EXPLORING INNOVATIVE APPROACHES IN GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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Abstract:
The development of gastroretentive drug delivery systems has raised the possibility of improving the bioavailability and effectiveness of a variety of medicinal substances. The benefits and drawbacks of using gastroretentive systems for medication delivery are carefully assessed in this research. The principal aim is to conduct a thorough analysis of their mechanisms, formulation methodologies, and prospective uses. Particular attention will be paid to their capacity to extend the stomach residence time and enhance medication absorption. Gastroretentive drug delivery systems have the advantage of slowing down drug release, preserving therapeutic concentrations, and requiring fewer doses. For medications that target particular parts of the gastrointestinal tract or have a limited window of absorption, this prolonged gastric residence duration offers a practical strategy. These technologies may also enhance patient compliance, which would enhance the effectiveness of treatment. The review does, however, also point out a number of difficulties with gastroretentive devices. Significant restrictions include the possibility of gastrointestinal side effects, danger of local irritation, variability in stomach emptying, and intricate formulation and manufacturing procedures. Furthermore, cautious thought must be given to regulatory issues as well as the possible risk of device dislodgement or aspiration.The present knowledge of gastroretentive drug delivery systems is consolidated in this review, which also highlights the need for more study to overcome these shortcomings. To maximize the safety, effectiveness, and practicality of these systems in clinical practice, it will be necessary to make further strides in formulation processes, creative design approaches, and an improved understanding of patient variability.

Keywords: Gastroretentive drug delivery system, Mucoadhesive, Bioavailability, Polymer, Floating drug delivery system, Effervescent

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Introduction:

Oral administration is still widely used today despite continuous improvements in drug delivery methods because it is comfortable and easy for patients. Oral administration is the intended mode of administration for drug release systems. These drug delivery techniques release the medication in a controlled, predictable, and planned manner. They should not be used with drugs that have low bioavailability because of stability or absorption issues. The goal of these modern procedures is to help resolve issues such that these medications are more frequently found in the stomach over extended periods of time. Gastroretentive drug delivery systems, or GRDDS, are the term used to describe these drug delivery techniques. For drugs that are absorbed from the stomach, like albuterol, labile at alkaline pH, like metformin, and ranitidine-containing drugs, like furosemide and diazepam, that are poorly soluble at alkaline pH levels and have a narrow window of absorption, GRDDS are suitable. The ability of dosage forms to control and prolong the emptying time—which remains in the stomach longer than with conventional dose forms—is a helpful characteristic. The main problem is physiological variability, which involves the duration of stomach retention and gastrointestinal transit, both of which are essential for the total transit of the dose form. These formulations release the medication gradually over an extended period of time into the gastrointestinal tract (GIT), allowing for an effective concentration of the drug in the systemic circulation. If this medication is taken orally, it will stay in the stomach and eventually be released. As a result, the medicine is continuously delivered to the particular GIT absorption site. Drug solubility has increased, and the duration of drug retention in the stomach has increased for those whose solubility is low at high intestinal pH. Many medications, including captopril, metronidazole, and ranitidine HCL, can degrade in the colon.

Anatomy and physiology of the stomach:

To create gastroretentive dose forms that work, it is essential to understand the anatomy and physiology of the stomach. Anatomically, the stomach is made up of three parts: the body, which holds food after it has been eaten; the fundus, which is the part that faces the esophagus and is closest to it; and the antrum, which is the last and joins the body to the small intestine. Antrum facilitates churning and emptying the stomach.

Every 120–180 minutes during a fast, the stomach and intestine go through a contraction cycle called the migrating myoelectric cycle. It is divided into four more stages.

"Digestive motility pattern" describes the changes in the pattern of contractions in fed conditions. Phase 1- (base phase) and Phase 2- (preburst), phase 3- (burst phase); and phase 4 make up this pattern.

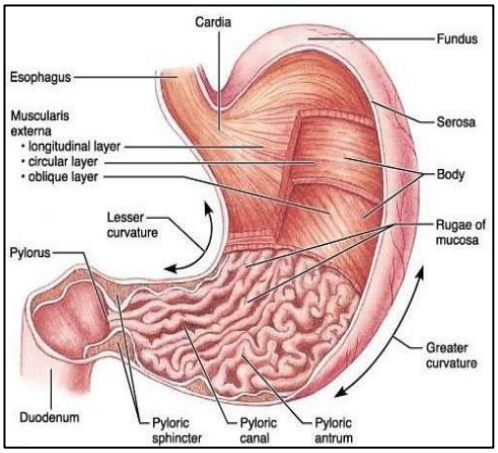

Fig.1: Anatomy and physiology of the stomach

Advantages of Gastroretentive drug delivery system:

- Prolonged drug release: They allow for a sustained release of drugs, ensuring a controlled and prolonged drug action within the body
- Enhanced bioavailability: By retaining the drug in the stomach for an extended period, these systems can enhance the absorption of drugs that have solubility or absorption issues in the gastrointestinal tract.
- Improved therapeutic efficacy: The controlled release and prolonged presence of the drug in the stomach can improve the therapeutic effect by maintaining optimal drug levels over an extended period.
- Reduced dosing frequency: Extended retention in the stomach can reduce the frequency of drug administration, improving patient compliance and convenience.

- Minimized fluctuations in drug concentration: By controlling the release of the drug, these systems can minimize fluctuations in drug concentration, ensuring a more consistent therapeutic effect.
- Targeted drug delivery: Gastroretentive systems can be designed to target specific regions of the gastrointestinal tract, ensuring localized drug delivery, especially useful for treating conditions in the stomach.
- Improved safety profile: They can reduce the risk of side effects by regulating the release of the drug, thereby minimizing sudden peaks in drug concentration.
- Adaptability to various drugs: Gastroretentive systems can be adapted to a wide range of drugs, making them versatile for different therapeutic applications.
- Potential for improved patient outcomes: Better control over drug release and absorption can lead to improved treatment outcomes for various conditions [4].

However, the design and development of these systems must consider various factors, such as gastric motility, food effects, and patient variability, to ensure optimal performance and efficacy.

Disadvantages of Gastroretentive drug delivery system:

- Variability in Gastric Emptying: The rate of gastric emptying can vary among individuals, leading to inconsistent drug release and absorption. Factors like food intake, gastric motility, and physiological differences can affect this, impacting the drug's effectiveness.
- Risk of Local Irritation: Prolonged contact of the drug delivery system with the gastric mucosa might lead to local irritation, inflammation, or even ulceration, especially if the system isn't designed appropriately.
- Gastrointestinal Side Effects: The prolonged presence of the drug in the stomach may cause gastrointestinal side effects like nausea, vomiting, bloating, or discomfort, impacting patient compliance and tolerance.
- Limited Applicability: Gastroretentive systems might not be suitable for drugs that are absorbed in specific areas of the gastrointestinal tract or those that require a particular release profile.
- Complex Formulation and Manufacturing: Developing gastroretentive drug delivery systems often involves complex formulation techniques and manufacturing processes, which can increase production costs.
- Regulatory Challenges: Obtaining regulatory approval for such delivery systems might be challenging due to the variability in gastric emptying among individuals and the need to demonstrate consistent drug release and absorption.
- Potential Risk of Aspiration: In certain cases, especially with devices that remain in the stomach for an extended period, there's a risk of dislodgement, leading to aspiration or blockage in the digestive tract.

Careful consideration of these disadvantages is crucial in the development and utilization of gastroretentive drug delivery systems to ensure their safety, efficacy, and patient compliance.

Physicochemical properties of GRDDS:

Drug delivery methods that are gastroretentive have special physicochemical characteristics that extend the duration of stomach residency. Because of their high buoyancy, these formulations stay afloat on the surface of the stomach fluid. Their bioadhesive or swelling properties encourage adhesion to the stomach mucosa. Drug absorption is improved by sustained release, which is facilitated by optimal density and size. Furthermore, these systems frequently have regulated medication release profiles that enhance patient compliance by preserving therapeutic concentrations. Overall, the physicochemical characteristics of gastroretentive drug delivery systems work to increase drug bioavailability by extending the time that the drug is present in the stomach. This is a useful way to provide different pharmaceutical substances a controlled release.

Classification of GRDDS:

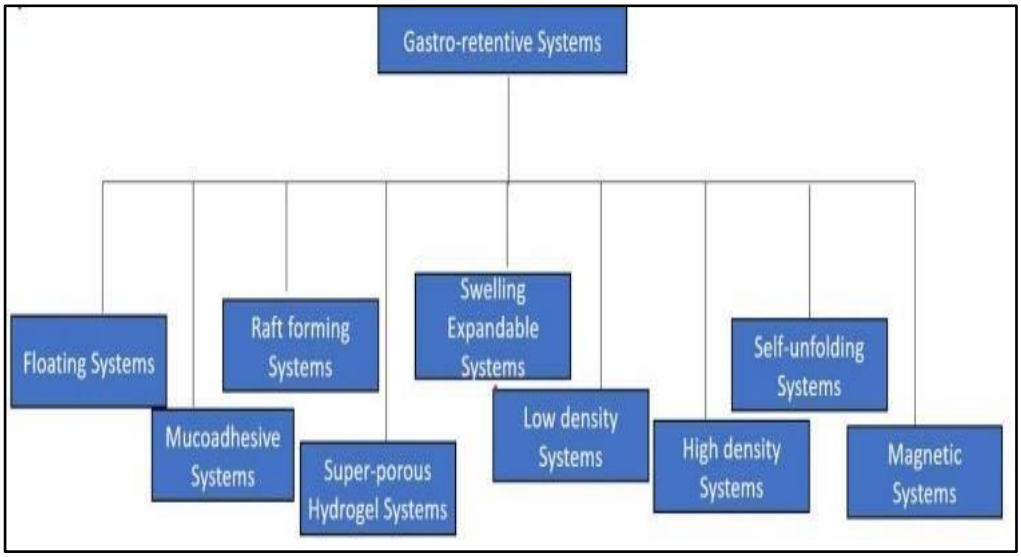

Fig. 2: Classification of GRDDS

The two primary categories of GRDDS are floating and non-floating systems. Based on how they float, floating systems are further divided into effervescent and non-effervescent systems, and nonfloating systems are divided into four groups according to how they use gastroretention.

1. High-density system: The density of the dosage form is an important factor in the formulation of the GRDDS. A high-density system's weight acts as a retention mechanism. A drug's density must be greater in the stomach than the typical stomach content (1.004 g/mL) in order for it to work better there. When a system's density equals 3 g/ml, it can be stored in the stomach and tolerate peristaltic movements throughout this time. Gastric fluid has a density of 1.004 g/ml, which is the same as that of water.

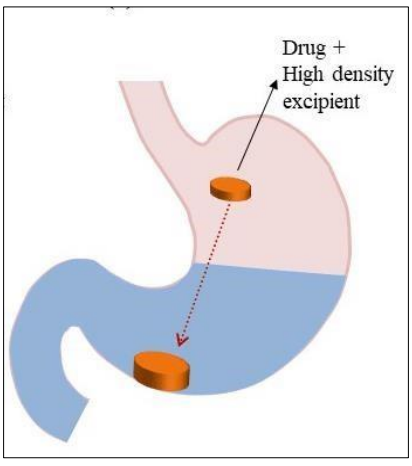

Fig.3: High Density System

2. Floating or low-density system: Reducing the dose form's density relative to the typical stomach content is another strategy for increasing gastric residence. This system was first introduced by J. Davis in 1968. Another word for it is hydrodynamically balanced systems. For floating, the bulk density should be less than 1.004 g/cm.
They therefore allow a dose form to float for a longer amount of time in the stomach. These are crucial tactics for increasing drug absorption and prolonging the duration of gastric retention.
Low-density systems or floating systems are of the two types as

a. Effervescent systems
b. Non-effervescent systems

- **Effervescent systems:** Polyethylene oxide (PEO)N12K, xantham gum, eudragit L100, ethylcellulose, and release-retardant polymers are all present in these compositions. The component in that mixture that produces gas. blends hydrophilic polymers to increase the tablet's buoyancy in gastrofloating systems. Since no thorough investigation has been done to date, it is imperative to look at the impact of sodium bicarbonate's function in the effervescent process on the drug release kinetics of more water-soluble drugs.Typically, the gas-entrapped membrane was discovered during storage, which led to issues with sustained release and floating. Applying talc as an anti-tacking agent in conjunction with glyceryl monostearate can resolve these issues.

It is categorized into three types:

- **Gas generating systems:** The effervescent reaction among carbonate/bicarbonate salts, citric/tartic acid, CO2 is released in presence of water when the formulation is put in the beaker it will sink with a production of gas it rises up and floats.

• **Volatile liquid containing system:** It consists of a liquid, such ether, in an inflatable chamber that expands when the liquid produces gas at body temperature. This inflatable chamber holds a pool of drugs contained in a gelatin capsule. Following ingestion, the capsule releases the inflatable and the medicine reservoir. due to the interplay between the stomach area and the integration of carbonates or bicarbonates, which results in the production of CO2 gas bubbles.

• **Raft forming systems:** This method creates a thick gel with trapped carbon dioxide bubbles by reacting carbonates or bicarbonates with stomach juice. Antacids such as aluminum hydroxide or calcium carbonate are commonly added to formulations to lessen gastric acidity. They accumulate as a layer on top of gastric fluids, which are commonly used in GI treatment, just like water does.

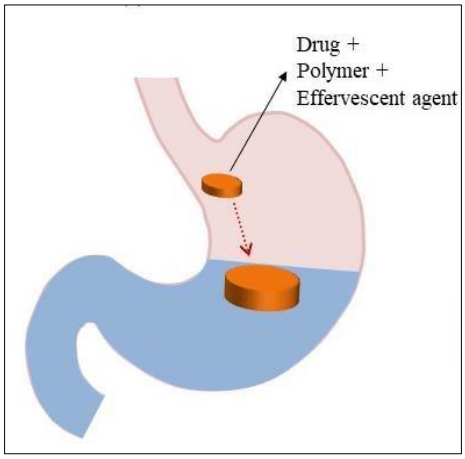

Fig.4: Floating system

• **Non-effervescent systems:** The main advantages of noneffervescent systems—which were first mentioned by Sheth PR and Tossounlan J in 1984—are the stability of acid- or base-labile medications and the fact that gastric pH is unaffected by floating lag time. In noneffervescent floating systems, the medication expands upon contact with stomach fluid. Because it maintains its shape and has a density of less than one, it floats in gastric fluid. Hydrocolloids of the swellable kind, gel-forming hydrocolloids, or matrix-forming polymers are used for these kinds of floating systems. An ideal dispersion of a combination of swellable and action retardant polymers, such as polyethylene oxide and xantham gum, was used to construct the tablet. Drugs containing gelforming agents, hydrocolloids of the swellable cellulose type, polysaccharides, and matrixforming agents are also included in the hydrodynamically balanced system. Polymers lengthen gastrointestinal stays and improve drug absorption. Microporous compartment systems are composed of drug encapsulation reservoirs inside microporous compartment pores. The trapped air in the flotation chamber allows the device to buoy over the contents of the stomach.
They are further classified as follows:

• **Hydrodynamically balanced systems (HBS):** The main component of these devices is a drug hydrocolloid mixture that, upon swelling, forms a gelatinous barrier upon contact with gastric juice. It survives in the stomach for a long time because its bulk density is lower than that of gastric fluid. Gasteroretentive theophylline HBS capsules were developed by Nayak and Malakar33 using HPMC, polyethylene oxide, polyvinylpyrrolidone, ethylcellulose, liquid paraffin, and lactose. This allowed the theophylline to be distributed in the stomach for an extended amount of time, with a minimum floating time of six hours.

• **Microballoons:** It is the process of progressively introducing a drug-containing emulsion into a volatile solvent. When the solvent evaporates and produces gas in a dispersed polymer droplet, an inner opening form in the drug's polymer microsphere. This technique is also known as the emulsion solvent diffusion method. The type and amount of polymer used in the formulation influence how long the microspheres float.

• **Alginate beads:** The interlocking agents in these systems are made of sodium alginate and a hydrocolloid gel-forming agent. The hydrocolloid absorbs water from the stomach juice and forms a barrier that traps air inside the polymer, causing the polymer to inflate. This causes the dose form to float and releases the drug gradually over time.

3. Mucoadhesive and bioadhesive systems: Mucoadhesive drug delivery systems function by utilizing the bioadhesion property of a particular polymer, which becomes adhesive when hydrated and permits the long-term distribution of a medication to a particular part of the body. When two materials—at least one of which is biological—are held together by interfacial forces, a phenomenon known as "bioadhesion" takes place.
One example of how an artificial substance and biological substrate could attach is adhesion between a polymer and a biological membrane. The term "mucoadhesion" describes a polymer that is adhered to the mucin layer of a mucosal tissue.

Mucoadhesive drug delivery systems can be delivered by various routes: -

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Usually, bioadhesive or mucoadhesive polymers are used for this.Natural polymers like sodium alginate, gelatin, guar gum, etc., as well as semisynthetic polymers like HPMC, lectins, carbopol, and sodium carboxymethyl cellulose, are commonly used for mucoadhesion. Adhesion is mediated by receptor contacts, bonding, or hydration.

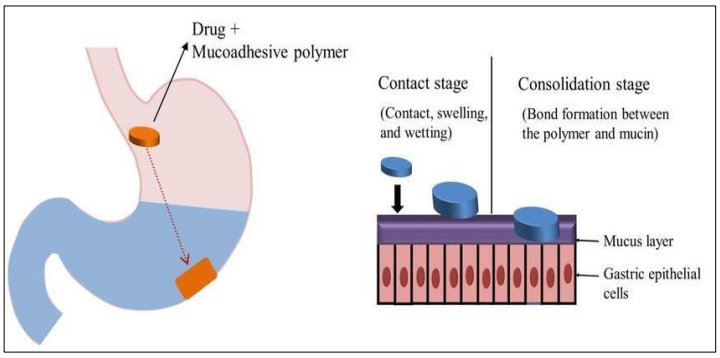

Fig.5: Mucoadhesive drug delivery systems

4. Swelling system: Because these systems are larger than the pyloric sphincter, they increase upon contact with stomach fluid. They remain stuck in the stomach as a consequence.
These are also known as "plug type systems. "The release of medication can be controlled and extended with the appropriate excipient. The main factor influencing the polymer's capacity to swell is the degree of cross-linking within its hydrophilic polymer network. While a low degree of cross-linking causes substantial swelling and rapid polymer disintegration, a high degree of crosslinking maintains the system intact.

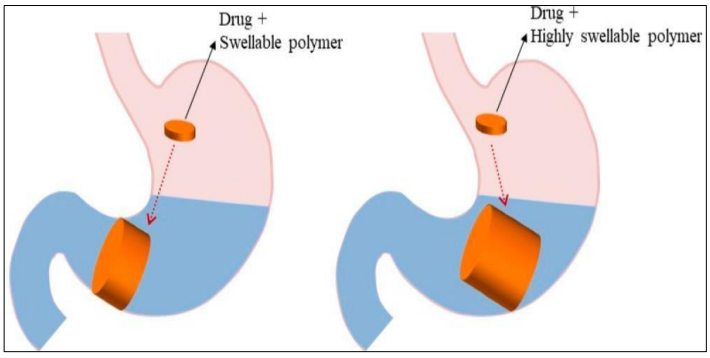

Fig.6: Swelling System

5. Superporous hydrogels: A superporous hydrogel is a three-dimensional network of hydrophilic polymers that contain several super-size pores. The process responsible for the swelling of superporous hydrogels is capillary wetting through networked open pores. To produce superporous hydrogels, a few ingredients—initiators and cross-linkers, for example—are used to initiate the cross-linking process. Additional chemicals included foam stabilizers, foaming agents, and foaming aids.

6. Magnetic system: This system applies a strong magnet with a strong magnetic field to the body surface, controlling the movement of a gastroretentive formulation with a small internal magnet. Several studies demonstrate the benefits of the system; however, for the system to function well, the magnet position needs to be selected extremely precisely.

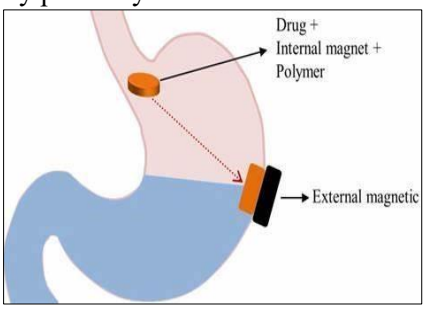

Fig.7: Magnetic System

Challenges Involved in Grdds:

The stomach is the only place where the GRDDS can be kept in place. Consequently, the biggest challenge in creating GRDDS is retaining the dose form in the upper part of the small intestine or stomach for a long period of time until the medication is completely eliminated from the body at a predetermined pace. The stomach empties itself in a variety of ways depending on a number of factors. The main variables, however, are the dosage type and whether the stomach is fed or fasting. The stomach emptying time is also influenced by food, calorie intake, age, and gender. Foods high in calories and fat also slow down the emptying of the stomach. The patient's age, gender, body mass index, level of disease, and the size and form of the dose forms all affect the GRT, which varies. The GRT is also impacted by the pylorus. Another fact is that animals (such dogs and rabbits) have smaller pylori and move differently during peristalsis than do humans. When consumed, indigestible polymers and fatty acid salts alter the motility pattern of the stomach, slowing down the rate at which the stomach empties. Therefore, it is imperative that the study's findings be thoroughly considered.

Gastro Retentive Innovative Device (GRID):

With this procedure, medications can only be absorbed by the stomach or small intestine. GRID was created to enable the longer than eight-hour retention of pharmaceuticals in the stomach. Extended stomach availability enhances the absorption of prescription drugs. The tablet offers a combination of quick and sustained medication release properties, which also helps with patient compliance. manufacturing of dosage forms with a multilayer covering GRID holds its shape to allow medication to be administered in a controlled manner during periods of extreme stomach movements. Consequently, because drug plasma concentrations are sustained in the therapeutic range for longer, this manner of dosing can be used as a "Once-a-day" strategy. With the help of this novel medication form, drug expected release can be tailored to produce pairs with both instantaneous and slow releases.

For many oral medications, keeping the medicine type close to the absorption site might help reduce the dose and consequently the negative effects.

Excipients used in floating systems:

- **Hydrocolloids:** The substances that have the ability to produce gels are called hydrocolloids. When the stomach contents come into contact with it, it swells. For example, pectin, agar, sodium alginates, ethyl cellulose, and HPMC.
- **Release rate accelerants:** It is an agent that increases the rate of drug release e.g., lactose, mannitol.
- **Release rate retardant:** It is an agent that uses substances such as calcium phosphate, magnesium striates, and talc to decrease the solubility of the medication, hence delaying its release effect.
- **Buoyancy increasing agent:** For increasing or enhancing the buoyancy by using the lowdensity materials like ethylcellulose.
- **Effervescent agent:** These are the substances that, upon coming into touch with an acidic medium, release carbon dioxide. Gas-generating agents like sodium bicarbonate and citric acid are employed in floating systems.

Conclusion:

Over the past thirty years, the significance of GRDDS systems has increased. They are unique systems. It offers several advantages, such as the capacity to gradually, precisely, and sitespecifically release drugs from a variety of gastroretentive dosage forms. By decreasing the frequency of doses, this improves patient compliance and reduces side effects. It is therefore expected that more pharmaceutical companies will come forward in the future to be the first to employ gastroretentive drug delivery technology in order to offer better advantages, increase the validity of their patents, and enhance the efficacy of their marketing formulations. Significant disadvantages include the complicated formulation and manufacturing procedures, the possibility of local irritation, gastrointestinal side effects, and variability in stomach emptying. To guarantee safety and efficacy, it is much more imperative to have careful design, extensive testing, and a good grasp of patient variability due to regulatory obstacles and the possible risk of aspiration.

Although gastroretentive systems have a lot of potential, these issues must be resolved before they can be successfully implemented. Enhancing these technologies to make them safer, more efficient, and suitable for a wide range of therapeutic situations will require ongoing research, creative design strategies, and a thorough grasp of patient physiology.

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