●GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

(GRDDS)

"Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine."

➢ Rationale of GRDDS-

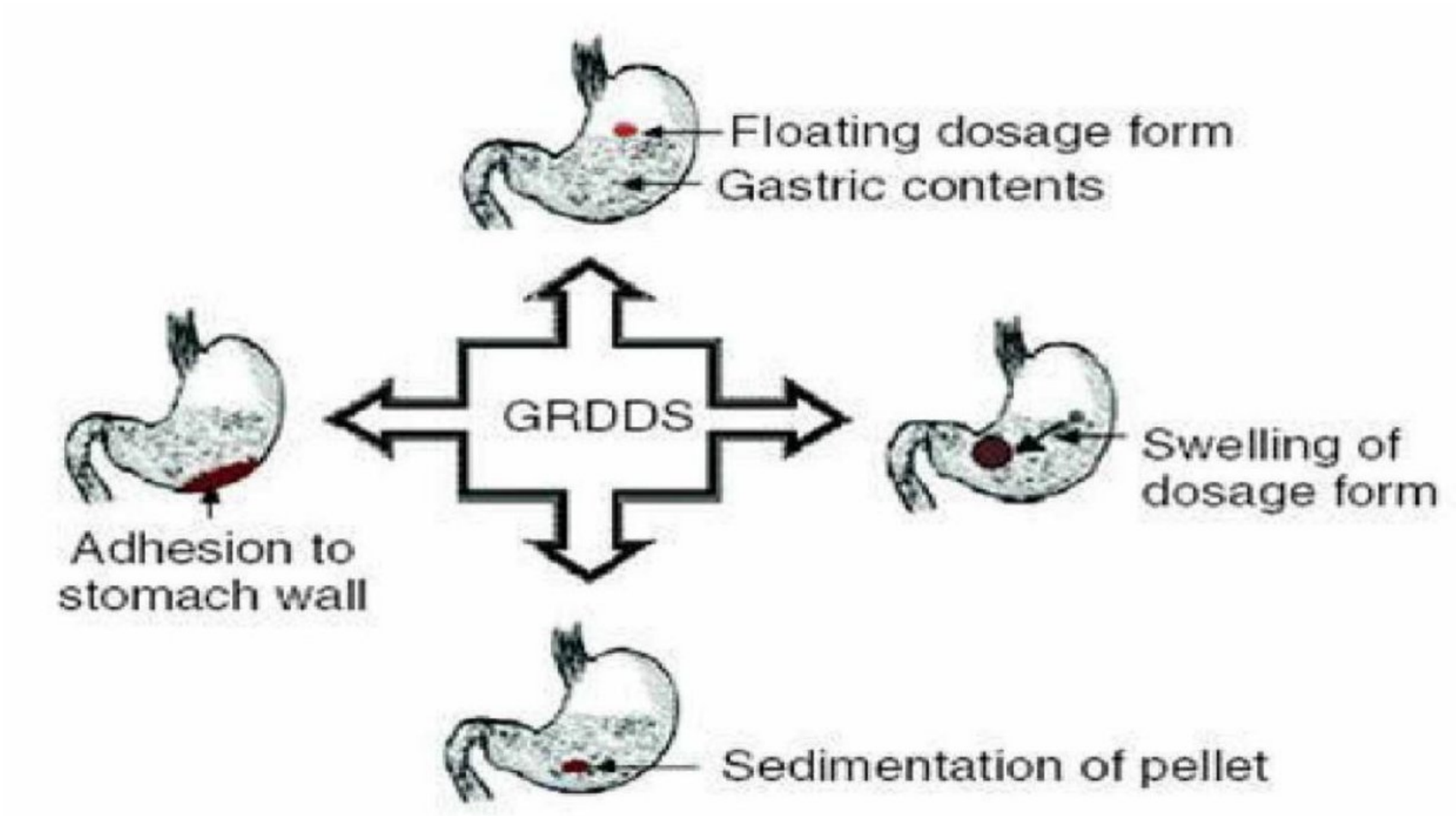
- Delivery of drugs with narrow absorption window in the small intestine region.
-Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
-Improved bio-availability is expected for drugs that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

→ Drugs benefited by 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. Metronidazole, tetracycline.
- ✓ Drugs that degrade in the colon.
  E.g. Ranitidine, Metformin HCl.

❖ Approaches for GRDDS:-

(1) Low density systems (Floating drug delivery)
(2) Expandable/Swellable systems
(3) Bio/Muco-adhesive systems
(4) High density systems
(5) Raft forming systems



Low Density Approach (Floating drug delivery) / HBS:-

- **Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems (HBS) 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.

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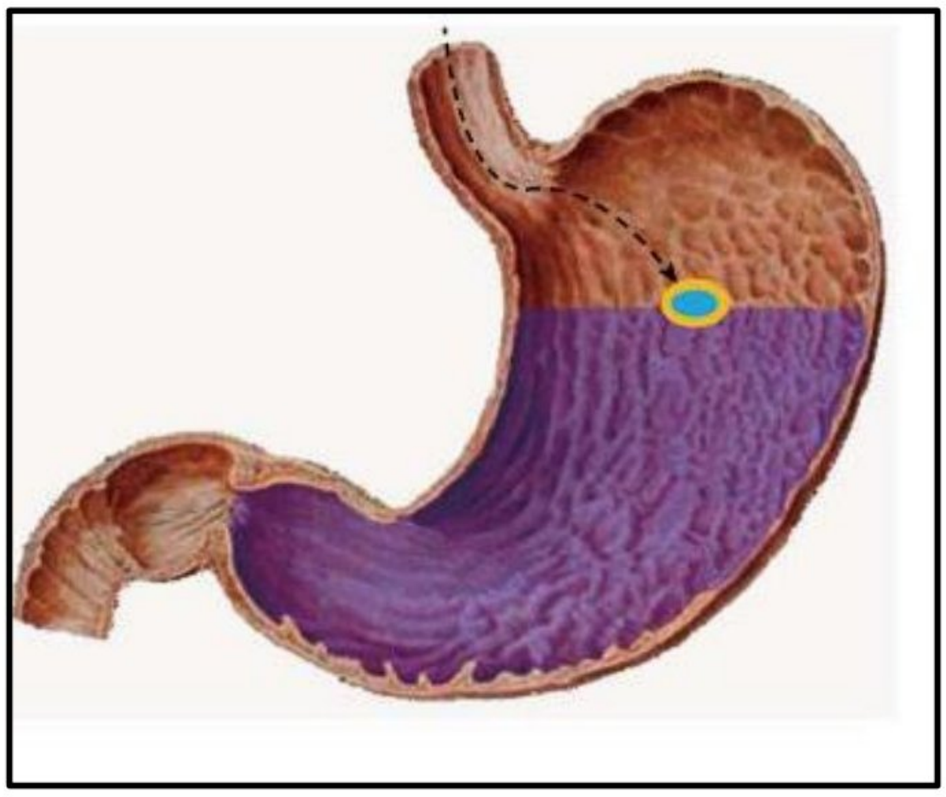


Low Density Approach/ Floating systems

CLASSIFICATION OF THE FLOATING SYSTEMS

- Effervescent systems
- Non-Effervescent systems

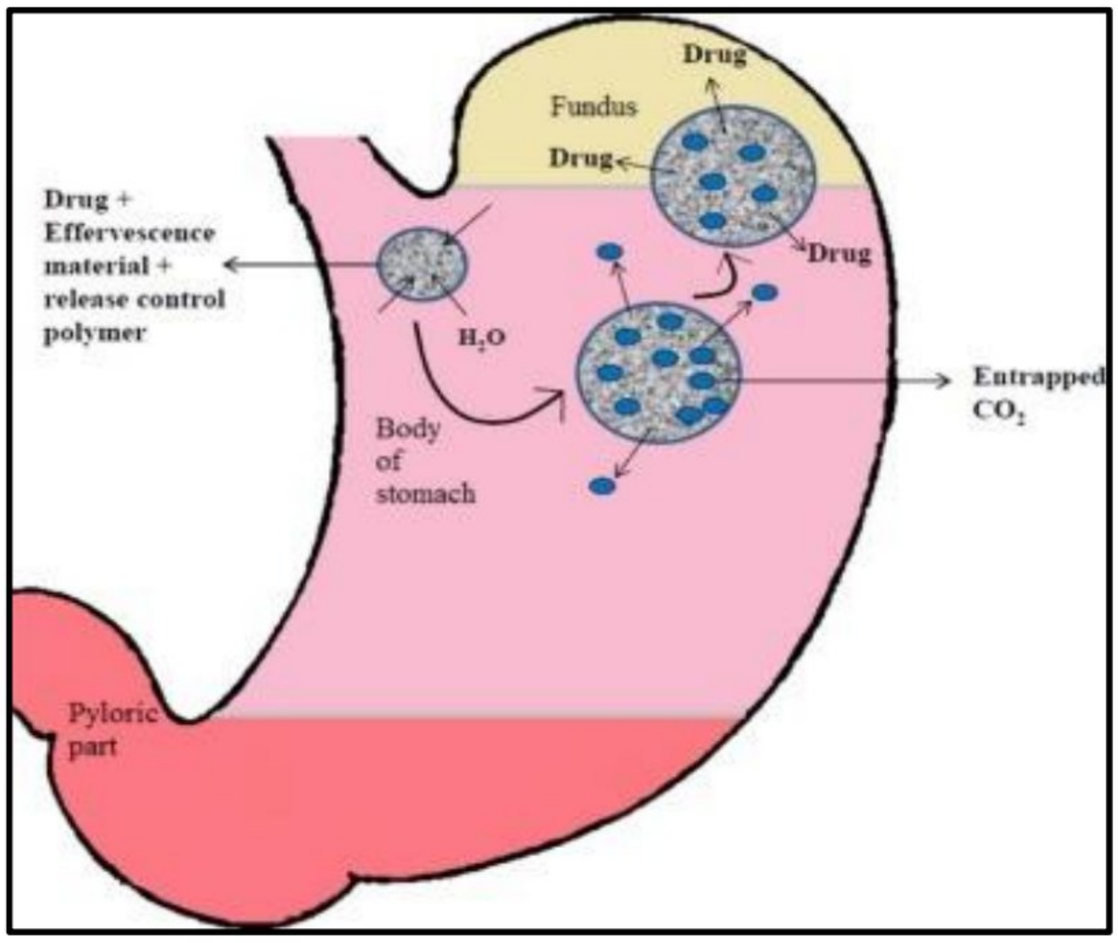
[1] Effervescent systems-

-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, **CO_2 is liberated and gets entrapped in swollen hydrocolloids**, which provides buoyancy to the dosage forms.

-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.



Effervescent systems

[2] 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 GI fluid.

-Within the outer gelatinous barrier, the air entrapped by the swollen polymers confers to the buoyancy of these dosage forms.

➢ Evaluation of FDDS/ HBS/ Low density systems-

a) Floating 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) Total Floating Time-

-Test is usually performed in SGF-Simulated Gastric Fluid maintained at 37° C. 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-

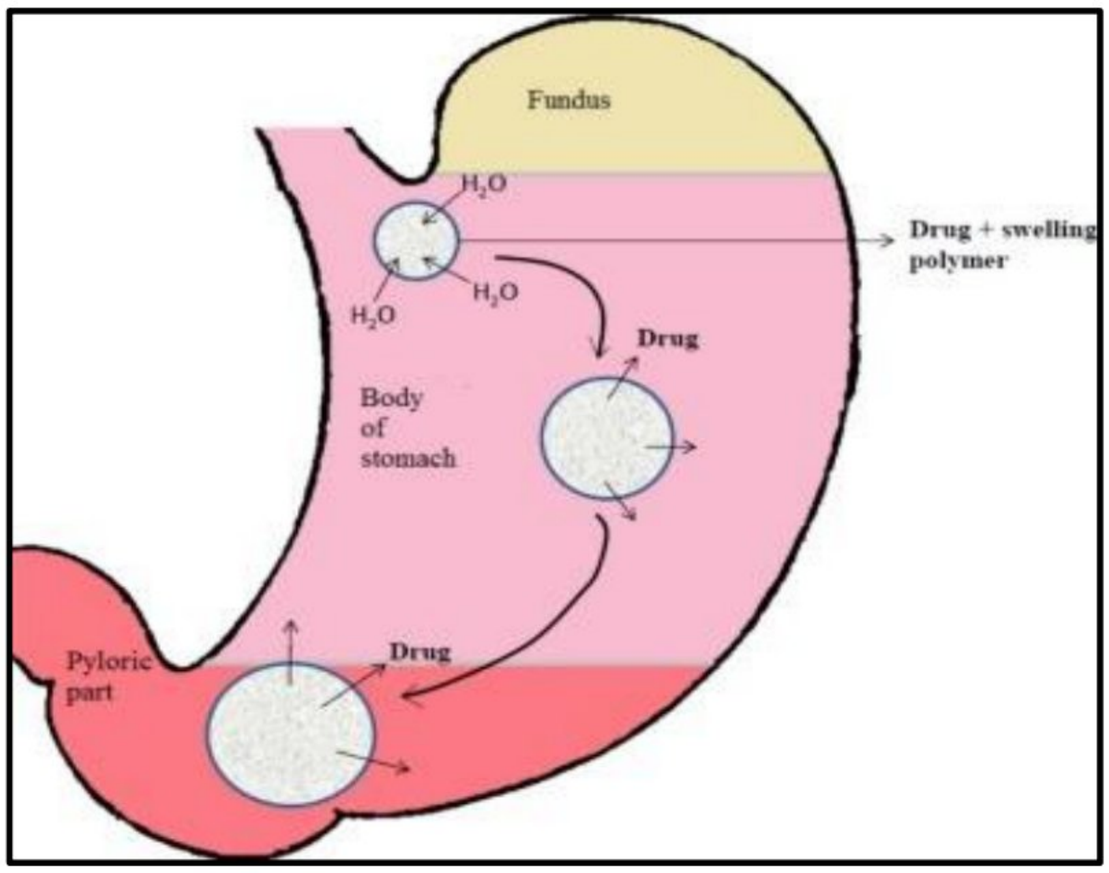
-It is the weight of dosage form after complete swelling and floating.

-Used to determine the final wt. because as the drug release from the intact tablet, the weight decrease leading to entry of GI fluids and sinking of tablet.

e) *In-vivo* test-

Expandable/ Swelleble 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.



Expandable Approach

-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.

➢ Evaluation of Swelling/ Expandable 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-

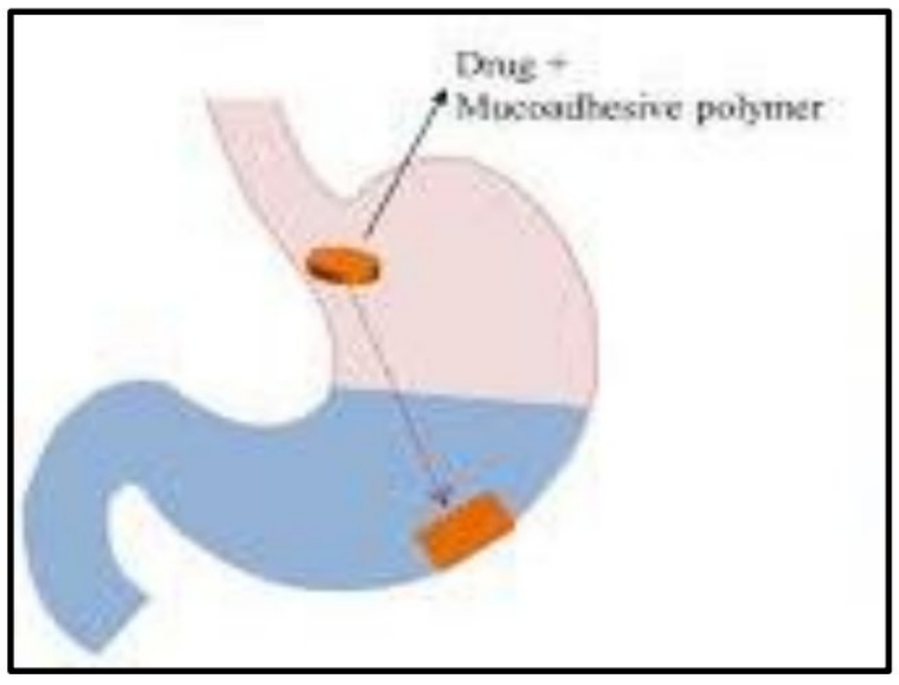
-It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as Weight Gain.

Mucoadhesive 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.

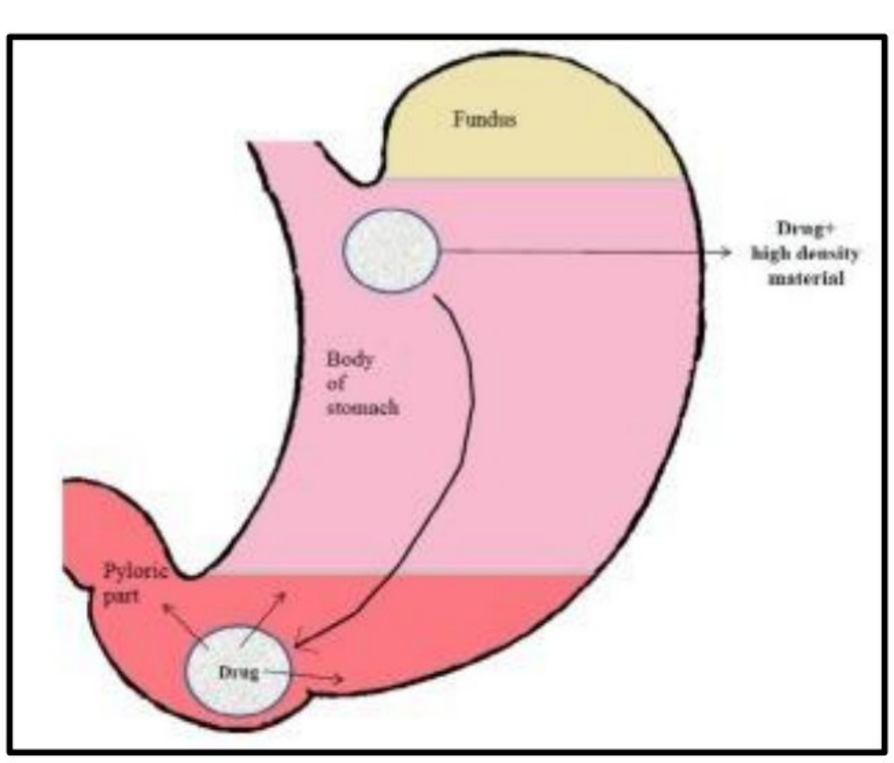


Mucoadhesive Approach

High Density Approach:-

-The bottom part of stomach has curved shape 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.

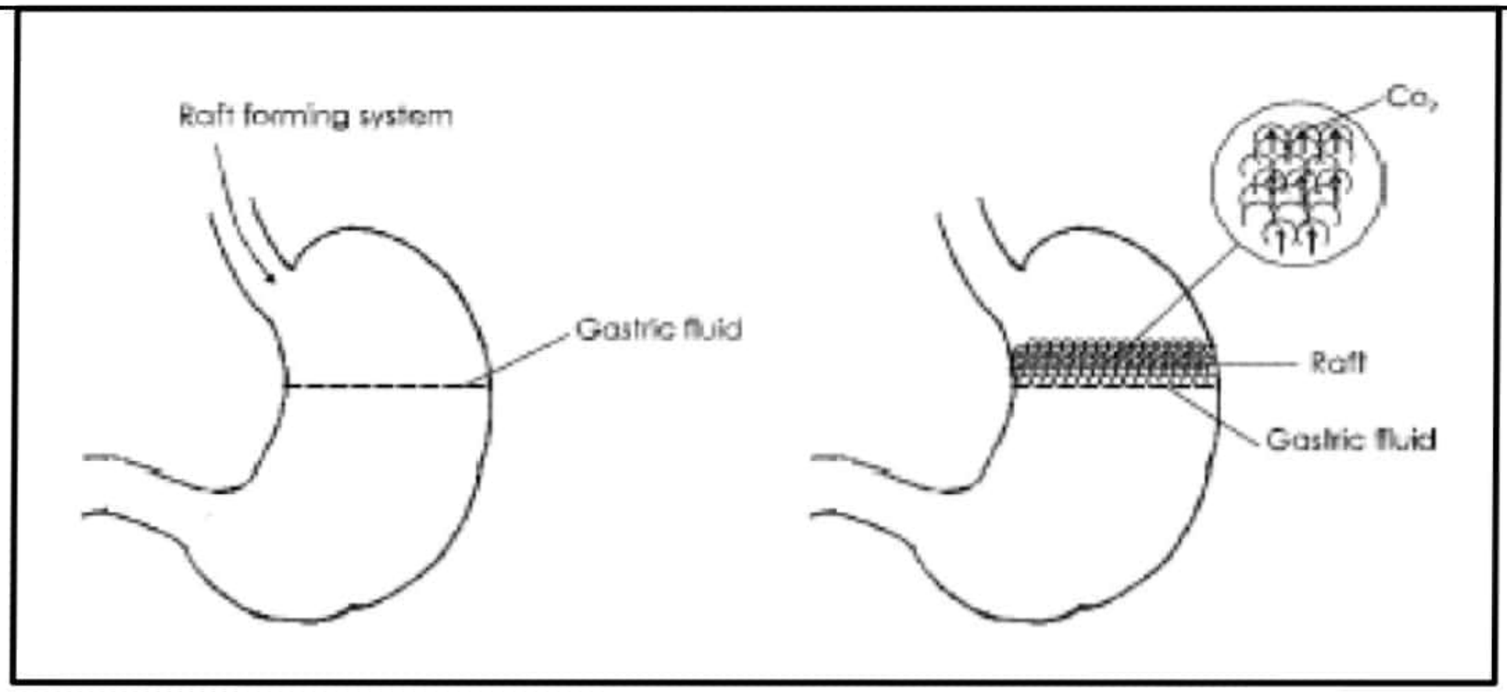
-These type of formulations having high density around 2-3 can be prepared by coating drug or mixing drug with heavy inert material like Iron powder, Zinc oxide, TiO_2 or $BaSO_4$ (Density = 4.9).



High Density Approach

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 CO_2.
-Usually this contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense to float on the gastric fluids.



Raft forming systems

Advantages of GRDDS-

-Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction in dose.

-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 anti-biotics.

-Retention of drug delivery systems in the stomach prolongs.

Disdvantages 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 .