Gastroretentive Drug Delivery Systems

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Introduction :

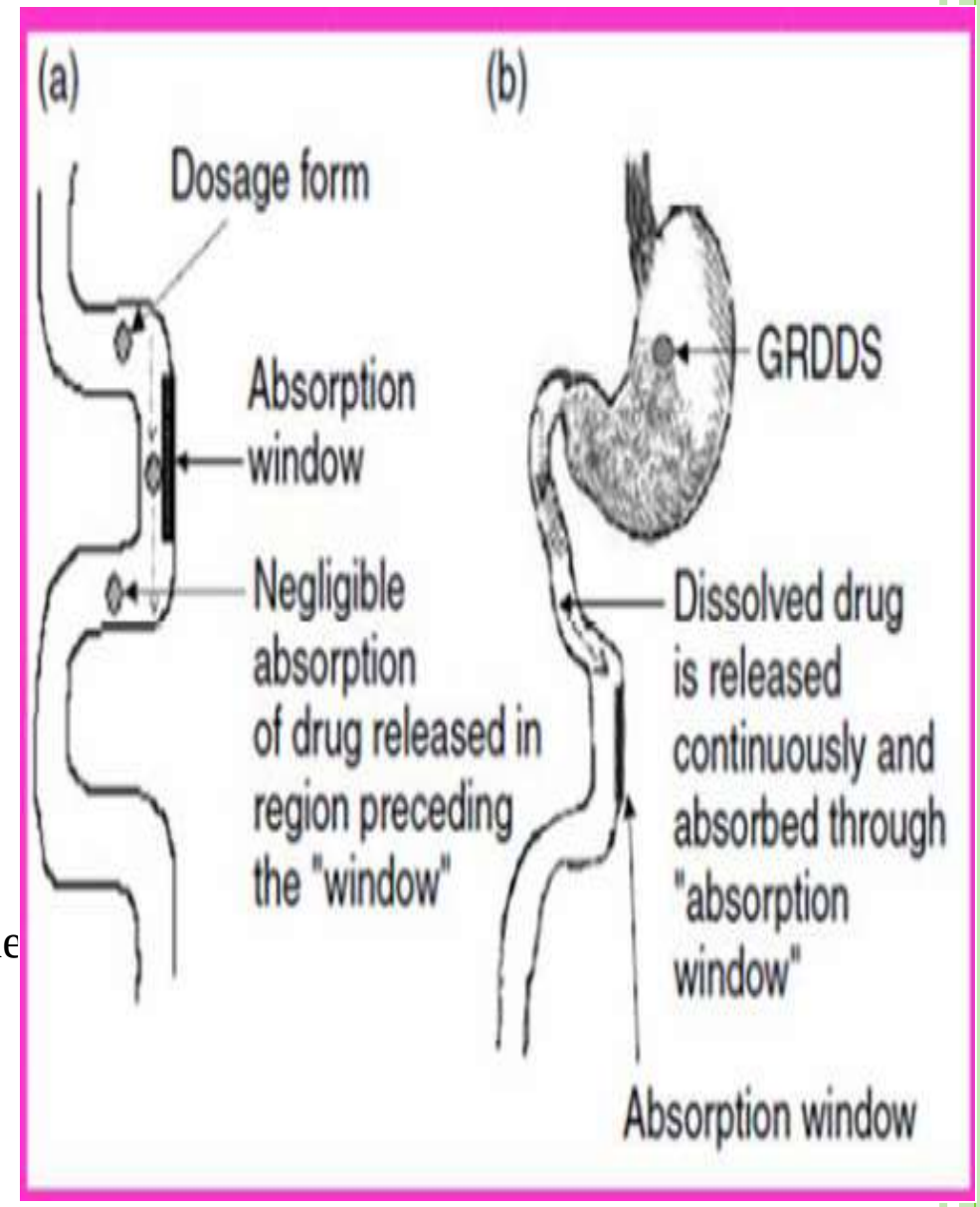
1. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.

2. Prolonged gastric retention improves the bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

3. It has applications also for local drug delivery to stomach and proximal small intestine.

Requirements of Drugs for Gastro Retention

- Drugs that absorb from stomach
  Ex: Levodopa, Furosemide
- Acting locally in stomach
  Ex: Antacids, Antiulcer and Enzymes
- Antibiotic therapy.
- Poorly soluble at alkaline pH.
  Ex: Diazepam, Salbutamol
- Degrade in colon.
  Ex: Captopril, Ranitidine, Metronidazole
- Narrow window of absorption



Gastric Retention Is Unsuitable For:

- Drugs having limited acid solubility.
  Ex: Phenytoin
- Instable in gastric conditions.
  Ex: Erythromycin
- Extensive first pass metabolism.

ADVANTAGES

- Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs.
- Minimizing mucosal irritation by releasing drugs slowly at a controlled rate.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux, providing local action.
- Ease of administration and better patient compliance.

LIMITATIONS

- Retention in the stomach is not desirable for drugs that cause gastric lesions (e.g. Non- steroidal anti-inflammatory drugs NSAIDs).
- Drugs that are degraded in acidic environment of stomach (e.g. Insulin).
- Drugs that undergo a significant first-pass metabolism (e.g. Nifedipine).
- Drugs that have very limited acid solubility (e.g. Phenytoin).

Factors Affecting Gastric Retention:

I. Density

II. Size and shape of the dosage form

III. Single or multiple unit formulation

IV. Fed or unfed state

V. Nature of meal

VI. Frequency of meal

Classification :

I. Floating drug delivery systems

II. High density systems

III. Expandable, unfoldable and swellable systems

IV. Super porous hydrogels

V. Bioadhesive or mucoadhesive systems

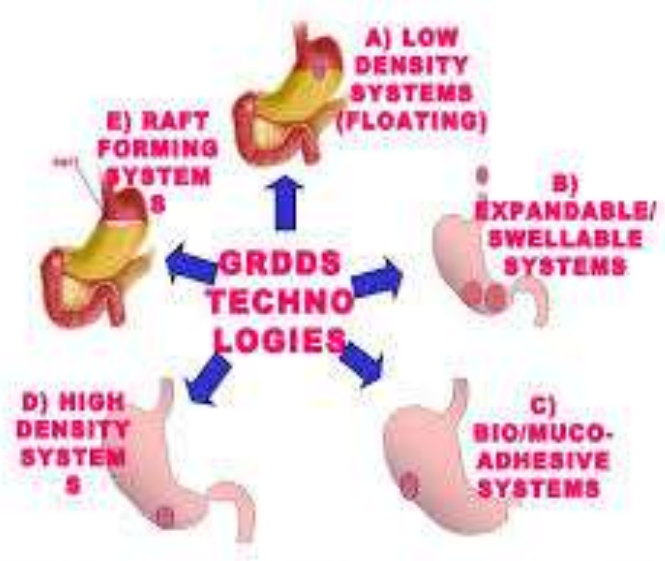
VI. Magnetic systems

Floating drug delivery systems

Effervescent systems

a. Gas generating systems

b. Raft forming systems



Non Effervescent systems

a. Hydrodynamically balanced systems (HBS)

b. Microprous compartment systems

c. Alginate beads

d. Hallow microspheres / microballoons

Mechanism of Floating Drug Delivery Systems (FDDS):

- FDDS have bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

- The drug is released slowly at the desired rate from the system.

- A minimal level of floating force (F) required to keep the dosage form reliably buoyant on the surface of the meal.

F= F buoyancy – F gravity = (Df – Ds)gv
Where , Df is fluid density
Ds is object density
v is volume
g is acceleration due to gravity

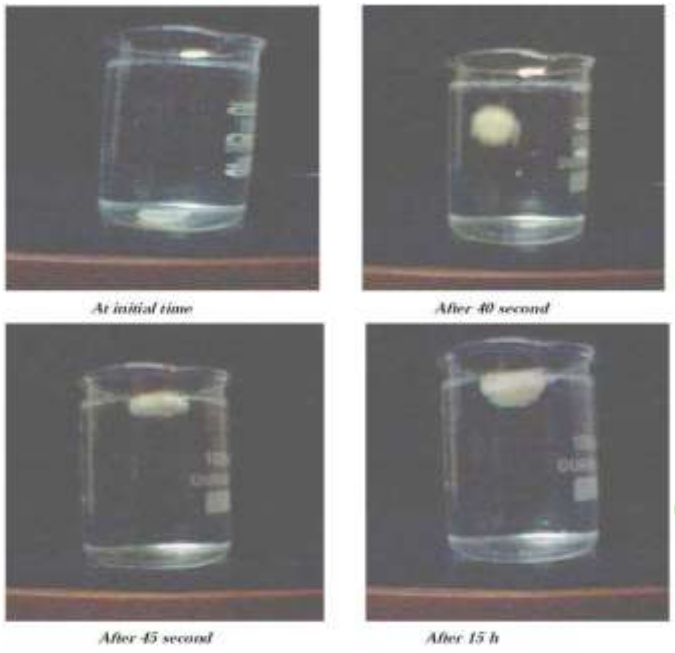


Figure 1- In vitro buoyancy studies of batch JE10H20CH80

I. Effervescent systems

a. Gas generating systems

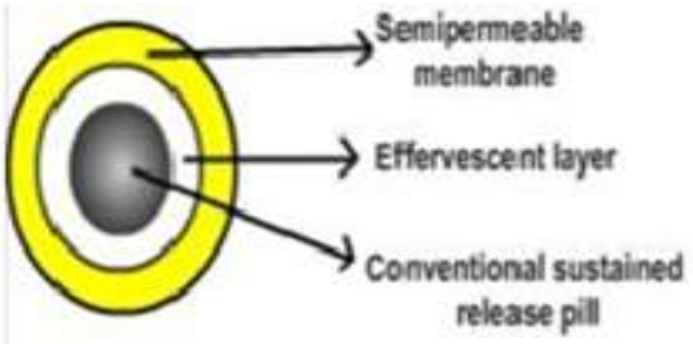
Utilizes effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid.

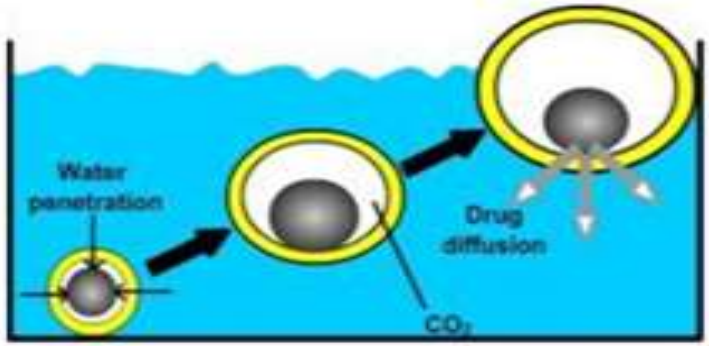
CO_2 is released in presence of H_2O.

When tablet is put in beaker it will sink

$$2NaHCO_3 + C_4H_6O_6 \longrightarrow C_4H_4Na_2O_6 + 2CO_2 + 2H_2O$$

With production of gas it rises up and floats.





b. Raft forming systems :

• This system is used for the delivery of antacids and drug delivery for gastrointestinal infections and disorders.

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

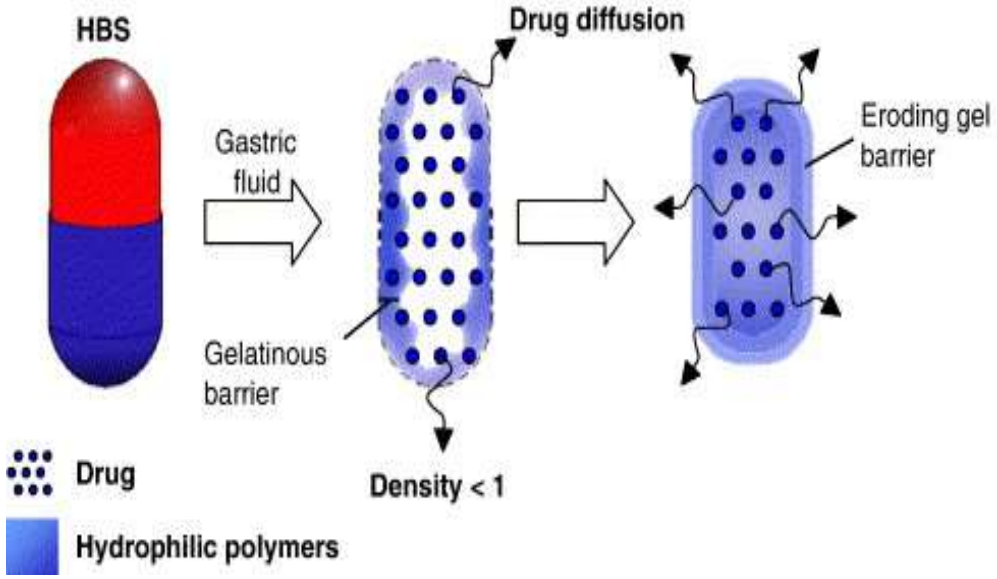
• The raft formed prevents the reflux of the gastric contents (i.e gastric acid) into esophagus by acting as barrier between stomach and esophagus

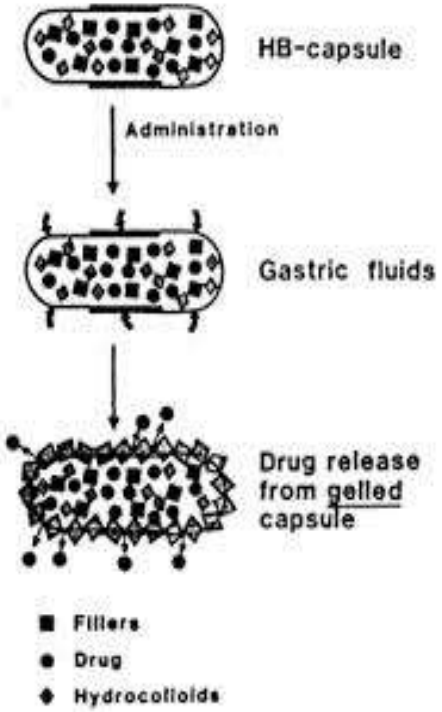
Barrier formed by a raft -forming system

II. Non Effervescent systems

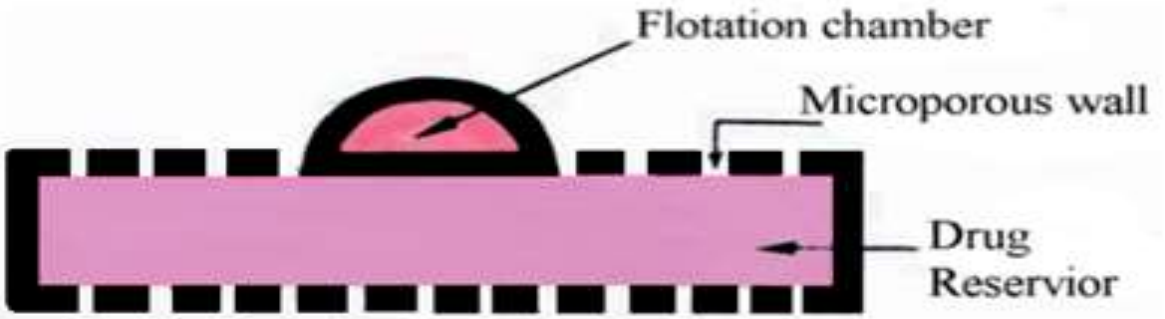
These systems may be referred to as the ‘ Plug-type systems ‘ since they have tendency to remain lodged near the pyloric sphincter.

a. Hydrodynamically balanced systems (HBS)

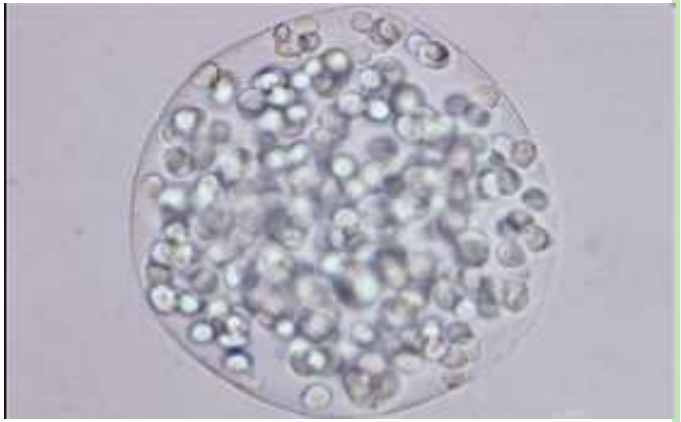




b. Microporous compartment systems



c. Alginate beads



• Prepared by dropping sodium alginate solution into aqueous solution $CaCl_2$, causing precipitation of Calcium alginate.

• Freeze dry in liquid nitrogen – 40 c for 24hrs.

• Beads are spherical and 2.5mm in diameter.

d. Hollow microspheres / Microballons :

Prepared by a Novel emulsion solvent Diffusion method.

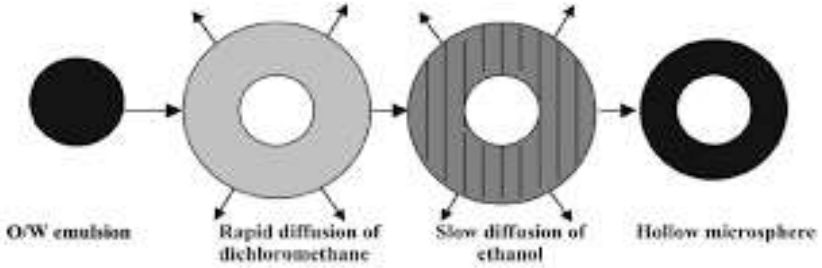
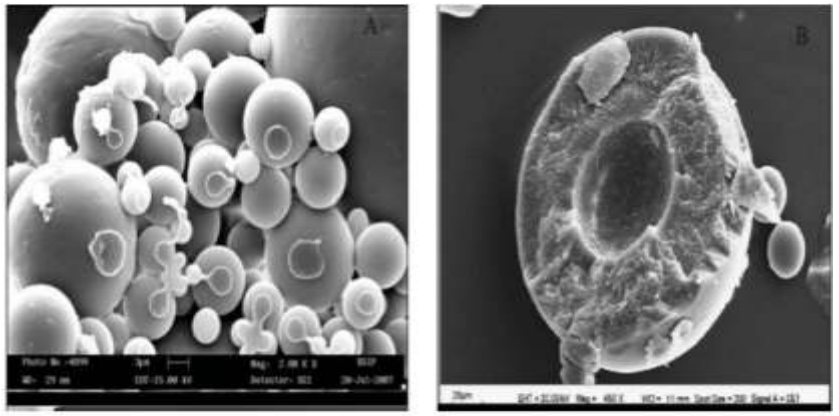
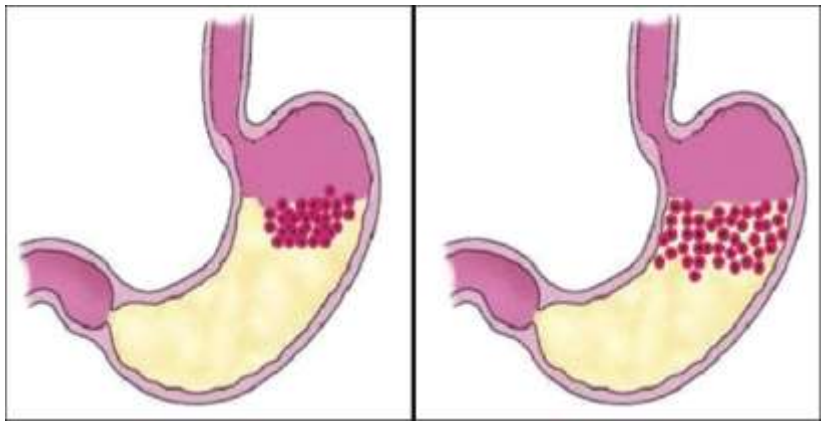


Figure 1: Formulation of floating microspheres



Scanning electron micrograph of microballoons. A. Outer surface of microballoons, B. Inner surface of a broken half of a microballoon

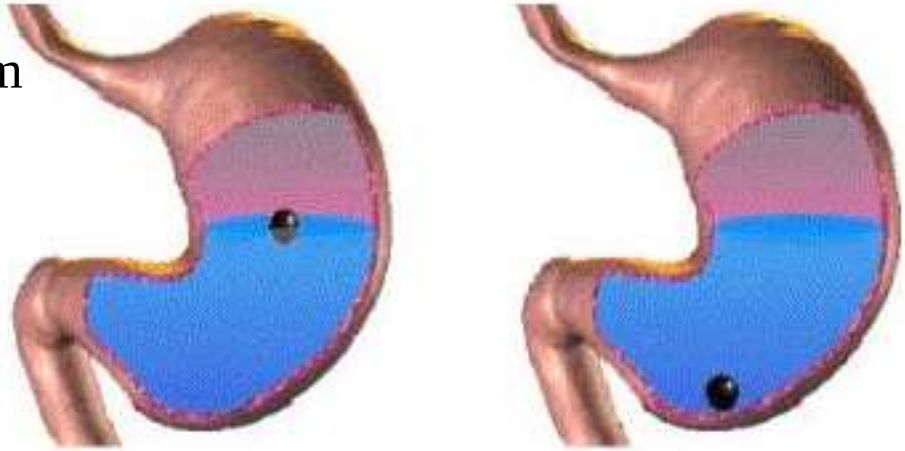


The microballons float continuously over the surface of an acidic dissolution media containing surfactant for more than 24hrs.

III. High Density systems :

• Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder etc.,

• These materials increase density by up to 1.5- 2.4g/ cubic cm-3.



Intragastric floating system (density > 1 g.cm^{-3})

High-density system (density > 1 g.cm^{-3})

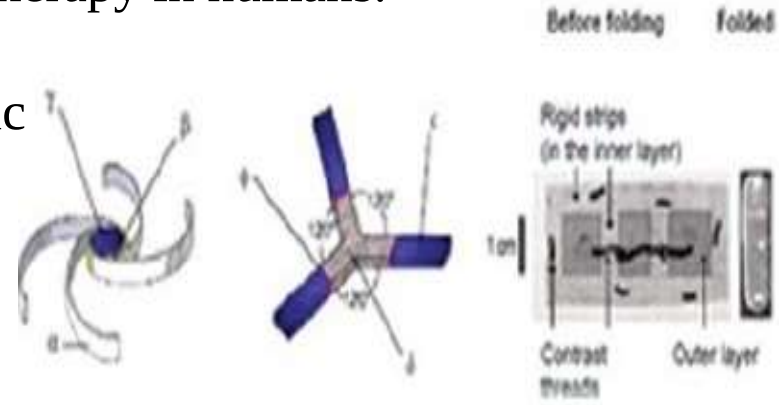
• Dense pellets (apporx 3g/ cm) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall.

• With the pellets , the GI transit time can be extended from an average of 5.8 -25 hrs, depending more on density than on diameter.

IV. Expandable, unfoldable and swellable systems :

• These were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans.

• They are available in different geometric forms like tetrahedron, ring or planner membrane of bioerodible polymers compressed within a capsule which extends in the stomach.

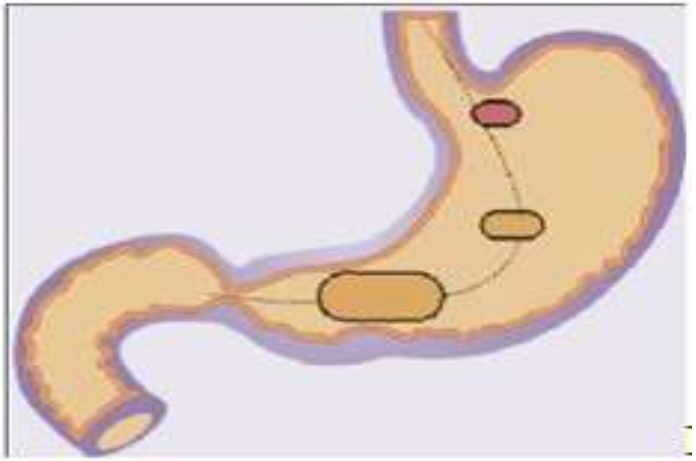


• Narrow absorption window drugs formulated as these systems have improved *Invivo* absorption properties

IV. Super porous Hydrogel Systems:

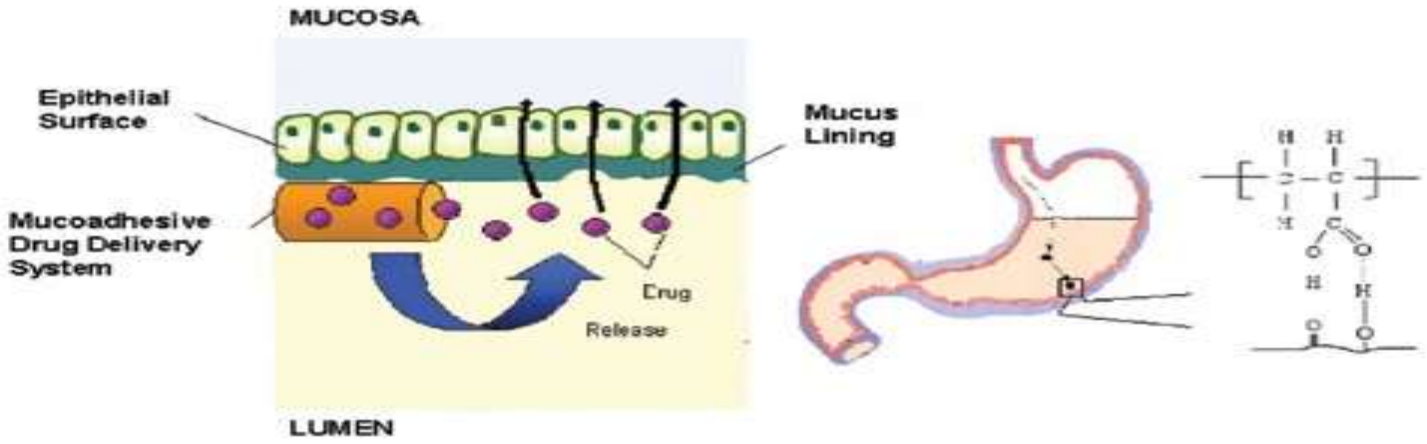
• These systems swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores (avg pore size > 100 or more).

• They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.



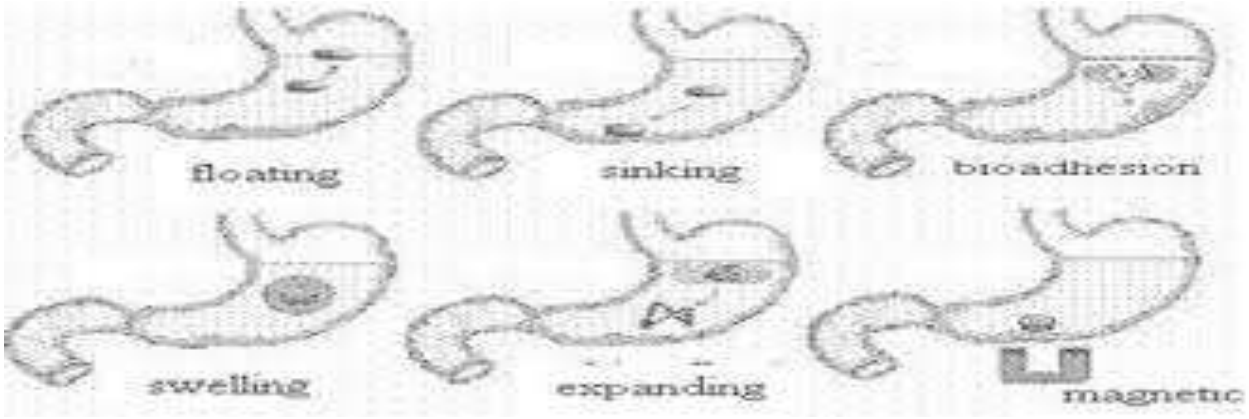
V. Bio/ Muco – adhesive Systems :

Illustration of the action of a mucoadhesive drug delivery system showing the adhesion of a poly(acrylic acid) and mucin molecules through numerous hydrogen bonding.



Some of the most promising excipients that have been used commonly In these systems include Polycarbophil, Carbopol, Lectins, Chitosan and Gliadin

VI. Magnetic Systems :



Formulation of Floating Dosage Form :

The following types of the ingredients can be incorporated into FDDS.

1. Hydrocolloids
2. Inert fatty materials
3. Release rate accelerants
4. Release rate retardants
5. Buoyancy increasing agents
6. Miscellaneous

Evaluation of of Floating Drug Delivery Systems :

1. Pre – formulation parameters :

a. Infra red spectroscopy
b. Differential scanning calorimetry
c. Angle of repose
d. Bulk density
e. Percentage porosity

2. Post formulation parameters:

A. Physical parameters

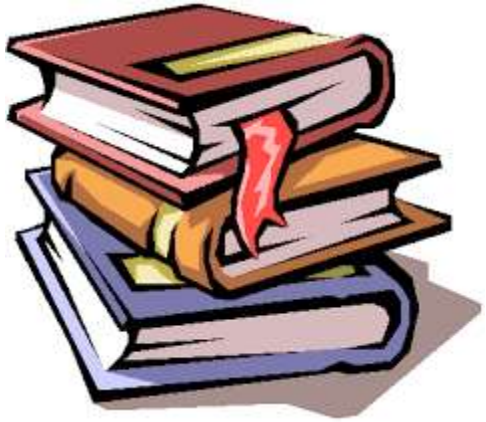
a. Particle size analysis, surface characterization
b. Buoyancy capabilities
c. Weight variation
d. Hardness & friability

B. Chemical parameters

a. Drug content
b. % entrapment efficiency
c. *Invitro* floating & dissolution behaviour
d. *Invivo* studies
e. Pharmacokinetic parameters

Applications:

Name	Type and drug	Remarks
MadoparHBSâ (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules
Valrelease	Floating capsule, Diazepam	Floating Capsules
Topalkan	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation
Conviron	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD	Ciprofloxacin (1 gm)	Gas generating floating form



References

Recent advancements and developments in floating drug delivery system – An approach for Gastroretention., Dandagi P.M, Dhople N.G., Dessai.G.A and Gadad.

An overview on recent advancements and developments in gastroretentive buoyant drug delivery system, Pelgia Research Library. 2011,2 (1),161-169.