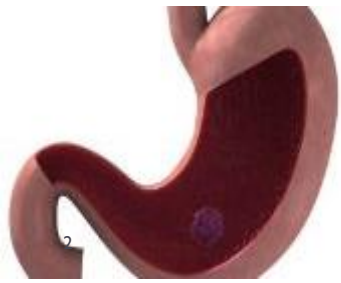
Floating gastro-retentive systems

1

Absorption window

- Not all drugs get uniformly absorbed throughout the GIT.
- Some drugs show absorption variability
- Such drugs have an "absorption window" - region from where absorption primarily occurs
- There can be various reasons for presence of such a window.

Absorption window in stomach or upper small intestine
IDEAL CANDIDATES



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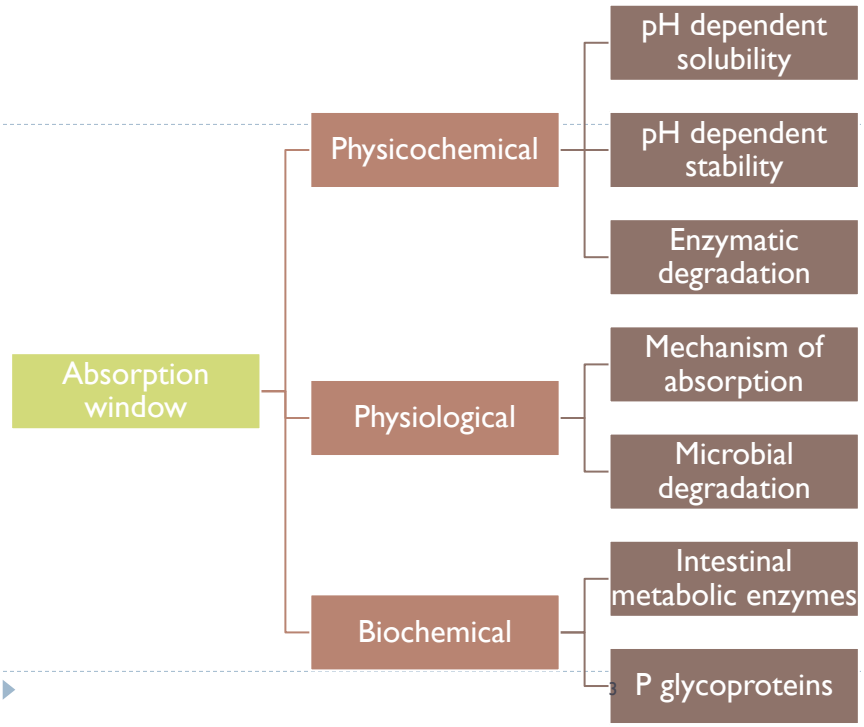

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Table 2: List of drugs which exhibit narrow absorption window in GIT

Drugs which are having narrow absorption window	Location of absorption window
Levodopa	Upper intestinal tract
p-Amino benzoic acid	Small intestine
Furosemide	Stomach
Riboflavin	Proximal intestinal tract
Acyclovir	Small intestine
Biphosphonates	Small intestine
Metformin	Upper intestinal tract
Gabapentin	Upper intestinal tract
Baclofen	Small intestine
Repaglinide	Proximal intestinal tract
Ciprofloxacin	Upper intestinal tract
Ofloxacin	Upper intestinal tract

4

GRDDS are preferred for drugs

Acting locally in the stomach

e.g. 5- Fluorouracil, anti *Helicobacter pylori* drugs, misoprostol

Primarily absorbed in the stomach or upper parts of the small intestine

e.g. ranitidine hydrochloride, atenolol, furosemide, riboflavin

Poorly soluble at an alkaline pH (pH dependent solubility)

e.g. verapamil, propranolol, quinidine, metoprolol

5

Narrow window of absorption

e.g. sulphonamides, penicillins, amino- glycosides, tetracyclines

Unstable in colonic environment (pH dependent stability)

e.g. ranitidine hydrochloride, captopril

Enzymatic degradation in intestine

e.g. leuprolide

6

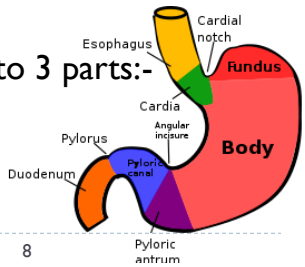
Drugs unsuitable for GRDDS

- Enteric coated systems.
- Drugs intended for selective release in the colon e.g. 5-aminosalicylic acid and corticosteroids.
- Drugs that have very limited acid solubility e.g. phenytoin.
- Drugs that suffer instability in the gastric environment e.g. erythromycin

7

Anatomy of stomach

- The stomach is a J- shaped dilated portion of the alimentary tract
- Its volume is 1.5 L in adults and after food has emptied a "collapsed" state is obtained with a resting volume of only 25-30mL
- The stomach is anatomically divided into 3 parts:-
  1) Fundus.
  2) Body.
  3) Antrum.



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- The proximal stomach, made up of fundus and body serves as a reservoir for ingested material
- The distal stomach is made up of antrum and pylorus
- The antrum serves as major site for mixing actions and acts as a pump for gastric emptying by propelling actions
- The fasting gastric pH is usually steady and approximately 2
- Food neutralizes gastric acid thus increasing the pH up to 6.5

9

- After meal ingestion is complete the pH rapidly falls back below 5 and then drastically declines to fasting state values over a period of a few hrs
- The pylorus is an anatomical sphincter situated between the terminal portion of the antrum and the duodenum. The pyloric sphincter has a diameter of 12.8 ± 7mm in humans
- It acts as a sieve as well as a mechanical stricture to the passage of large particles

10

Gastric motility and gastric emptying

- The contractile motility of the stomach causes the food to breakdown into small particles.
- The contractions results in mixing of the food particles with the gastric juices and consequent emptying of the gastric contents.
- The gastric emptying occurs during ***fasting*** and ***fed*** states but pattern of GI motility differs distinctly in the 2 states.

11

- In the ***fasting*** state it is characterized by an inter-digestive series of electrical events which cycle both through stomach and intestine every 2 to 3 hrs.
- This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC).
- It is generated in the stomach and its aim is to clear the stomach and small intestine of the ingested debris; swallowed saliva and sloughed epithelial cells

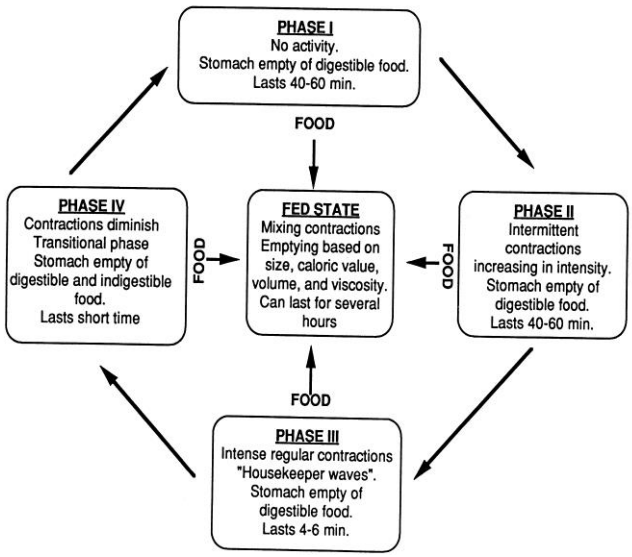
12

Migrating Myoelectric Cycle

4 phases

1. Basal phase – lack of secretory or electrical activity or contractile motions
2. Pre-burst phase – intermittent contractions
3. Burst phase – intense regular contractions, sweeps all undigested material out – housekeeper wave
4. Transitional phase

13



14

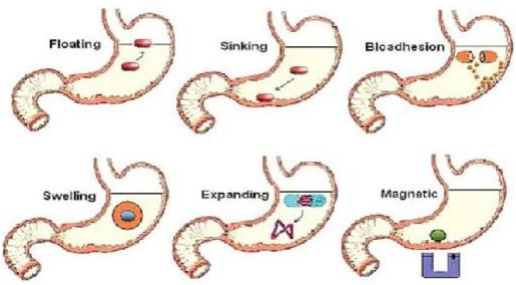
- In the ***fed*** state MMC is delayed, due to presence of food, resulting in slowdown of gastric emptying rate

- Gastric emptying rate depends on:
  i. Nature and caloric content of meal
  ii. Posture
  iii. Gender
  iv. Age
  v. Osmolarity
  vi. pH of food
  vii. Mental stress
  viii. Disease state

15

Approaches for gastro retention

- Floating systems.
- Superporous hydrogels
- Swelling and expanding systems
- Mucoadhesive & Bioadhesive systems.
- High density systems
- Magnetic systems
- Ion exchange resins
- Osmotic regulated system
- Incorporation of passage delaying food agents



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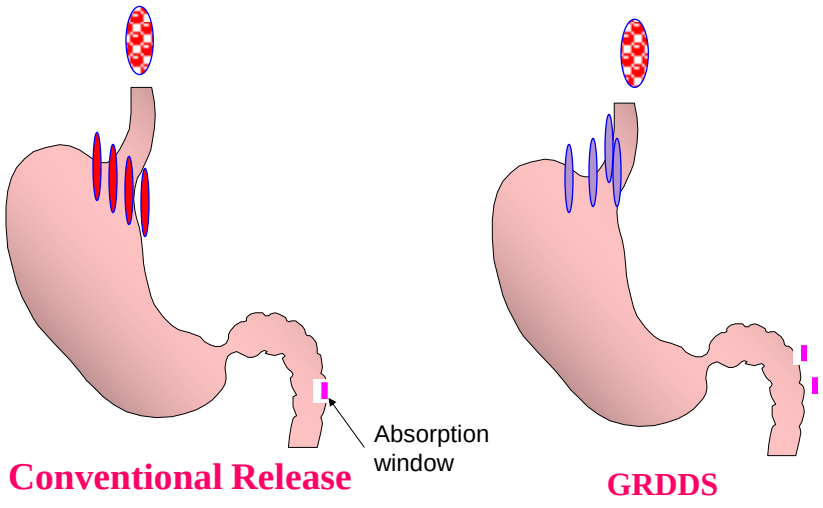


17

Floating Systems

- *Non effervescent systems*

1. Single unit system
2. Multiple unit systems

- *Effervescent systems*

1. Single unit system
2. Multiple unit systems

- *Raft-forming systems*

18

Non-effervescent systems

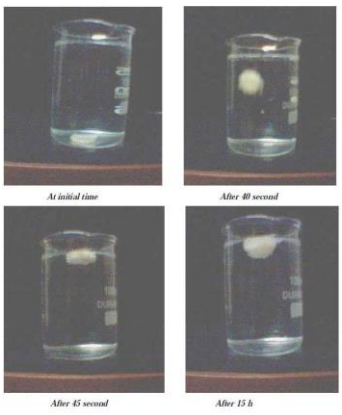
- They are further classified as:

1. Colloidal gel barrier system (HBS)
2. Microporous compartment system
3. Alginate beads
4. Hollow microspheres (microballoons)

19

Single unit - HBS

- These systems contain one or more hydrocolloids and are made into a single unit along with drug and other additives.
- When coming in contact with water, the hydrocolloids at the surface of the system swell and facilitate floating.
- The coating forms a viscous barrier, and the inner polymer slowly gets hydrated as well, facilitating the controlled drug release. Such systems are called "*hydrodynamically balanced systems (HBS)*".



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- The polymers used in this system includes HPMC, HEC, HPC, Na CMC, agar, carrageenans and alginic acid
- They incorporate a high level of one or more polymers (20-80%)
- On contact with gastric fluid the hydrocolloid hydrates and forms a gel barrier around its surface.
- Air is trapped in the swollen polymer to maintain density < 1 to confer buoyancy.
- The gel barrier will also control the rate of drug release

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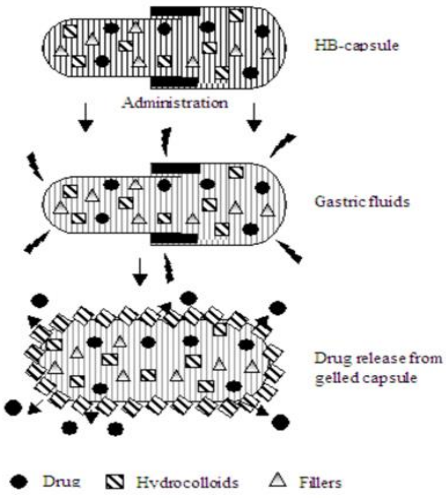


Mechanism of release of Non effervescent DDS

22

Non effervescent systems – multiple unit

- Further classified into:

1. Microporous compartment system
2. Alginate beads
3. Hollow microspheres

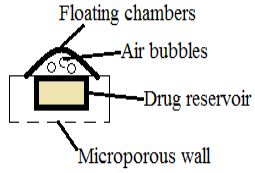
Microporous compartment system

Encapsulation of drug reservoir inside a microporous compartment with apertures along its top and bottom walls.

Peripheral walls are completely sealed.

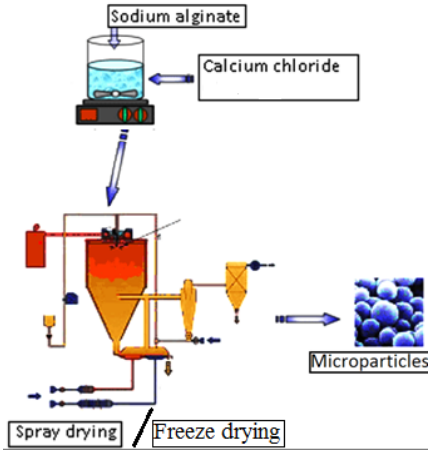
The floatation chamber contains entrapped air which allows the system to float over the gastric contents.

Gastric fluid enters through the aperture, dissolves the drug and carries it outside



Alginate beads

- Spherical beads can be formed by dropping sodium alginate solution in aqueous solution of calcium chloride forming calcium alginate beads.
- Beads are then isolated by freeze drying/ spray drying



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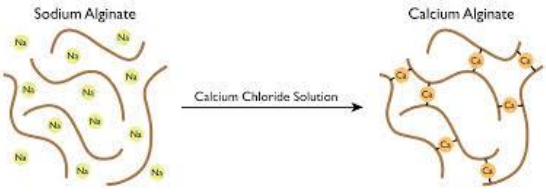


26

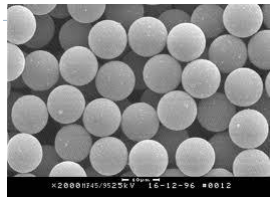
Hollow microspheres

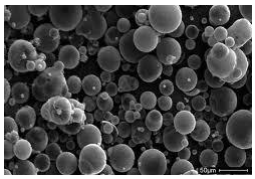
Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method.

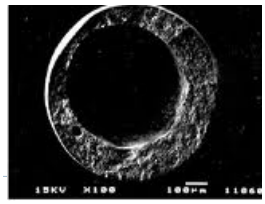
The ehanol:dichloromethane solution of the drug and an acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°.

The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug.

The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h in vitro.

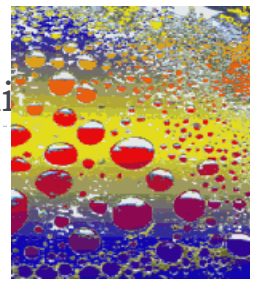






27

Effervescent system – single uni

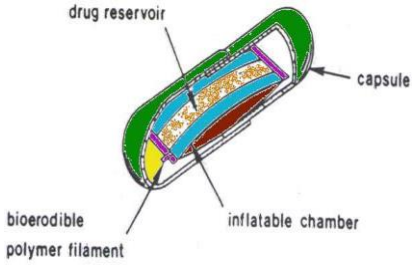


- They are further classified as:
- Volatile liquid containing systems
- Gas generating systems

28

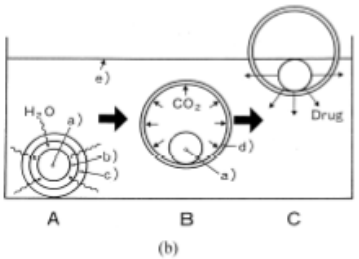
Volatile liquid containing systems

- There are two chambers – inflatable and deformable
- Inflatable chamber which contains a volatile liquid eg. Ether, cyclopentane
- They volatalise at body temperature and cause inflation of the chamber
- Deformable chamber is at the top and has the drug .
- There is a impermeable, pressure sensitive movable barrier between the two chambers



29

Gas generating – single unit



(b)

- They utilize effervescent reaction between carbonate/ bicarbonate salts and citric/ tartaric acid to liberate carbon dioxide.
- This CO_2 gets trapped in the gellified hydrocolloid layer, thereby decreasing its density and aid floatation.
- Tablets can be single or multi layered

30

- Another approach – collapsible spring
- Body consists of non-digestible, acid-resistant and high density polymer with a gelatin cap
- The lower end of body has an orifice to control drug rele

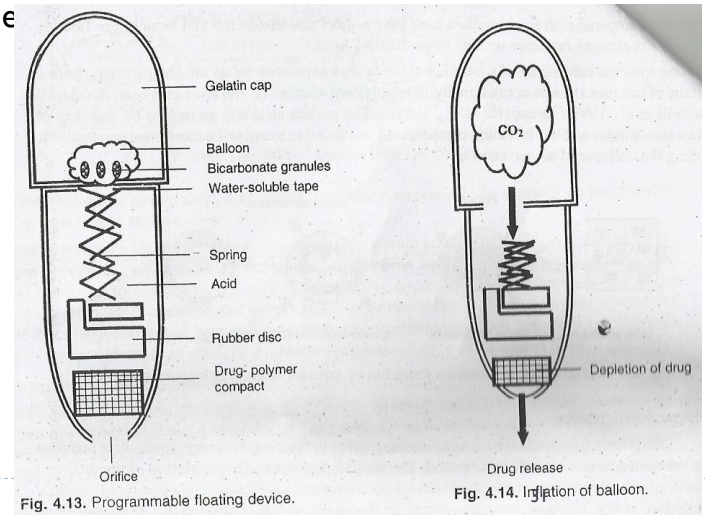


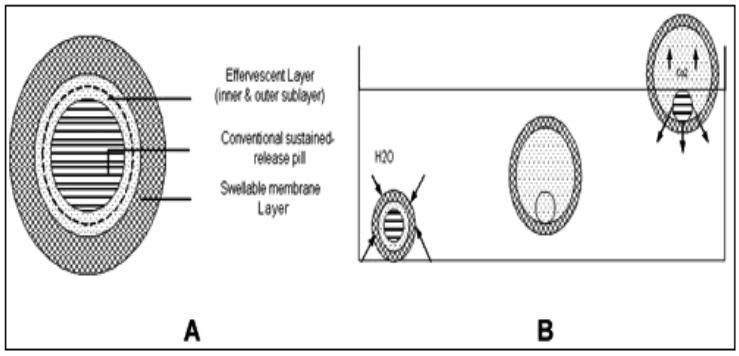
Fig. 4.13. Programmable floating device.

Fig. 4.14. Inflation of balloon.

31

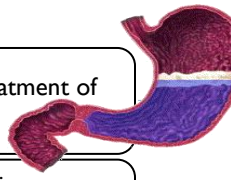
Effervescent systems – multiple unit

- Effervescent granules can be made on same principle as effervescent tablets



32

Raft forming systems



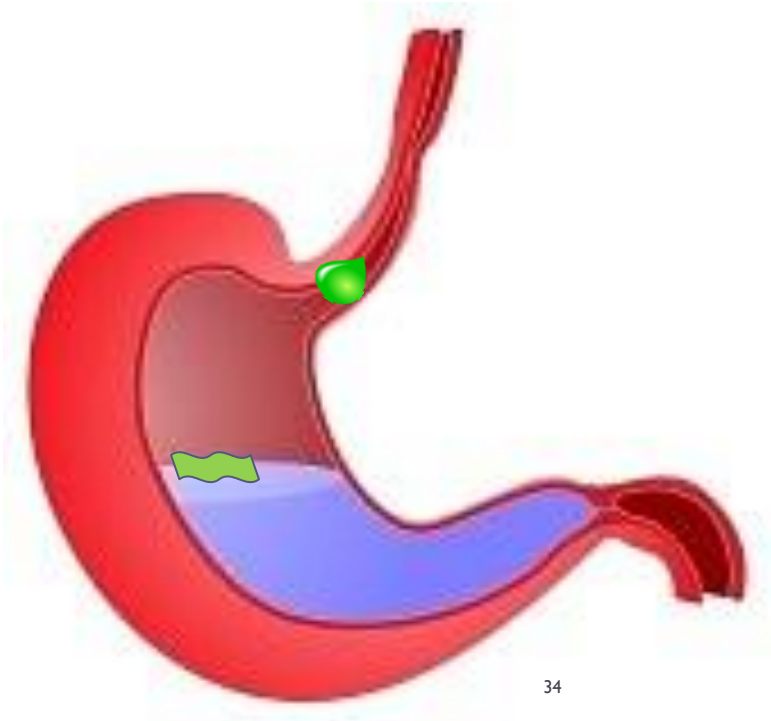
This system is used for delivery of antacids and drug delivery for treatment of gastrointestinal infections and disorders.

The mechanism involved in this system includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells, forming a continuous layer called raft.

This raft floats in gastric fluids because of the low bulk density created by the formation of CO_2.

Usually 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 more apt to float on the gastric fluids.

33



34

Superporous hydrogels

Swellable agents with pore size ranging between 10nm and 10µm, absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach as equilibrium state during which premature evacuation of the dosage form may occur.

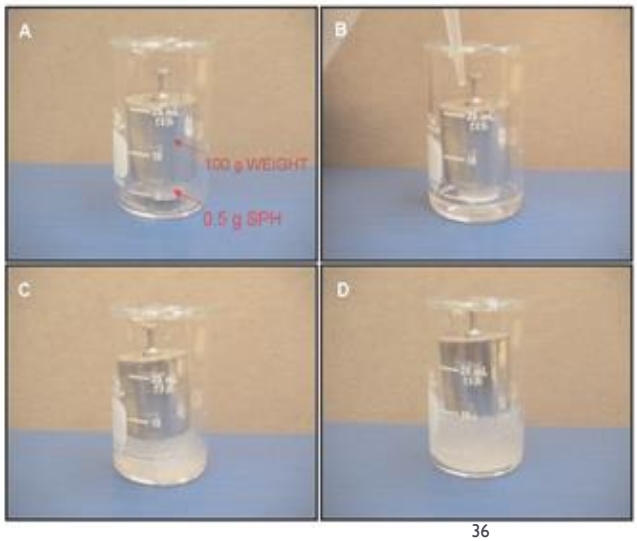
Superporous hydrogels swell to equilibrium size with in a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores.

They swell to large size and are intended to have sufficient mechanical strength to withstand pressure by the gastric contraction.

This is achieved by co-formulation of a hydrophilic particulate material, Ac-Di-Sol.

35

Pressure exerted by a swelling superporous hydrogel. A 100-g weight is placed on top of a dried superporous hydrogel (0.5 g) (A). Upon addition of water (B), the superporous hydrogel starts swelling immediately (C) to lift the 100-g weight (D).



36

Advantages of GRDDS

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

37

Limitations of GRDDS

1. GRDDS like FDDS require a sufficiently high level of fluids in the stomach for the delivery system to float and work efficiently.
2. GRDDS are not feasible for drugs that have solubility or stability problems in the gastric fluid.
3. Drugs which have nonspecific, wide absorption sites in the GIT, drugs that are well absorbed along the entire GIT are not suitable candidates for GRDDS; e.g. nifedipine.
4. Similarly drugs that undergo significant first-pass metabolism are not preferred for GRDDS

38