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INNOVATIONS IN GASTRO RETENTIVE DRUG DELIVERY SYSTEMS: FROM CONCEPT TO CLINICAL APPLICATION

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ABSTRACT

Gastro-retentive drug delivery systems (GRDDS) are designed to enhance the bioavailability and therapeutic efficacy of drugs by prolonging their residence time in the stomach. These systems offer significant advantages for drugs with narrow absorption windows or those that require a controlled release profile to optimize their therapeutic action.

Recent advancements in GRDDS have focused on improving the design and functionality of these systems to address challenges such as variability in gastric emptying times, stomach pH fluctuations, and drug degradation in the acidic environment of the stomach.

Key innovations include floating systems, mucoadhesive systems, bioadhesive polymers, and expandable systems, each with its own advantages and limitations.

In addition, newer techniques, such as the use of stimuli-responsive materials and nanotechnology, have shown promise in achieving more precise and efficient drug delivery. This review discusses the latest advances in the development of GRDDS, with a focus on novel materials, technologies, and the clinical implications of these systems.

KEYWORDS: *Gastro retentive drug delivery system, floating system, swelling, expanding system, bio/mucoadhesive system, H Pylori infection and its application.*

INTRODUCTION

Gastro-retentive drug delivery systems (GRDDS) represent an innovative approach in the field of pharmaceutical technology aimed at prolonging the residence time of a drug in the stomach, enhancing its bioavailability. These systems are designed to overcome challenges associated with drugs that are poorly absorbed in the intestine or have a short half-life, by ensuring their sustained release and controlled delivery in the upper gastrointestinal tract. [1]

The innovation of GRDDS lies in its ability to improve the therapeutic efficacy of drugs through various mechanisms, such as floating, swelling, which help the drugs remain in the stomach for an extended period. This extended retention allows for a more gradual release of drug, reducing fluctuation in drug plasma concentration, minimizing side effects, and enhancing patient compliance, especially for drugs requiring sustained therapeutic levels.

Recent advancements in GRDDS technology have focused on optimizing the formulations and mechanisms used to achieve gastric retention, including floating tablets gastric-evacuating systems, and mucoadhesive systems. These innovations not only offer potential solutions for poorly soluble or unstable drugs but also open doors to improve treatment for chronic condition like diabetes, hypertension, and infections, where sustained release and optimal drug delivery are crucial for effectiveness. [2]

ANATOMY AND PHYSIOLOGY OF STOMACH

- Anatomically stomach is divided into three region – Fundas, Body and Antrum (pylorus)
- The fundus and body of proximal portion serve as a repository for undigested materials, whereas the antrum is the primary location for mixing motions and propels processes that act as a pump for stomach emptying.
- Gastric emptying occurs in both the fasting and fed states.
- During the fasting state an inter-digestive series of electrical event take place which cycle both through stomach and intestine every 2-3 hours, which is called as Inter Myoelectric Cycle or Migrating Myoelectric Cycle (MMC) which is further divided into four phases.
- After the ingestion of a mixed meal, the pattern of contraction changes from fasted to fed state which is also termed as Digestive Motility Pattern. [3]

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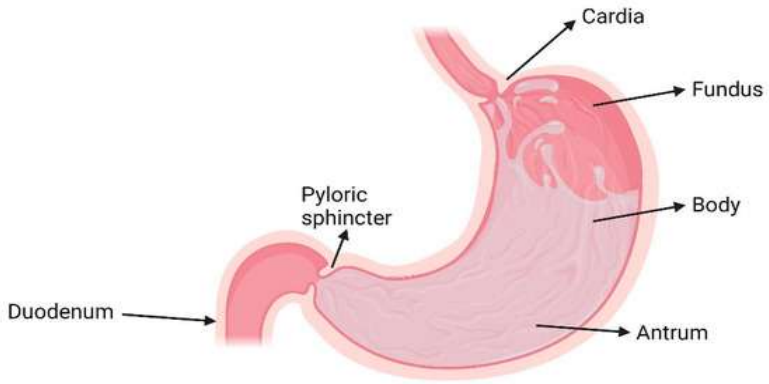


Fig.: Structure of Stomach

Phases of the MMC

1) Phase 1- (Basic Phase) last from 30-60 minutes with rare contractions.
2) Phase 2- (Pre-burst Phase) last from 20-30 minutes with intermittent action potential and contractions.
3) Phase 3- (Burst Phase) late from 10-20 minutes which includes intense and regular contractions for short period.
4) Phase 4- last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles. [4]

Advantages of gastro retentive Drug Delivery System

1. Drug releases in controlled manner for prolonged period.
2. Site-specific drug delivery to stomach can be achieved.
3. Avoidance of gastric irritation, because of sustained release effect.
4. Better therapeutic effect of short half-life drugs can be achieved.
5. Maintenance of constant therapeutic level over longer period of time.
   e.g.: Beta lactams antibiotics.
6. Controlled drug delivery of drugs.
7. It improves the stability.
8. Reduction in adverse action of colonic site.
9. There is a higher patient compliance. [5]

Disadvantages

1. Not suitable for drugs that may cause gastric lesions.
2. High variability in gastric emptying time due to variations in emptying process, unpredictable bioavailability.
3. The mucus on the walls of the stomach is in a state of constant renewal, resulting in erratic adherence.
4. In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.
5. Aspirin and NSAID'S can cause gastric lesions and slow release of such drug in the stomach is unwanted.
6. Floating drug delivery systems require high fluid level in stomach to float and work effectively. [6]

Factors affecting the Gastric Resistance time (GRT) of Dosage Form: [7]

A. Formulation factors
B. Intake & its nature
C. Patient related Factor

A. Formulation Factors

(i) Density of dosage form

Low density -Float
High density-Sink

(ii) Size of dosage form

should be more than 7.5mm in diameter.

(iii) Shape of dosage form

Either round or spherical or tetrahedron shape have better property for GRT.

(iv) Single/multiple unit formulation

Multiple unit formulation gives more desirable or predictable longer release profile.

B. Food intake & its nature

(i) Fed/Unfed State

Fasting condition GRT is less because of high GI motility GRT is less if motility is high.

(ii) Nature of meal

High amount of fatty acids or indigesable polymer can change the GRT because of variation in GI motility.

(iii) Caloric content of food

High protein & fat rich diet can increase the GRT by 4 to 10 hrs.

(iv) Frequency of food

GRT can be increased by 400 min when successive meal is taken.

C. Patient related factors

(i) Gender

Mean GRT for male is less as compared to Female mean GRT.

(ii) Age

Elderly people have significant longer GRT.

(iii) Disease Condition

Chron's disease, hyper or hypo thyrodism, duodenal ulcer can affect the GRT.

(iv) Emotional State

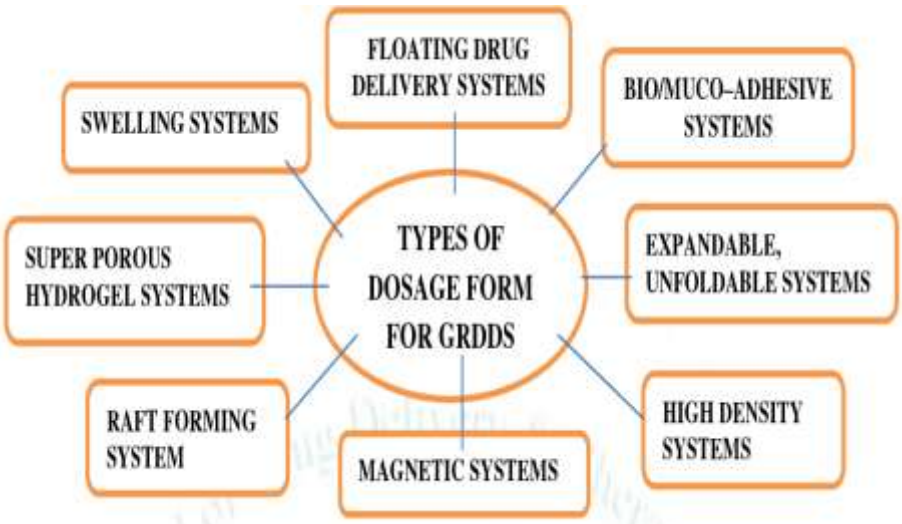
Emotions can also affect the GRT.

(v) Posture

Upright or supine position can affect the GRT.

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APPROACH FOR GRDDS



1) FLOATING DRUD DELIVERY SYSTEMS/ LOW DENSITY SYSTEMS

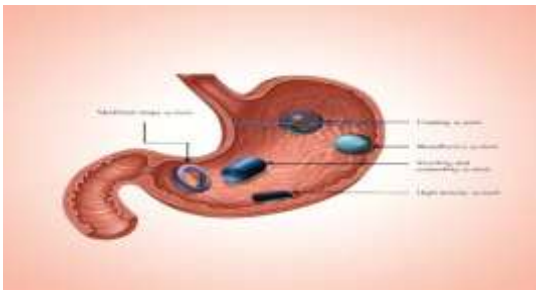
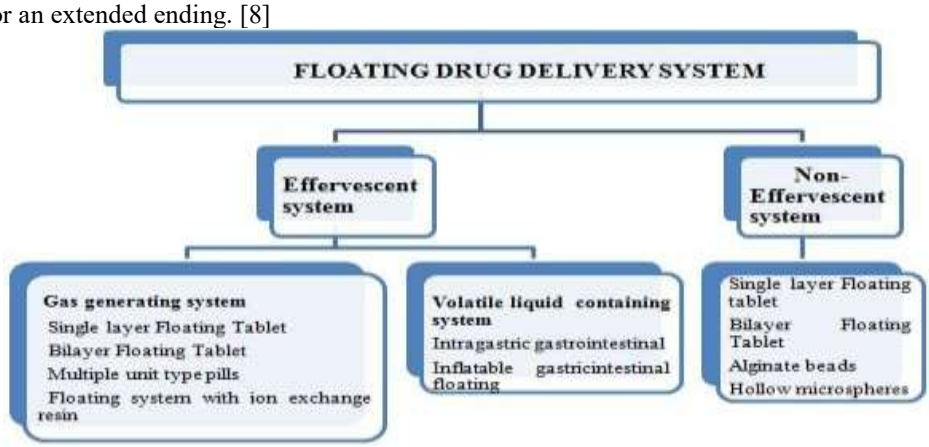


Fig.: Floating Drug Delivery System

FDDS is productive electronics to extend the pertaining to the stomach condo time in order to increase the bioavailability of the drug. FDDS are reduced-mass structures that have enough elasticity to float over the pertaining to the stomach details and wait in the stomach for an extended ending. [8]

Floating systems may be top-secret as

1. Effervescent and
2. Non foaming /Non effervescent system



A. Effervescent Systems: [9]

- Effervescent system includes use of gas generating agent Carbonate (Sodium bicarbonate) and Organic acid (Tartaric acid And Citric acid) present in formulation to produce co2 gas.
- Thus, reducing the density of system and making it float on gastric fluid.
- An alternative is the incorporation of matrix containing portion of liquid.\, which produce gas that evaporate at body temperature.
- These effervescent systems further classify into two types:
  - i. Gas generating systems
  - ii. Volatile liquid/vacuum systems

i. Gas generating systems:

- These Floating System utilize effervescent responses between Carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO2, that gets involved in the jellified hydrocolloid layer of the arrangements

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so diminishing its distinguishing importance and making it to wash over gastric content.

a) Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

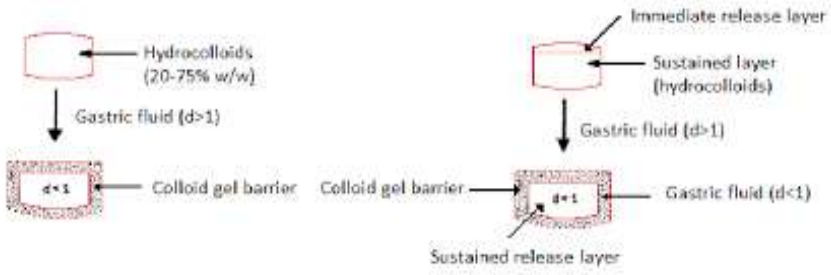


Fig.: Single Layer Floating Table

- These are planned by closely joining the CO2 create powers and the drug inside the mold medicine.
- These have a most mass inferior pertaining to the stomach fluids and so wait buoyant in the stomach unfavourable the stomachic purging rate for an extended ending.
- The drug is slowly released at a desired rate from the buoyant order and later the complete release the leftover method is discharged from the stomach.
- This leads to an increase in the grt and a better control over vacillation in red body fluid drug aggregation.

b) Bilayer Floating Tablets

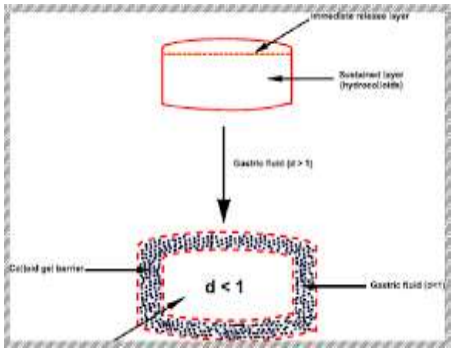


Fig.: Bilayer Floating Tablet

- These are also compressed tablet as shown in Fig and containing two layers i.e. (1) Immediate release layer (2) Sustained release layer.
- The interlining consists of bouncy powers while the external layer is of swellable sheath coating.
- When bureaucracy is immersed in death medium at body hotness, it sinks immediately and therefore forms swollen pills like balloons, that glide as they have lower mass.

c) Multiple Unit Type Floating Pills

- These orders include sustained release pills as ‘sources’ among double coatings.

d) Ion Exchange Resin

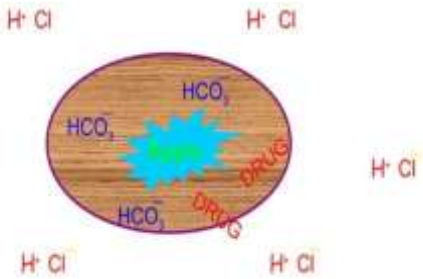


Fig.: Ion Exchange Resin

- The drug-resin complex beads that make up the system are coated in a hydrophobic polymer and loaded with bicarbonate ions.
- The way the system is set up, bicarbonate and medication ions are swapped out for chloride ions once the beads go to the stomach. The beads float

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because the produced CO2 is trapped in the polymeric-coated resins.

ii. Volatile Liquid/Vacuum Systems

- The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contain a liquid like ether and cyclopentane.

a) Intragastric Floating Gastrointestinal Drug Delivery

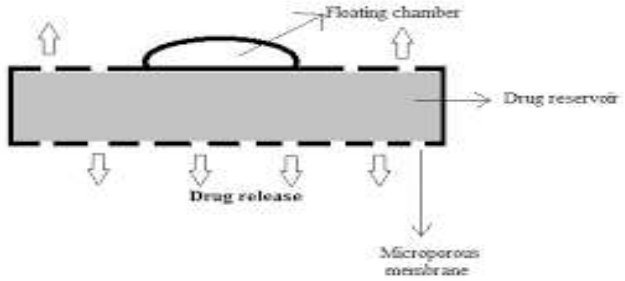


Fig.: Intragastric Floating Gastrointestinal Drug Delivery

- These methods maybe created to float in the stomach by way of floatation room, that grant permission be an emptiness or filled accompanying air or a naive smoke, while drug accumulation is encapsulated inside a Microporous compartment.

b) Inflatable Gastrointestinal Delivery Systems

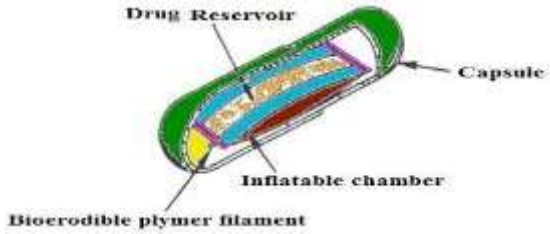


Fig.: Inflatable Gastrointestinal Delivery Systems

- In these methods, an inflatable chamber is incorporated, that holds liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach.
- These structures are concocted by stowing the inflatable chamber accompanying a drug reservoir, that may be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule.
- After oral administration, the capsule dissolves to release the drug accumulation in addition to the inflatable chamber.
- The inflatable chamber certainly inflates and retains the drug reservoir into gastric fluid.
- That gasifies at body temperature to cause the inflammation of the chamber in stomach.
- The device may also consist of a bioerodible plug made up of poly vinyl alcohol, polyethylene etc.

B. Non-Effervescent: [10]

- Non-effervescent schemes include an extreme level (20– 75% w/w) of individual or more gel-making, well swellable, cellulosic hydrocolloids (for instance, Hydroxy ethyl hydrogen, Hydroxy Propyl organic compound composed of carbon, Hydroxy Propyl methylcellulose [HPMC], and sodium carboxy methyl and oxygen), polysaccharides, or mold-making polymers into pill or capsules.
- When enters place trade pertaining to the stomach fluid, these coagulate something, polysaccharides, and polymers hydrate and form a colloidal coagulate obstruction that controls the rate of fluid penetration into the maneuver and resultant drug release.

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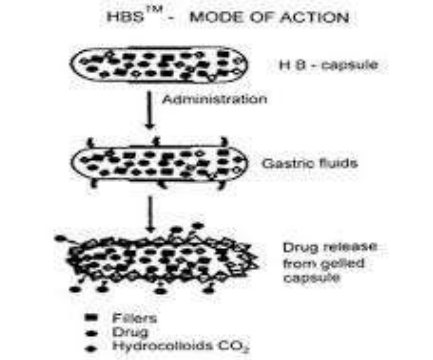


Fig.: Non-Effervescent System

2) BIO/MUCO ADHESIVE SYSTEMS: [11]

- Bio/mucoadhesive schemes bind to the pertaining to the stomach epithelial container surface, or mucin, and increase the GRT by growing the relates and event of contact between the dosage form and the organic sheath.
- The idea is established the self-covering system of the GIT. Mucus hidden steadily for one specific cup containers located during the whole of the GIT plays a cytoprotective duty. Mucus is a viscoelastic, coagulate-like, thin muck composed principally of glycoproteins.
- The basic function of mucin searches out insulates the surface mucosal containers from acid and peptidases. In addition, it serves as a lubricator for the passage of mass of material and as a hurdle to antigens, microorganisms, and viruses.
- The traits of these polymers are microscopic adaptability, hydrophilic working groups, and specific microscopic pressure, chain distance, and shape.
  A. Hydration-mediated adhesion
  B. Bonding-mediated adhesion
  C. Receptor-mediated adhesion

A. Hydration-mediated adhesion
Certain hydrophilic polymers likely to swallow many of water and enhance sticky, through achieving bioadhesive properties.

B. Bonding-mediated adhesion
It involves Mechanical or Chemical bonding. Chemical bonds involve ionic or covalent bonds or Vander walls forces between the polymer molecules and the mucous membranes.

C. Receptor-mediated adhesion
Certain polymers can bind to particular receptor sites on the surface of containers, through reinforcing the stomachic memory of portion of drug or other consumable forms.

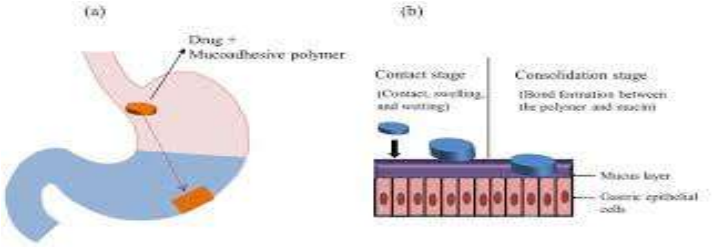


Fig.: Mucoadhesive System

3) SWELLIG/EXPANDING SYSTEMS: [12]

Sustained and reserved drug release can be attained by selecting a polymer with the correct microscopic pressure and lump possessions. As portion of drug or other consumable form coming in trade pertaining to the stomach fluid, the polymer imbibes water and swells. These cross-links hinder the destruction of the polymer and so uphold the material honor of the portion of drug or other consumable form. A balance between the magnitude and event of lump is claimed for one strength of cross-linking 'tween the polymeric chains.

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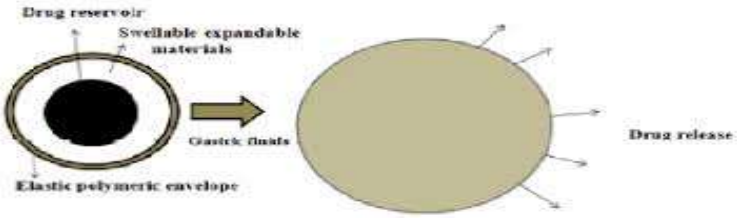


Fig.: Swelling System

A large size of cross connecting retards the lump talent of bureaucracy and maintains allure material uprightness for an extended ending. On the additional help, a low scope of cross-connecting results in thorough lump understood apiece rapid rupture of the polymer.

4) HIGH DENSITY SYSTEMS

Gastric elements of larger object have a mass close to water (1.004 g/cm3). When extreme mass pellets are likely to the patient, it will fall to the bottom of the stomach and are captured in the folds of the cavity and endure the peristaltic waves of the stomach divider 40, 41.

A mass ~3 g/cm3 appears essential for significant extension of pertaining to the stomach home opportunity. Barium sulphate, zinc group of chemical elements, iron powder, titanium dioxide grant permission be used to plan a for mentioned high mass arrangements on account of their extreme density. The only important disadvantages at this moment orders that it is technically difficult to produce ruling class accompanying a many of drug (>50%) and to achieve the necessary mass of 2.4–2.8 g/cm3.

5) MAGNETIC SYSTEMS: [13]

This method is established a plain plan that the dosage form holds a narrow within bait and a bait established on the tummy over the position of the stomach. They guided ruling class to the neck accompanying an extrinsic bait (1700 G) for the primary 2 min and principal part the granules were employed in the domain following in position or time 2 h. Although these schemes appear to work, the extrinsic magnet must be arranged accompanying a strength of accuracy that ability compromise patient agreement.

Applications of GRDDS: [14]

Sustained Drug Delivery

Floating structure remnants in the stomach for lengthier ending and release the drug over a extend range. This arrangement has largeness mass inferior 1 so it concedes possibility float on the pertaining to the stomach content.

Site Specific Drug

This method is specifically favourable for the drugs that are involved from the stomach or proximal unspecified the part of digestive tract.

Absorption Enhancement

Drugs bearing a weak bioavailability are potential candidate for planning as a buoyant arrangement to enhance allure incorporation.

Maintenance Of Constant Blood Flow

This whole provides a smooth habit for maintaining loyal ancestry flow with rather ease of presidency.

Improve Bioavailability

Certain drugs, such as those with poor solubility, can benefit from prolonged contact with the stomach, which improve absorption and bioavailability.

Controlled Drug Release

GRDDS enables a gradual and controlled release of medication, which can decrease the frequency of doses and enhance patient adherence to treatment regimens.

Targeted Gastric Delivery

These systems are employed for drugs intended for local action within the stomach, such as those used in the management of peptic ulcers or gastroesophageal reflux disease (GERD).

Mitigation of Side Effects

By ensuring a consistent release of the drug, GRDDS can help lower peak plasma concentration, thereby reducing the potential side effects associated with immediate release formulation.

Sustained Therapeutic Action in Chronic Condition

GRDDS is particularly beneficial for chronic illnesses that require a prolonged therapeutic effect, such as diabetes or cardiovascular disorders, by maintaining drug concentration within the therapeutic range.

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TABLE: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems [15]

Dosage Forms	Drugs
Floating Tablets and Pills	Cinnarizine, p-aminobenzoic acid, Prednisolone and Piretanide
Floating Films	Acetaminophen, p-aminobenzoic acid, Isosorbide mononitrate, Ampicillin, Atenolol, Theophylline, Aspirin, Verapamil hydrochloride, Sotalol
Floating Microspheres	Aspirin, p-nitroaniline, Griseofulvin, Ketoprofen, Ibuprofen, Verapamil and Terfinadine
Floating Capsules	Diazepam, Furosemide, Misoprostol, L-Dopa and Benserazide, Pepstatin, Verapamil HCL and Nicardipine
Floating Powders	Riboflavin, Phosphate, Sotalol and Theophylline
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone, Cinnarizine, Diltiazem, Fluorouracil and Isosorbide mononitrate

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