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Beyond the Stomach: Emerging Paradigms in Gastroretentive Drug Delivery Systems

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Abstract:

Gastric emptying is a complex and extremely variable process. This causes the unpredictability of the bioavailability of drug delivery systems. Gastro retentive drug delivery systems (GRDDS)s have received significant attention in the past decades primarily due to the fact that they can overcome the limitation of conventional oral controlled release drug delivery systems related to fast gastric emptying time. An optimum GRDDS can be defined as a system which remains in the stomach for a sufficient time interval and releases active ingredients in a controlled manner. This, significantly extends the duration of drug release, prolongs dosing interval and increases bioavailability of drugs and therefore improves compliance of the patients and effectiveness of pharmacotherapy. This article gives an overview of the main concepts used to design pharmaceutical dosage forms with prolonged gastric residence times as well as the parameters-affecting gastric emptying, advantages, shortcomings, formulation considerations and, factors that affect gastro retentive systems. The main emphasis is on the entire classification and different types of GRDDSs. Finally, evaluation methods of these systems have been summarized.

Keywords: GRDDS, floating system, non-floating system, gastric retention time, applications.

Introduction:

Oral drug administration has traditionally been the most common method of drug delivery. Many oral delivery systems have been created over the last 20 years to serve as drug reservoirs from which the

active ingredient can be delivered at a controlled and predefined rate over a specified amount of time. For human administration, oral drug delivery systems have supplanted alternative drug delivery methods because of their many benefits, which include high patient compliance, affordability, ease of storage and transportation, formulation flexibility, and ease of administration. But oral medication delivery systems encounter difficulties such limited bioavailability brought on by the gastrointestinal tract's variability. system, commensal flora's pH, the dose form's stomach retention period, surface area, and enzymatic activity. Traditional medication delivery methods might not be able to address the problems brought up by the gastrointestinal tract (GIT), such as insufficient medication release, a decline in dosage efficacy, and need for repeated doses.

Consequently, GRDDS may arise as a result of traditional drug delivery methods' inability to keep medications in the stomach. These systems have a number of advantages, including the capacity to deliver tailored medication administration to the stomach, enhanced therapeutic efficiency of pharmaceuticals through improved drug absorption, and extended gastric resident time (GRT) of dose forms in the stomach for up to several hours. Furthermore, by continuously releasing the medication for a prolonged amount of time at the intended rate and to the intended absorption site until the medication is entirely released from the dosage form, GRDDS can improve the controlled delivery of medications.

Physiology of stomach:

The stomach is a hollow organ that is a component of the digestive system. It produces chyme, produces proteins required for the absorption of vitamins, acts as a barrier against microbes, and triggers the peristaltic reflex. Despite what is commonly believed, the stomach has no role in nutritional absorption. This organ serves as a conduit for food from the neurological system to the endocrine system. It can be found in the peritoneal cavity, which is situated in the left upper abdominal quadrant, or in the epigastric abdominal region. The integration of the parasympathetic nervous system, the enteric nervous system, and the secretion of several neurohormonal molecules (such as gastrin, HCl acid, and others) allows for the precise control of gastric acid secretion, peristaltic propulsion, and other physiological processes of the stomach (i.e., gastrin, HCl acid, intrinsic factor, bicarbonate, mucus, etc.) [4,5]

The stomach is separated into three areas anatomically. Body, Antrum, and Fundus (pylorus) The closest portion created the use of gastro retentive drug delivery systems, or GRDDSs, is one innovative strategy in this field. Forms of dosage that can be kept in the GRDDs are the stomach. The GRDDSs can enhance the regulated administration of medications with a window for absorption by distributing the medication consistently over an extended length of time duration prior to it reaching the site of absorption. Extending the in some cases, it is preferable for medications to remain in the stomach for attaining the medication's therapeutic effects that are absorbed from the gastro intestinal tract's (GIT) proximal portion or those are less soluble in alkaline pH or are broken down by it, or they encounter in the lower GIT. GRDDS are advantageous.GRDDS help these medications by enhancing them.

1. Bioavailability

2. Therapeutics efficiency and
3. Possible reduction of the dose
4. safeguarding of stable therapeutic levels for an extended length of time and thereby less variation in the therapeutic levels.
5. Reduce drug wastage.
6. Improves solubility of drugs that are less soluble at high pH environment (e.g., weakly basic drug like domperidone, papaverine)

whereas the antrum is the primary location for mixing motions and functions as a pump for gastric emptying by propelling actions, the fundus and body serve as a reservoir for undigested materials. Both when a person is fed or fasting, gastric emptying happens. An electrical sequence known as the interdigestive myoelectric cycle, or migrating myoelectric cycle (MMC), which is further split into four phases, occurs during the fasting state and cycles through the stomach and intestine every two to three hours. The contraction pattern, also known as the digestive motility pattern, shifts from the fasted to the fed state following the consumption of a mixed meal. [6-9]

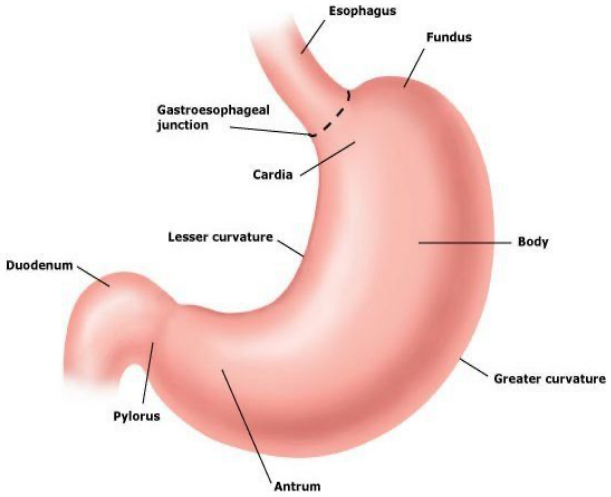

Figure: 1 Physiology of stomach

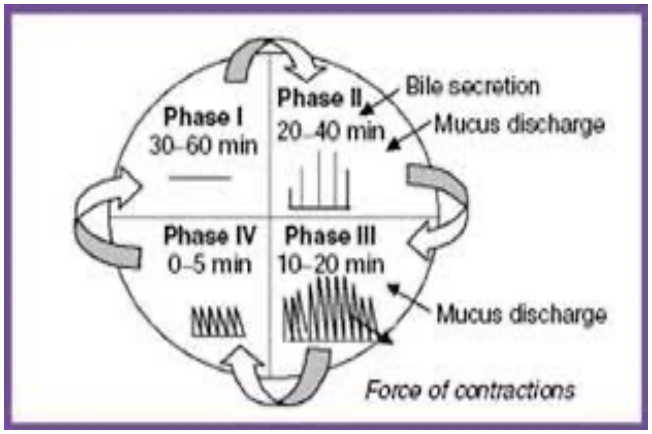

Figure: 2 Schematic representation of inter digestive motility

Table: 1 Conventional drug delivery verses Gastro retentive drug delivery systems:

S. No.	Parameters	Conventional drug delivery	Gastro retentive drug delivery systems
1.	Patient Compliance	Poor	Better
2.	Dose Dumping	Risk of dose dumping is higher	No risk
3.	Drug having low absorption in small intestine	Not appropriate	Appropriate
4.	Drug acting locally in the stomach	Not vary much useful	Much useful
5.	Toxicity	Greter susceptibility towards toxicity	Low susceptibility
6.	Drugs with poor solubility at higher pH	Not much beneficial	Much beneficial
7.	Drugs that undergo degradation in colon	Not much beneficial	Much beneficial
8.	Drug that has fast GIT absorption	Not much beneficial	much beneficial

Factors affecting gastric retention time of the dosage form:

1. **Density and Buoyancy:** The density of the dosage form relative to the gastric contents can influence its buoyancy. Floating dosage forms, such as floating tablets or capsules, are designed to stay buoyant on the gastric fluid, prolonging their residence time in the stomach.
2. **Size and Shape:** Larger and irregularly shaped dosage forms may remain in the stomach for a more extended period. However, extremely large particles may be more prone to causing irritation or obstruction.
3. **Food Intake:** The presence of food in the stomach can affect gastric emptying. In general, food can delay gastric emptying, influencing the retention time of a dosage form. This factor is crucial for drugs with food-dependent absorption.
4. **Hydration and Swelling:** Dosage forms that swell upon contact with gastric fluid or absorb water can increase in size, leading to prolonged gastric retention. Hydrogels and swellable polymers are often used for this purpose.

5. **Surface Coating:** Coating the dosage form with materials that resist the action of gastric fluids or that adhere to the gastric mucosa can influence retention time. Such coatings may dissolve, erode, or peel off slowly, affecting the release of the drug.
6. **Gastric Motility:** Gastric contractions and motility patterns play a significant role in the movement of contents through the gastrointestinal tract. Changes in gastric motility, which can be affected by factors like age, disease, or medications, can impact the retention time of dosage forms.
7. **pH of Gastric Fluid:** The pH of the stomach can influence the dissolution and stability of drugs. pH-sensitive dosage forms are designed to respond to changes in gastric pH, potentially prolonging retention time.
8. **Gastrointestinal Diseases:** Conditions such as gastroparesis (delayed gastric emptying) or other gastrointestinal disorders can affect the movement of dosage forms through the stomach.
9. **Dosage Form Composition:** The composition of the dosage form, including excipients and the nature of the drug itself, can affect its interaction with gastric fluids and mucosa, influencing retention time.
10. **Physiological Variability:** Variability among individuals in factors such as gastric pH, motility, and emptying rates can impact the gastric retention of dosage formsdifferently from person to person. [10-14]

Rationale for the use of GRDDS:

Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastroretentive drug delivery system (GRDDS). On the basis of the mechanism of mucoadhesion, floatation, sedimentation or by the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved, which delay gastric emptying.

1. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of nongastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.
2. For drugs with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time

(GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

4. Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence, they are useful in the treatment of disorders related to stomach and small intestine.
5. The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
6. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.
7. Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
8. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
9. The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes. [15-21]

In simple ways it can be shown as follows:

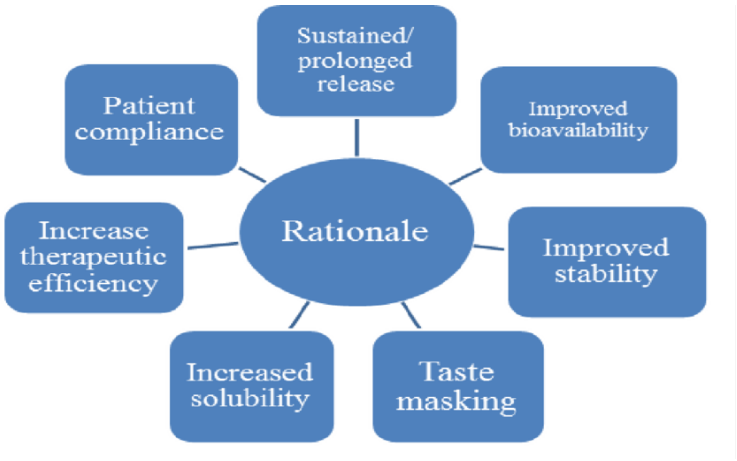

Figure: 3 Rationale for the use of GRDDS

Need for Gastro Retention:

1. Drugs that are absorbed from the proximal part of the GIT.
2. Drugs that are less soluble or are degrade by alkaline pH they encounter at lower part of
3. Drugs that are absorbed due variable gastric emptying time.
4. Local or sustained delivery to the stomach to treat certain conditions

5. Particularly useful for the treatment of peptic ulcers caused by H. pylori infections.

Gastrointestinal Transit Time:

Food content remains in each segment of the gastrointestinal tract for different periods of time. The resident time for both liquid and solid foods in each segment of the gastrointestinal tract is shown in Table 2.

Table 2: Transit time of food in each segment of the gastrointestinal tract

S. No.	**Segment**	**Liquid**	**Solid**
1.	Stomach	10-30min	1-3 hours
2.	Duodenum	<60sec	<60sec
3.	Jejunum and ileum	3 hours ± 1.5 hours	4 hours ± 1.5 hours
4.	Colon	-	20-50 hours

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hours. So, one has to take most of the drugs 3-6 times a day. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slowdown of gastric emptying rate. Orally administered controlled release dosage forms are subjected to basically 2 complications that are, short gastric residence time and unpredictable gastric emptying rate. [22-27]

Advantages of Gastro Retentive drug delivery:

Prolonged Drug Release:

Gastro-retentive systems can provide a sustained and controlled release of drugs over an extended period, leading to a more consistent therapeutic effect.

Prolonged drug release can reduce the frequency of dosing, improving patient compliance.

Improved Bioavailability:

By prolonging the residence time of the drug in the stomach, gastro-retentive systems can enhance drug absorption and bioavailability, especially for drugs that are absorbed primarily in the stomach.

Reduced Variability in Plasma Drug Levels:

Maintaining a consistent drug concentration in the bloodstream can be crucial for drugs with a narrow therapeutic window. Gastro-retentive systems help reduce fluctuations in plasma drug levels.

Enhanced Solubility of Poorly Water-Soluble Drugs:

Gastro-retentive systems can be designed to improve the solubility and dissolution of poorly water-soluble drugs, leading to better absorption.

Minimized Side Effects:

Controlled release and prolonged gastric retention can help minimize side effects associated with high peak drug concentrations, as seen in conventional immediate-release dosage forms.

Targeted Drug Delivery:
Gastro-retentive systems allow for targeted drug delivery to specific regions of the gastrointestinal tract, depending on the site of drug absorption.
Improved Therapeutic Effect for Local Action:
For drugs that exert their therapeutic effect in the stomach or upper part of the gastrointestinal tract, gastro-retentive systems ensure a more prolonged exposure to the target site.
Flexibility in Formulation:
Various formulation approaches, such as floating systems, bioadhesive systems, and expandable systems, offer flexibility in designing gastro-retentive drug delivery systems to meet specific drug and patient requirements.
Reduced Dosing Frequency:
Extended gastric retention can lead to a decrease in the number of doses required per day, which can contribute to improved patient adherence to the prescribed treatment regimen.
Improved Treatment of Gastrointestinal Disorders:
Gastro-retentive systems can be particularly beneficial for the treatment of gastric or duodenal ulcers, as they provide prolonged contact with the affected mucosa, enhancing drug efficacy.
Better Treatment for Paediatric and Geriatric Populations:
Gastro-retentive systems can be especially useful in populations like children and the elderly, where swallowing conventional dosage forms may be challenging. These systems offer an alternative that is easier to administer and may improve patient compliance. [28-32]

Table: 3 Other Stumbling Block of Specific Types of Gastroretentive Drug Delivery Systems Are Listed in The Table Below:

S. No	Technology	Stumbling block
1.	Expandable system	Hydrolysable and biodegradable polymers cause storage problems, making it difficult and expensive to make.
2.	Floating system	The ability to float is heavily dependent on the stomach's ability to digest food, and a larger amount of fluid is necessary in the stomach
3.	High density system	Large amounts of medicines are difficult to integrate. To present, there are no such systems accessible on the market
4.	Mucoadhesive system	Due to the fast turnover of mucus and the peristaltic wave of the stomach, it might get separated from the

		gastric mucosa. In addition, it may attach itself to the mucus of the intestines
5.	Magnetic system	Patient compliance is an issue

Strategies for delaying drug transit through GIT:

Pharmacological approach

It involves the co-administration or incorporation of a drug into the dosage form. This drug delays gastrointestinal emptying. Examples include antimuscarinics, e.g., propantheline

Physiological approach

It is the use of natural materials or fat derivatives such as triethanolamine myristate, which stimulate the duodenal or jejunal receptors to slow gastric emptying

Pharmaceutical approach

First two approaches are not used due to toxicity problems. The various pharmaceutical approaches are. This approach involves formulation of dosage forms with density that must exceed density of normal stomach content.

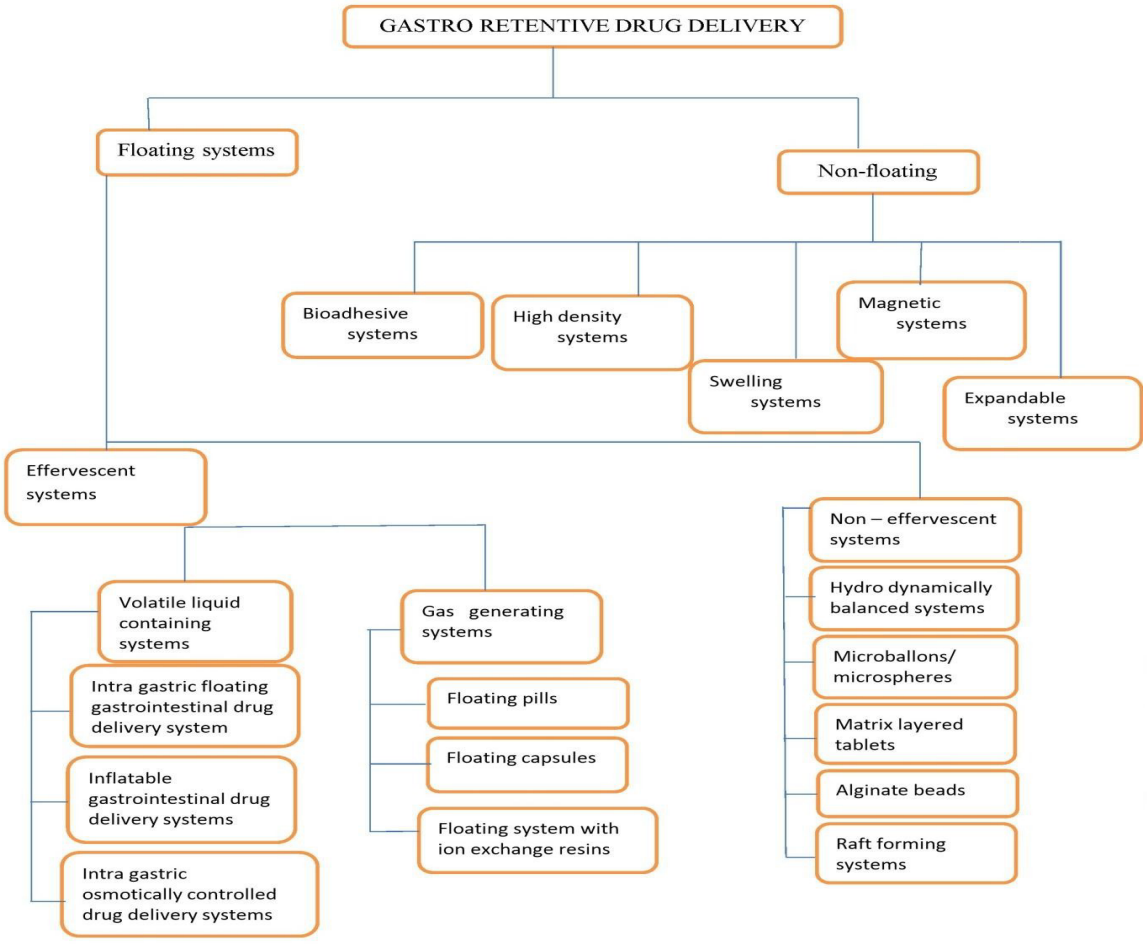

Figure:4 Differentapproachesforgastroretentivedrugdeliverysystems

Classification of Gastro retentive drug delivery systems:

Floating drug delivery systems:

Gas-Generating Systems:

Gas-Generating Tablets/Capsules: These systems contain effervescent agents (such as sodium bicarbonate and citric acid) that generate carbon dioxide gas upon contact with gastric fluids, leading to the formation of a floating layer.

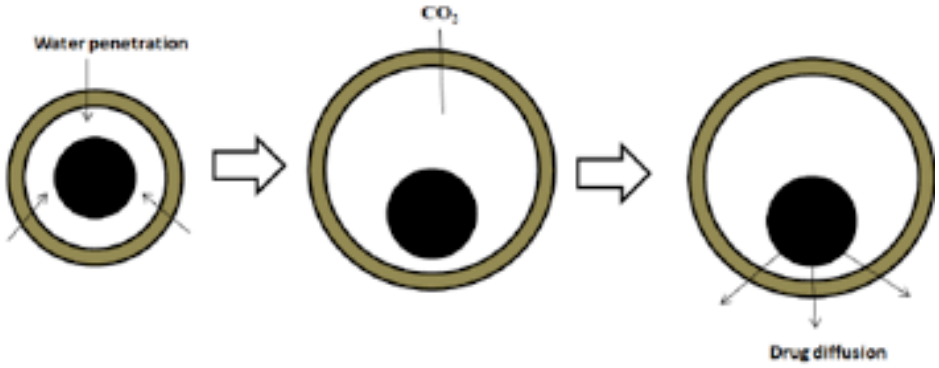

Figure: 5 Floating drug delivery systems

Gas-Generating Floating Beads/Granules: Similar to tablets and capsules, these systems use effervescent agents in the form of beads or granules.

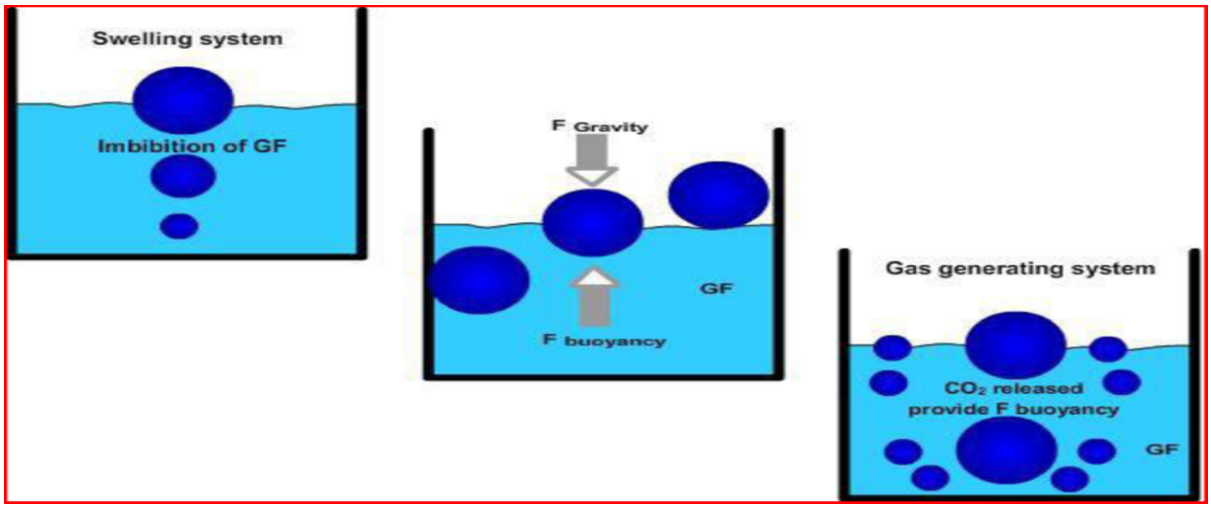

Figure: 6 Mechanism of Floating drug delivery systems

Non-Effervescent Systems:

Hydrodynamically Balanced Systems (HBS): These systems are designed to have low-density components, ensuring buoyancy in gastric fluids. This can be achieved using low-density materials like polymers, microspheres, or hollow particles.

Swelling Systems: These systems rely on polymers that swell when in contact with gastric fluids, forming a gelatinous layer around the dosage form. This layer provides buoyancy and controls drug release.

Bioadhesive Systems: Floating drug delivery systems can also use bioadhesive polymers that adhere to the gastric mucosa, preventing the dosage form from sinking. This approach enhances drug absorption.

Raft-Forming Systems:

Alginate-Based Raft Systems: Alginate is a natural polymer that can form a gelatinous raft upon contact with gastric fluids, providing buoyancy and sustained drug release.

Magnetic Systems:

Magnetic Tablets/Capsules: These systems contain magnetic components, and an external magnetic field is used to keep the dosage form in the desired region of the stomach, promoting prolonged gastric residence time.

Ion-Exchange Resin Systems:

Ion-Exchange Resin Beads/Granules: These systems use ion-exchange resins that can swell and remain buoyant in gastric fluids. The drug is typically adsorbed onto the resin and released slowly.

Low-Density Foam Systems:

Foam Tablets/Capsules: These systems incorporate low-density foaming agents that produce a foam layer in the stomach, resulting in buoyancy.

Non-Floating drug delivery systems:

Immediate Release Systems:

Conventional Tablets and Capsules: These are the most common drug delivery systems where the drug is released immediately upon administration.

Extended-Release Systems:

Sustained Release Systems: These systems release the drug at a controlled rate over an extended period, reducing the frequency of dosing. This can be achieved through various mechanisms such as matrix tablets, osmotic pumps, or microencapsulation.

Controlled Release Systems: Similar to sustained release, controlled release systems maintain drug concentrations within a therapeutic range but may not necessarily provide a constant release rate.

Modified Release Systems:

Delayed Release Systems: These systems release the drug after a predetermined lag time, often to protect the drug from the acidic environment of the stomach. Enteric-coated tablets and capsules fall into this category.

Pulsatile Release Systems: These systems release the drug in pulses, mimicking the body's natural rhythm. This can be particularly useful for drugs with circadian rhythms or those that require release at specific times.

Targeted Drug Delivery Systems:

Ligand-Targeted Systems: Drug carriers are modified with ligands that specifically bind to receptors on target cells or tissues, enhancing drug delivery to specific sites.

pH-Sensitive Systems: These systems take advantage of the pH variations in different parts of the gastrointestinal tract. For example, drugs can be coated with polymers that dissolve or swell at specific pH levels, releasing the drug in the desired region.

Polymer-Based Systems:

Microparticles and Nanoparticles: Drug-loaded particles, often made of biodegradable polymers, provide controlled release of drugs. These can be administered orally or through other routes.

Hydrogels: These are three-dimensional networks of hydrophilic polymers capable of absorbing and retaining water. Hydrogels can be designed to release drugs in a controlled manner.

Lipid-Based Systems:

Liposomes: Lipid vesicles that can encapsulate both hydrophobic and hydrophilic drugs, providing controlled release.

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs): These lipid-based carriers offer controlled release and improved drug stability.

Implants and Depot Injections:

Polymer Implants: Biodegradable polymer implants can be placed under the skin to release drugs over an extended period.

Injectable Depots: These are formulations that release drugs slowly after being injected into the body, offering a sustained therapeutic effect. [33-37]

Marketed Products of Grdds:

Table: 4 Following are some gastroretentive products which are available in market.

S. No.	Brand name	API	Dosage form
1.	Cifran OD®	Ciprofloxacin	Tablet
2.	Oflin OD	Ofloxacin	Tablet
3.	Madopar®	LDopa and Benserazide	Capsule
4.	Conviron®	Ferrous sulfate	Colloidal gel
5.	Valrelease®	Diazepam	Capsule

Recent combinational approaches for Gastroretention:

Currently following combination approaches used in GRDDS

1. Swellable and floating.
2. Bioadhesive and floating.
3. Bioadhesion and swelling.
4. Bioadhesion and High density,
5. Floating pulsatile system.

Conclusion:

In recent years, retention technologies for the supply of medicines to the gastrointestinal system have been extensively explored. A gastro-retentive oral pharmaceutical approach can assist to decrease the dose frequency of different medicine and is undoubtedly beneficial for pharmaceuticals in the stomach or upper intestine. However, several barriers have to be overcome to get the most of the system. Because the human gastrointestinal tract is unpredictable, numerous scientists are still investigating the best approach to use it. Some of them were successful, while others failed. In order to be effective

in formulating medicines and excipients, a good GRDDS must take into account the physiological event in the gastrointestinal tract.

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