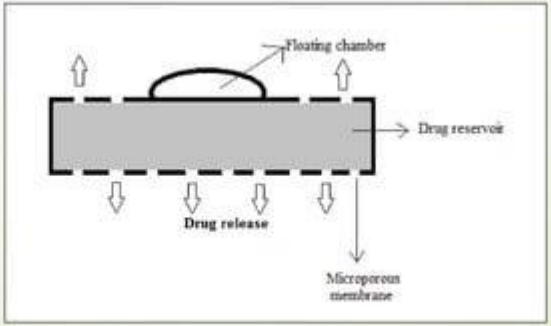
- **Multiple Unit type floating pills:** These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the system.

Effervescent Floating Systems

- Volatile Liquid / Vacuum Containing Systems: It may be classified in 3 types as:
  - Intragastric Floating Gastrointestinal Drug Delivery System,
  - Inflatable Gastrointestinal Delivery Systems and
  - Intragastric Osmotically Controlled Drug Delivery System

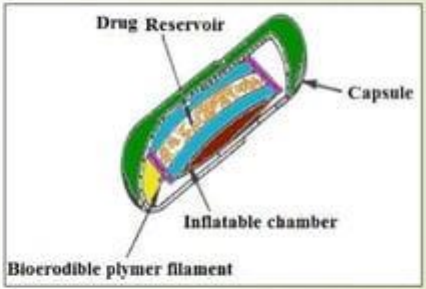
Effervescent Floating Systems

- Intragastric Floating Gastrointestinal Drug Delivery System:
  - These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

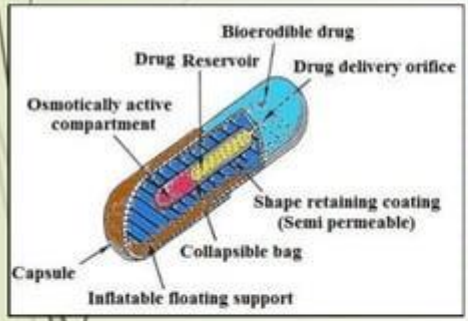


Effervescent Floating Systems

- **Inflatable Gastrointestinal Delivery Systems:**
  - In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach.
  - These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule.
  - After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber.
  - The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.



Effervescent Floating Systems

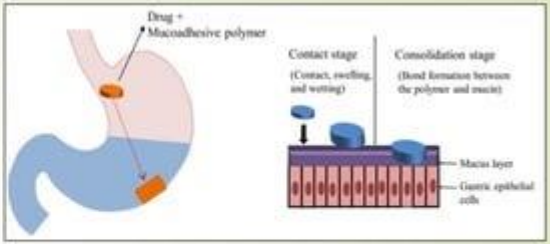


- **Intragastric Osmotically Controlled Drug Delivery System:**
  - It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule.
  - In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.
  - The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag.
  - The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment.
  - The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice.
  - The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing.
  - In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt.
  - An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.
  - The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support.
  - The deflated drug delivery system is then emptied from the stomach.

High-density systems

- This is also called as High density (sinking) system or non- floating drug delivery system.
- This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm^3).
- These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc.
- The materials increase density by up to 1.5- 2.4 gm/cm^3.
- A density close to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time.
- Non-floating systems are class of gastro retentive drug delivery systems which do not float but remain in the stomach for a prolonged time period.
- High-density systems have a density greater than that of gastric fluid.
- This system is classified into bioadhesive systems, magnetic systems, swelling and expandable systems, raft forming systems.

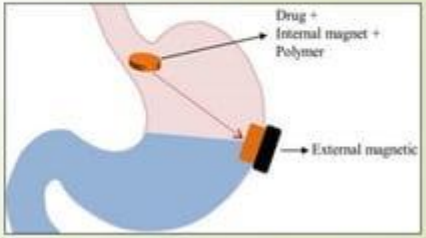
High-density systems



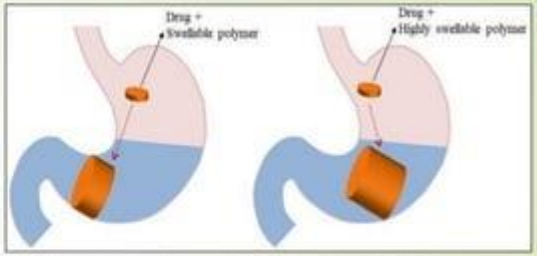
- **Bioadhesive / Mucoadhesive Systems:**
  - This system was designed to adhere to the gastric mucosa and prolong the GRT of drug compounds.
  - In this system, drugs are incorporated into a mucoadhesive agent, which may be natural or synthetic polymers.
  - These polymers are usually macromolecules, a hydrophilic gelling substance with hydrogen bond-forming groups and anionic.
  - Example for these polymers are sodium carboxymethylcellulose, sodium alginate, chitosan and carrageenan.
  - An ideal mucoadhesive polymer is inert, non-irritating, nontoxic adheres to the mucosal surface and possesses site-specificity and interacts with the mucin through electrostatic disulphide hydrogen and hydrophobic bonding.
- The mechanism of mucoadhesion is highly complex and is not fully understood different theories postulated are given below.
  - Wettability – Bioadhesive polymers penetrate and develop intimate contact with the mucous layer.
  - Diffusion – Physical entanglement of mucin strands and flexible polymer chains.
  - Adsorption – Bio adhesion is due to primary forces and secondary forces between surfaces.
  - Electronic – Attractive electrostatic forces between the main network and bioadhesive material.

High-density systems

- **Magnetic Systems:**
  - This system consists of an active pharmaceutical ingredient, excipients and also a small amount of internal magnet.
  - Studies have proved that GRT and bioavailability are improved by magnetic tablets. In this system, extracorporeal magnet is placed over the stomach to control the position of the dosage form containing an internal magnet, and plasma concentration can be increased in the presence of an extracorporeal magnet.
  - In this system, main drawback is the specific positioning of the magnet is difficult to achieve and which results in low patient compliance.



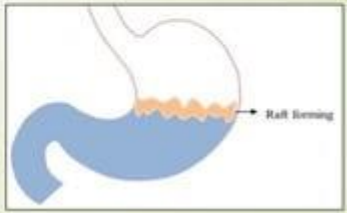
High-density systems



- **Swelling and expandable systems:**
  - This type of drug delivery systems is designed to have a longer GRT through an increase in their volume or shape.
  - Swelling should be above the diameter of the sphincter.
  - The diameter of the pyloric sphincter varies among individuals, it is reported 12.8 +/- 7.0 mm, but because the sphincter contains muscles, it has the ability to stretch and allow even large dosage form to pass through the sphincter during the migration myoelectric complex MMC, to avoid this defect the size of the dosage form should be greater than 20 mm.
  - The main mechanism for swelling and drug release from the system is diffusion. In these systems hydrophilic polymers (e.g.; HPMC, Poly ethylene oxide and Carbopol that can absorb water from the gastric fluids are used.
  - It is important to select a suitable polymer with appropriate molecular weight, viscosity grade and swelling properties to maintain a sustained release profile of the dosage forms.
  - Some of the limitations of expandable systems are difficulty in storing easily hydrolysable biodegradable polymers, being difficult to manufacture and may not be cost-effective, difficulty in maintaining the structural integrity and may cause bowel obstruction, intestinal adhesion and gastropathy.

High-density systems

- **Raft forming systems:**
  - This type of system formulated with effervescent excipients and get forming polymers in order to achieve sustained drug delivery.
  - This can effectively be used for the management of gastric oesophageal reflux diseases because floating rafts act as blockages between oesophagus and stomach.
  - Systems with a density of 1.3g/ml or higher are expected to be retained in the lower part of the stomach.
  - This system is mainly used for delivering antacid drugs, because the raft can remain intact in the stomach for several hours, promoting the sustained release of the drug.
  - In this system sodium alginate used as get-forming polymer, sodium bicarbonate and acid neutralizer as gas generating agents.
  - This type of polymer forms a viscous and cohesive gel when it swells and CO_2 bubbles produced by the reaction of carbonates and gastric fluid.



Commonly used drugs in formulation of GRDDS

Dosage form	Drugs
Tablets	Cephalexin, Ziduvudine, Losartan, Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Amoxycillin trihydrate, Dilitiazem, Florouracil, Piretanide, Prednisolone, Riboflavin- 5`Phosphate, Metformin Hydrochloride, Atenolol, Aceraminophen, Ampicillin.
Capsules	Nicardipine, L-Dopa and benserazide, chlordizepoxide HCl, Furosemide, Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid, Pepstatin, Celiprolol HCl.
Microspheres	Verapamil, Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Tranilast, Iboprufen, Terfenadine, Piroxicam, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Rosiglitazone maleate, Flurbiprofen, Orlistat.
Granules	Indomethacin, Diclofenac sodium, Prednisolone, Cinnarizine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, Ranitidine HCl.
Films	Albendazole, P-aminobenzoic Acid, Piretanide, Prednisolone, Quinidine gluconate, Cinnarizine.
Powders	Riboflavin, Sotalol, Theophylline
Bilayer tablets	Misoprostal, Trimetazidine hydrochloride and Metoprolol succinate, Diltiazem HCl and Lovastatin, Atenolol.
Beads	Ranitidine HCl, Loratadine, Curcumin β-cyclodextrin complex, Diltiazem HCl.

Mechanism and polymers used in non-floating GRDDS

Non-Floating Systems	Mechanism	Polymer/ Material Used
Bioadhesive Systems	Bioadhesive systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release	Polycarbophil , Carbopol, Lectins, Chitosan, Carboxy Methyl Cellulose, Gliadin, Polyethylene Glycol, Tragacanth, Dextrin, Chitosan, Sodium Alginate, Cholestyramine, Cholestyramine, Poly Acrylic Acid, Hydroxypropyl Methylcellulose, Sucralfate.
Swelling Systems	After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus.	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxy Propyl Methyl Cellulose (HPMC) (K4M, K100M and K15M), Gellan gum, Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC).
High Density Systems	These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach.	Zinc Oxide, Titanium Dioxide, Iron Powder, Barium Sulphate

Applications of GRDDS

- **Sustained Drug Delivery:** GRDDS float on the gastric contents over a prolonged period of time, as these systems have bulk density <1.
- **Site-Specific Drug delivery:** This delivery system is very useful for drugs that are absorbed from the stomach or the proximal part of the small intestine, especially with respect to their application for the treatment of H. Pylori infections.
- **The fluctuation of Drug Concentrations can be minimized:** This feature is important for drugs with a narrow therapeutic index. Fluctuations in drug effects are minimized and concentration-dependent adverse effects that are associated with peak concentration can be prevented.
- **Absorption Enhancement:** This is important in the case of drugs that are absorbed from the upper part if the GIT and by formulating this type of drugs as GRDDS can improve the poor bioavailability, thereby maximising their absorption.


Thank You