Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

CHAPTER-3- Unit:2- GASTRORETENTIVE DRUG DELIVERY SYSTEM

SYLLABUS:

Gastroretentive drug delivery system:

Introduction, advantages, disadvantages, approaches for GRDDS – Floating, high density systems, inflatable and gastroadhesive systems and their applications

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

Upon completion of the course the student shall be able to

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

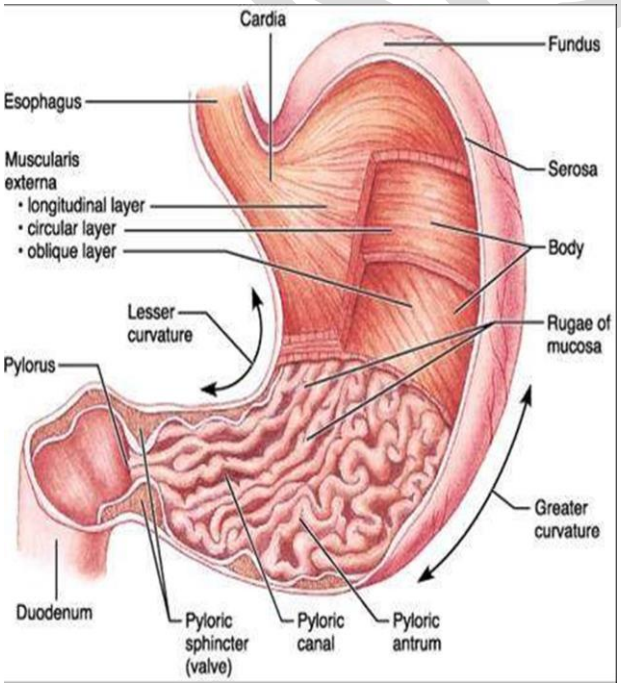
Gastroretentive Drug Delivery System

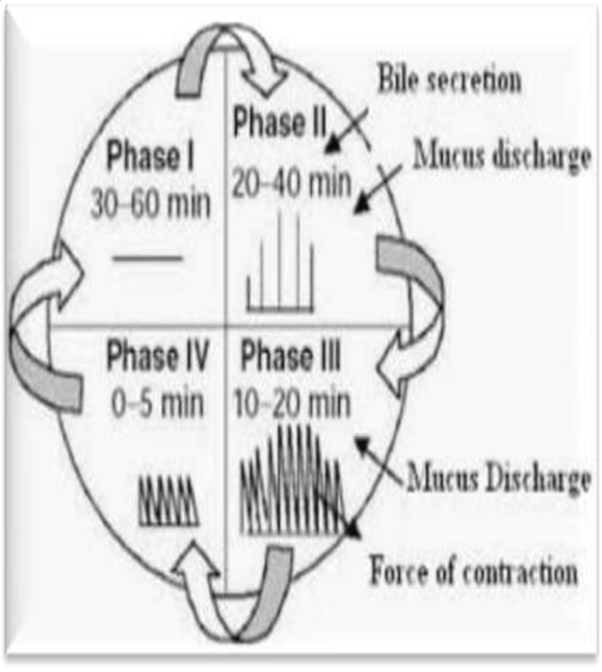
What is Gastroretentive Drug Delivery System (MDDS)

- Gastro retentive systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.
- This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration.
- Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.

BASIC GASTRO-INTESTINAL TRACT PHYSIOLOGY

1. Stomach
2. Fundus
3. Body
4. Pylorus or Antrum





Approaches for Prolonging the Gastric Residence Time

Importance of GRDDS

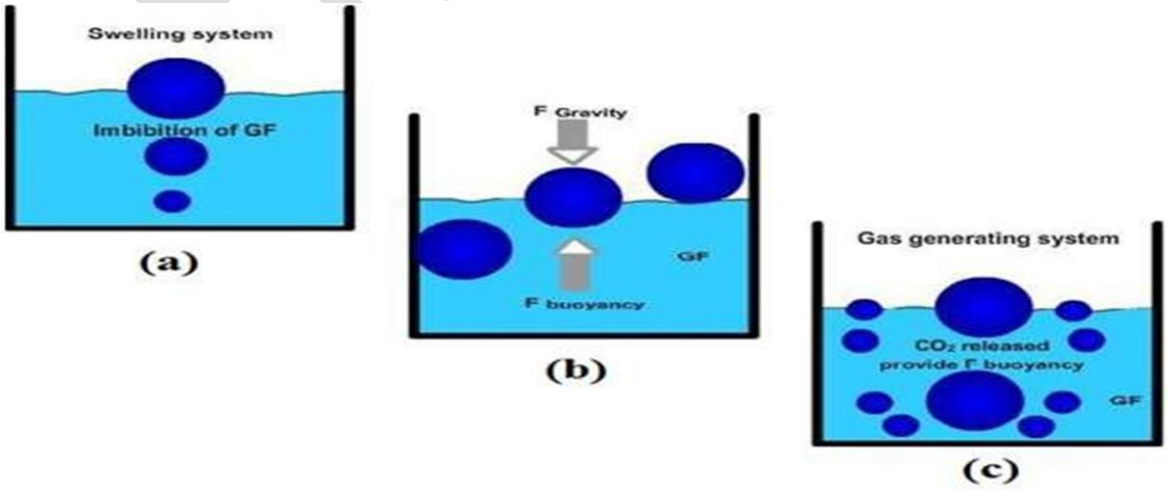
- The gastric emptying time in humans which normally averages 2-3 hours through the major absorption zone (stomach and upper part of intestine) can result in incomplete drug release from the drug delivery system leading to reduced efficacy of administered dose.
- Lower dosing and less side effects
- Beneficial in the treatment of gastric diseases.
- Suitable dosage forms for the drugs those are primarily absorbed in the stomach.

Mechanism Of Floating Systems

- GRDDS has a 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.

  F = F buoyancy - F gravity = (Df - Ds) gv

  Where, F= total vertical force, Df = fluid density,
  Ds = object density, v = volume and g = acceleration due to gravity.



One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time is called?	Gastro-retentive drug delivery system
2	Gastro retentive system is one of the system of?	buoyant system
3	Which system is improve gastric retention time and a better control of the fluctuations in plasma drug concentration	GRDDS
4	Normal Gastric emptying time of human is?	Average 2-3hr
5	How many approaches available for increasing Gastric emptying time?	Generally Four
6	What is Gastric emptying rate equation?	F = F buoyancy - F gravity = (Df - Ds) gv

Factors Affecting Floating Time

- Density, size and shape of dosage form.
- Single and multiple unit formulation.
- Fed and unfed stage.
- Frequency of feed.
- Nature of meal.
- Age and gender
- Posture

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.

Polymers used in formulation of GRDDS

- ***Hydrochlorides:*** HPMC 1000, HPMC 4000, β Cyclodextrin, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.
- ***Inert fatty materials:***
  Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.
- ***Effervescent agents:***
  Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di- Sodium Glycine Carbonate), CG (Citroglycine).
- ***Release rate accelerants (5%-60%):***
  eg. lactose, mannitol.
- ***Release rate retardants (5%-60%):***
  eg. Dicalcium phosphate, talc, magnesium stearate.
- ***Buoyancy increasing agents (upto80%):***
  eg. Ethyl cellulose.

- **Low density material:**
  Polypropylene foam powder (Accurel MP 1000).

Methodology

- Direct compression technique
- Melt granulation technique
- Melt solidification technique
- Spray drying technique
- Wet granulation technique

CLASSIFICATION OF GRDDS

Based on mechanism of **buoyancy GRDDS** can be classified into:

A) Single unit floating dosage systems:
  a) Non-effervescent system
  b) Effervescent system (gas-generating system)

B) Multiple unit floating dosage systems:
  a) Non effervescent system
  b) Effervescent system

C) Raft forming systems

D) Hallow microspheres

E) Magnetic system

Non effervescent systems:-

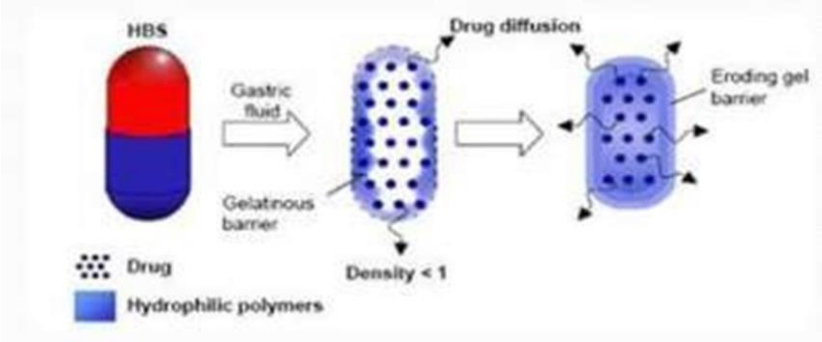
- ***One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxypropyl methyl cellulose [HPMC] etc, polysaccharides, or matrix forming polymers (e.g polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules.***

Hydrodynamically Balanced Systems

- Prepared by incorporating a high level (**20-75%w/w**) gel-forming hydrocolloids. E.g.:- Hydoxyethylcellulose, hydroxypropylcellulose, Sod. CMC into the formulation and then compressing these granules into a tablets or capsules.
- It maintains the bulk density less than 1.
- The gelatinous polymer barrier formation results from hydrophilic polymer swelling.

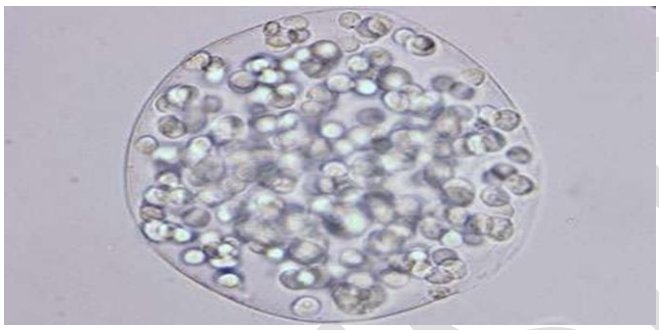
One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Nature of meal, Age and gender Posture are factors affecting on?	Floating time
2	Which main parameters of Pharmacokinetics parameters in GRDDS?	Bioavailability
3	Which Properties of drug is not suitable for GRDDS?	Poor solubility and stability
4	Give me example of release rate accelerants?	Lactose, Mannitol
5	Which system contains one or more gel forming, highly-swellable, cellulosic hydrocolloids?	Non-effervescent system
6	What is Accurel MP 1000?	Low density foam powder
7	Which system contains Gel forming hydrochloride?	HBS
8	How much bulk density in Non-effervescent system?	Less than 1
9	Examples of Hydrocolloids?	HEC, HPMC, Na.CMC
10	Ideal concentration range for hydrocolloid used in Nod-effervescent system?	20-75%



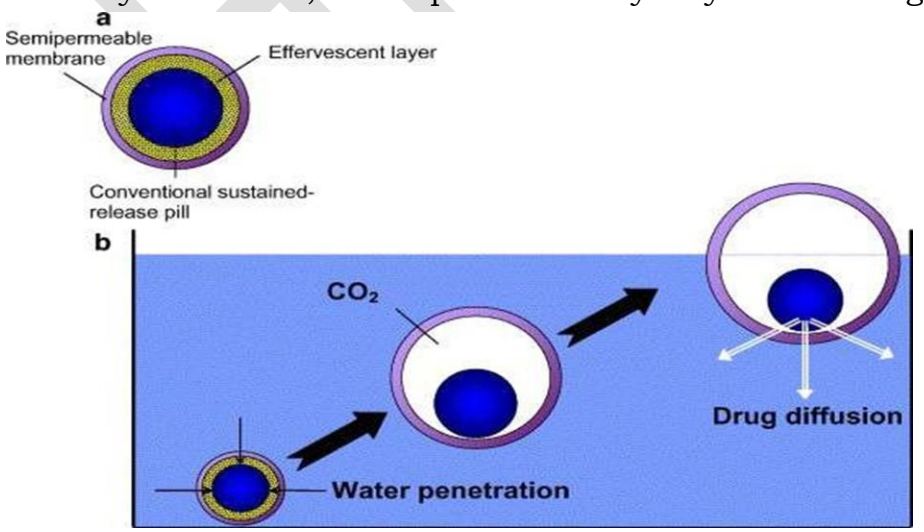
ALGINATE BEADS

- Prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate.
- Freeze dry in liquid nitrogen at -40^{o}c for 24h.
- Beads-spherical and 2.5 mm in diameter.



EFFERVESCENT FLOATING DOSAGE FORM

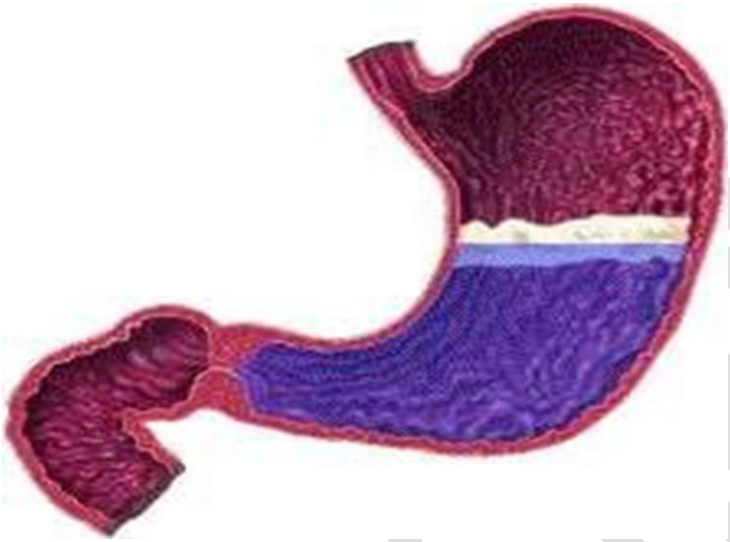
- These are matrix type of systems with the help of swellable polymers such as methylcellulose and chitosan ad various effervescent eg, sodium bicarbonate, tartaric acid and citric acid.
- They are formulated in such a way that when in contact with the acidic gas content, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form.



Gas generating system: schematic monolayer drug delivery system

RAFT FORMING SYSTEMS

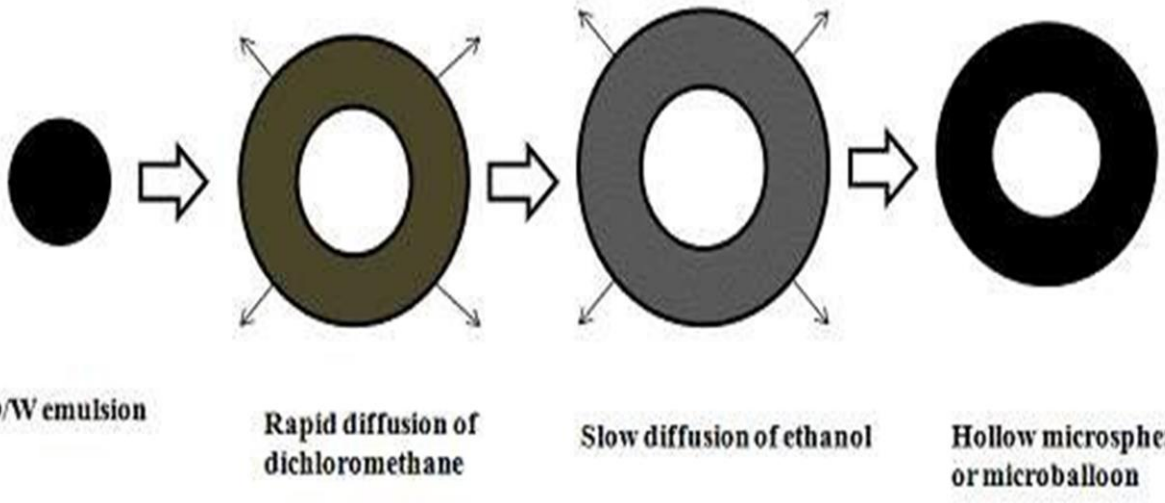
- This system is used for delivery of antacids and drug delivery for treatment of gastrointestinal infections and disorders.
- The mechanism involved in this system includes the formation of a viscous cohesive gel in contact with gastric fluids, forming a continuous layer called raft.



Barrier formed by a raft -forming system

HOLLOW MICROSPHERES

- Hallow microspheres as one of the most promising buoyant systems, as they possess unique advantages of multiple unit systems as well as better floating properties, because of central hallow spaces inside the microsphere.
- The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation.



One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Which systems are composed in matrix type of systems with the help of swellable polymers such as methylcellulose and chitosan ad various effervescent.	Effervescent floating dosage form
2	Which gas is liberated in Effervescent floating system?	CO_2
3	Effervescent system is composed of ?	Swelleable polymer
4	Which system is used for delivery of antacids and drug delivery for treatment of gastrointestinal infections and disorders?	Raft forming system
5	Formation of a viscous cohesive gel in contact with gastric fluids, forming a continuous layer is called?	Raft
6	The dosage form in which central hallow spaces inside the microsphere, is called?	Hollow microsphere
7	The hollow microsphere is prepared by which technique?	Solvent evaporation technique
8	What is shape and diameter of Alginate beads?	Spherical and 2.5 mm diameter

MAGNETIC SYSTEMS

- This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach.
- Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

PRE-COMPRESSION TESTS

- Angle of repose
- Tapped density and bulk density
- Carr's compressibility index
- Hausner ratio
- Size and shape

POST COMPRESSION TESTS

- Thickness
- Diameter
- Hardness test
- Weight variation test
- Friability test
- Content uniformity test

EVALUATION TESTS:

- *In-Vitro* test
- Floating lag time
- Floating time
- Dissolution study
- Resultant weight test
- *In-Vivo* Test
- X ray method
- Gamma-scintigraphy
- Gastroscopy
- Ultra sonography

Marketed Products of GRDDS

Brand name	Delivery system	Drug (dose)	Company name
Valrelease®	Floating capsule	Diazepam (15mg)	Hoffmann-LaRoche, USA

Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide (25mg) and L-dopa (100mg)	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India
Topalkan®	Floating liquid alginate Preparation	Al – Mg antacid	Pierre Fabre Drug, France
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

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach is called?	Magnetic system
2	What is location of magnetic system applied in human body?	Abdomen over the position of the stomach
3	Which system contains a number of small magnets?	Magnetic system
4	*In-Vivo* tests in GRDDS?	Gastroscopy, Gamma scientiography, Ultra sonography
5	First marketed tablet of GRDDS is?	Valrelease
6	What is main parameter of floating system?	Floating lag time