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Exploring Innovative Approaches in Gastro-retentive Drug Delivery Systems

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Abstract:
Gastroretentive drug delivery systems have emerged as a potential solution to enhance the bioavailability and efficacy of various pharmaceutical compounds. This review systematically evaluates the advantages and limitations of gastroretentive systems in drug delivery. The primary objective is to comprehensively analyze their mechanisms, formulationstrategies, and potential applications, focusing on their ability to prolong gastric residence time and improve drug absorption. Advantages of gastroretentive drug delivery systems include their capability to prolong drug release, maintain therapeutic concentrations, and reduce dosing frequency. This extended gastric residence time presents a viable approach for drugs with a narrow absorption window or those targeting specific regions of the gastrointestinal tract. Furthermore, these systems have the potential to improve patient compliance and, in turn, treatment outcomes. However, the review also highlights several challenges associated with gastroretentive systems. Variability in gastric emptying, potential gastrointestinal side effects,risk of local irritation, and complex formulation and manufacturing processes pose significantlimitations. Moreover, regulatory concerns and the potential risk of device dislodgement or aspiration require careful consideration.This review consolidates the current understanding of gastroretentive drug delivery systems, emphasizing the need for further research to address these limitations. Future advancements in formulation techniques, innovative design strategies, and a better comprehension of patient variability are essential to optimize the safety, efficacy,and applicability of these systems in clinical practice.

Keywords: gastroretentive drug delivery system, mucoadhesive, bioavailability, polymer, floating drug delivery system, effervescent.

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Introduction:

Oral administration is convenient and comfortable for patients, it remains popular even with ongoing advancements in drug delivery techniques. Systems for the controlled release of drugs are intended to be taken orally. These methods of delivering drugs release the drug in a scheduled, dependable, and regulated manner. They are inappropriate for medications with low bioavailability due to problems with stability or absorption. Such Modern techniques can help solve difficulties, which are intended to make these medications more prevalent in the stomach for a long period of time. These medication delivery methods are referred to as GRDDS, or gastroretentive drug delivery systems. GRDDS are appropriate for medications that are absorbed from the stomach, such as albuterol, labile at alkaline pH, such as metformin and ranitidine, such as furosemide and diazepam, are poorly soluble at alkaline pH levels and possessing low window of absorption. A useful feature of dosage forms is their capacity to regulate and extend the emptying time, which stays in the stomach longer than with traditional dose forms. The primary issue is physiological variability, which includes

gastric retention duration and gastrointestinal transit, both of which are crucial to the dose form's overall transit[1].

These formulations enable an efficient concentration of the medication in the systemic circulation by gradually releasing the medication into the gastrointestinal tract (GIT) over a lengthy period of time. This drug can be taken orally, where it will remain in the stomach and be released gradually over time. Consequently, the drug is continually supplied to the specific absorption site in the GIT. The solubility of medications has improved, and for those whose solubility is low at high intestinal pH, the retention of pharmaceuticals in the stomach has been prolonged. Numerous drugs, such as ranitidine HCL, metronidazole, and captopril, can break down in the colon[2].

Anatomy and physiology of the stomach:

Comprehending the structure and operation of the stomach is crucial to the development of effective gastroretentive dosage forms. Anatomically, the stomach is composed of three sections: the fundus, which is located closest to the esophagus and faces that direction; the body, which stores food that has been consumed; and the antrum, which is the last section andconnects the body to the small intestine. Antrum aids in stomach emptying and churning. During a fast, the stomach and intestine go through a round of contractions known as the migrating myoelectric cycle every 120–180 minutes. It is separated into four further phases. The term "digestive motility pattern" refers to the pattern of contraction alterations in a fed condition. Phase 1- (base phase) and Phase 2- (preburst), phase 3- (burst phase); and phase 4 make up this pattern[3].

Advantages of Gastroretentive drug delivery system:

- **Prolonged drug release:** They allow for a sustained release of drugs, ensuring a controlledand 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 overan 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 consistenttherapeutic effect.
- **Targeted drug delivery:** Gastroretentive systems can be designed to target specific regionsof the gastrointestinal tract, ensuring localized drug delivery, especially useful for treatingconditions 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 ofdrugs, making them versatile for different therapeutic applications.
- **Potential for improved patient outcomes:** Better control over drug release and absorptioncan 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 andefficacy.

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 gastricmucosa might lead to local irritation, inflammation, or even ulceration, especially if thesystem isn't designed appropriately.
- **Gastrointestinal Side Effects:** The prolonged presence of the drug in the stomach maycause 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 areabsorbed 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[5,6].

Physicochemical properties of GRDDS:

Gastroretentive drug delivery systems exhibit unique physicochemical properties to prolong gastric residence time. These formulations possess high buoyancy, ensuring they float on the gastric fluid surface. Their swelling or bioadhesive characteristics promote adherence to the gastric mucosa[7]. Optimized density and size contribute to sustained release, enhancing drug absorption. Additionally, these systems often exhibit controlled drug release profiles, maintaining therapeutic concentrations and improving patient compliance. Overall, the physicochemical attributes of gastroretentive drug delivery systems aim to enhance drug bioavailability by prolonging residence in the stomach, providing an effective means of controlled release for various pharmaceutical compounds[8].

Classification of GRDDS

GRDDS are classified into mainly two types: floating and non-floating systems. Floating systems are further classified into effervescent system and non-effervescent systems based onthe mechanism of floating, while non-floating systems classified into four different classes based on the mechanism used for gastroretention[9].

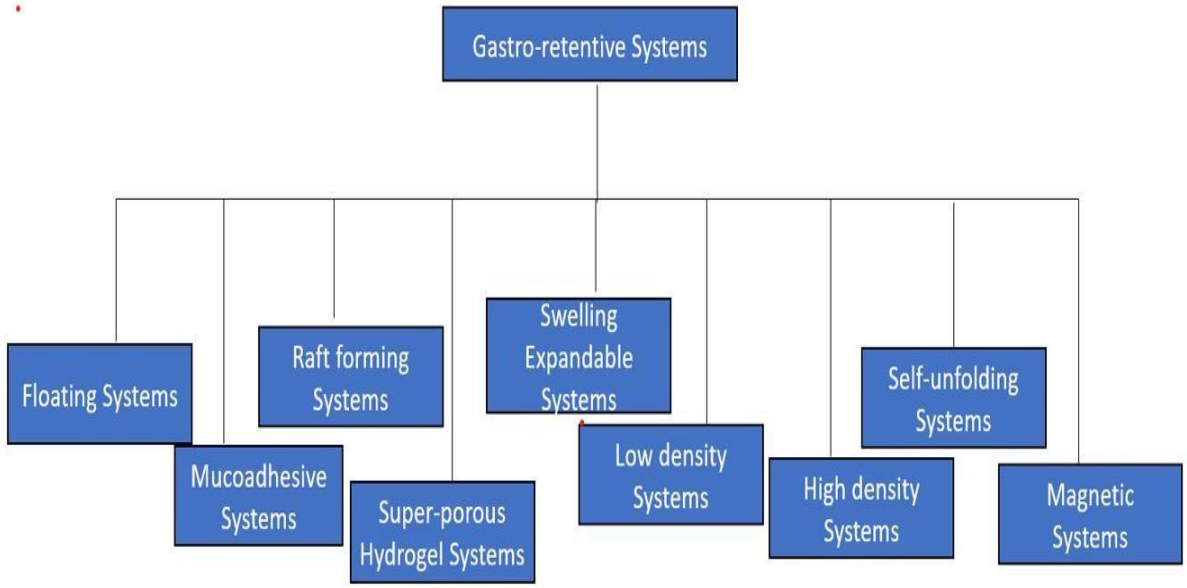

Fig. 1 classification of GRDDS

1. **High-density system:** A key component in the formulation of the GRDDS is the dosage form's density. The weight of a high-density system serves as a retention mechanism. For a medication to be more effective in the stomach, its density needs to be higher than the average stomach content (1.004 g/mL). Systems can be kept in the stomach when their density is equivalent to 3 g/ml, which allows the system to endure peristaltic motions in the stomach. The density of gastric fluid is the same as that of water, or 1.004 g/ml. They extend the retention duration by utilizing barium sulfate, titanium dioxide, iron powder, and zinc oxide.
2. **Floating or low-density system:** Another approach to increase gastric residence is to lower the density of dosage form than the normal gastric content. In 1968, J. Davis made the initial introduction of this system. Systems that are hydrodynamically balanced are another term for it. The bulk density for floating should be less than

1.004 g/cm.
As a result, they permit a dose form to float in the stomach for an extended period of time. These are important strategies for achieving greater medication bioavailability and a longerstomach retention period[10].
Low-density systems or floating systems are of the two types as

a) Effervescent systems
b) non-effervescent systems

- **Effervescent systems:** These preparations contain polyethylene oxide (PEO)N12K, xantham gum, eudragit L100, ethylcellulose, and release-retardant polymers. In that mixture, the gas-producing component. improves the tablet's buoyancy in gastrofloating systems by combining hydrophilic polymers.
  It is crucial to look at sodium bicarbonate's role in the effervescent process on the drugrelease kinetics of more water-soluble medications because no comprehensive study has yet been conducted to examine this relationship.The gas-entrapped membrane wastypically noticed during storage, which resulted in problems with floating and sustained release. These problems can be fixed by applying talc as an anti-tacking agent along with glyceryl monostearate[11].
  It is categorized into three types:
  (i). Gas generating systems: The effervescent reaction among carbonate/bicarbonate salts, citric/tartic acid, CO2 is released in presence of water when the formulation is putin the beaker it will sink with a production of gas it rises up and floats.
  (ii). Volatile liquid containing system: It is made up of a liquid, such as ether, in an inflatable chamber that produces gas at body temperature, which causes the stomach chamber to expand. A gelatin capsule containing a pool of medications is housed insidethis inflatable chamber. After consumption, the inflatable and the medication reservoirare released from the capsule. because of this integration of carbonates or bicarbonates and interaction with the stomach region, which causes the formation of gas bubbles of CO2[12].
  (iii). Raft forming systems: In this process, carbonates or bicarbonates react with stomach juice to form a viscous gel that contains trapped carbon dioxide bubbles. To reduce stomach acidity, antacids like calcium carbonate or aluminum hydroxide are frequently added to formulations. Similar to water, they form a layer on top of gastric fluids, which are frequently employed in GI treatment[13].
- **Non-effervescent systems:** The stability of acid or base labile drugs and the fact that gastric pH is unaffected by floating lag time are the primary benefits of non- effervescent systems, which were initially reported by Sheth PR and Tossounlan J in 1984. The drug expands when it comes into contact with stomach fluid in non- effervescent floating systems. It floats in gastric juice because it keeps its shape and its density is less than one. For these kinds of floating systems, matrix-forming polymers, gel-forming, or swellable type hydrocolloids are utilized[14].
  The tablet was created using a blend of action retardant and swellable polymers,including xantham gum and polyethylene oxide, in an optimally dispersed form. Thehydrodynamically balanced system also includes drugs with gel-forming agents, swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming agents. Polymers facilitate better medication absorption and increase the duration of GI stay. Drug encapsulation reservoirs inside microporous compartment pores make up microporous compartment systems. The device can buoy over stomach contents thanksto the trapped air in the flotation chamber[15,16].
  They are further classified as follows:
  (i). Hydrodynamically balanced systems (HBS): These systems primarily comprise of a drug-hydrocolloid mixture that, when the combination swells, forms a gelatinous barrier when it comes into contact with gastric fluid. Because its bulk density is lower than that of gastric fluid, it stays afloat in the stomach for a considerable amount of time. Using HPMC, polyethylene oxide, polyvinylpyrrolidone, ethylcellulose, liquid paraffin, and lactose, Nayak and Malakar33 created gastroretentive theophylline HBS capsules that controlled the distribution of theophylline for a prolonged period of timein the stomach with a minimum

floating time of 6 h[17,18].

(ii.) Microballoons: The process of gradually incorporating a drug-containing emulsion into a volatile solvent is known as microballooning. An inner opening forms in the drug's polymer microsphere as a result of the solvent evaporating and producinggas in a dispersed polymer droplet. Another name for it is the emulsion solvent diffusion
method. The kind and quantity of polymer utilized in the formulation affect themicrospheres' floating time.

(iii). Alginate beads: Sodium alginate and a hydrocolloid gel-forming agent are used to create these systems' interlocking agents. When gastric fluid is present, the hydrocolloid absorbs water and creates a barrier that traps air in the polymer, causing the polymer to inflate. As a result, the dosage form begins to float, releasing the medication over an extended period of time.

3. **Mucoadhesive and bioadhesive systems:** Mucoadhesive drug delivery systems work by taking use of a given polymer's bioadhesion feature, which becomes adhesive during hydration and allows a medicine to be delivered to a specific area of the body for prolongedperiods of time. The interfacial phenomena known as "bioadhesion" occurs when two materials, at least one of which is biological, are kept together by interfacial forces. Adhesion between a polymer and a biological membrane is one example of how an artificialsubstance and biological substrate might attach. The word "mucoadhesion" refers to a polymer that is affixed to a mucosal tissue's mucin layer.

   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

   Mucoadhesive or bioadhesive polymers are typically employed for this.For mucoadhesion, semisynthetic polymers including HPMC, lectins, carbopol, and sodiumcarboxymethyl cellulose as well as natural polymers like sodium alginate, gelatin, guar gum, etc. are frequently utilized. Receptor interactions, bonding, or hydration all play a role in the adhesion process[19].

4. **Swelling system**: These systems enlarge after coming into touch with gastric fluid becausethey are much larger than the pyloric sphincter. As a result, they stay lodged in the stomach. Another name for these is "plug type systems."With the right excipient, medication release can be regulated and prolonged. The degree of cross-linking within the hydrophilic polymer network is the primary determinant of the swelling ability of the polymer. A high degree of cross-linking keeps the system intact, whereas a low degree of cross-linking results in significant swelling and quick polymer disintegration[20].
5. **Superporous hydrogels:** A three-dimensional network of hydrophilic polymers with manysuper-size pores inside of them is known as a superporous hydrogel. Capillary wetting through networked open holes is the mechanism that causes superporous hydrogels to swell. Certain components, such as initiators and cross-linkers, are employed to start the cross-linking process in order to create superporous hydrogels. Foam stabilizers, foaming agents, and foaming aids were additional ingredients[21].
6. **Magnetic system:** This system regulates the movement of a gastroretentive formulation with a small internal magnet by applying a strong magnet with a powerful magnetic field onto the body surface. Numerous studies highlight the system's beneficial effects; nonetheless, the magnet position must be chosen with extreme precision for the system to be successful.

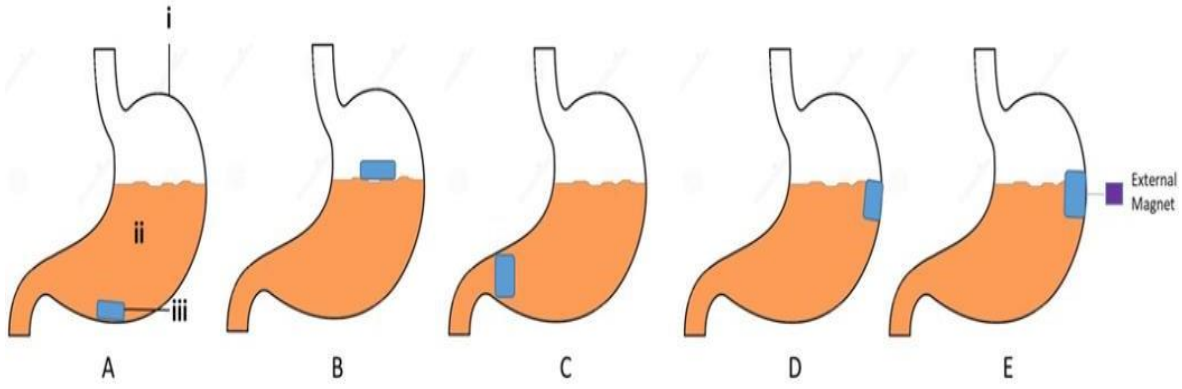

Fig.2 Different types of gastroretentive drug delivery system. A) High density system, B) floating/low density system, C) inflatable system, D) mucoadhesive system, E) magnetic system (i- stomach, ii- gastric fluid, iii- dosage form)

Challenges Involved in Grdds:

The GRDDS are exclusive to the stomach and must only be retained there. Therefore, the largest problem in developing GRDDS is keeping the dose form in the stomach or upper portion of the small intestine for an extended amount of time until all of the medication is released from the system at a predefined rate. The process of emptying the stomach varies greatly and is dependent on several things. The dosage form and thestomach's fed or fasted state, however, are the primary factors. Food, calorie intake, age, and gender are other factors that affect the stomach emptying time. Foods heavy in fat and calories also slow down the process of stomach emptying. The GRT varies and is influenced by the patient's age, gender, body mass index, illness state, and the size and form of the dosage forms. The pylorus also has an impact on the GRT. Anothertruth is that, in comparison to humans, animals (such as dogs and rabbits) have pylori that are smaller and move differently during peristalsis. Fatty acid salts and indigestiblepolymers also change the stomach's motility pattern when eaten, which helps to slow down the rate at which the stomach empties. As a result, it is essential to carefully consider the results of the study[22].

Gastro Retentive Innovative Device (GRID):

Only the stomach or small intestine can absorb drugs using this method. GRID was developed to allow medications to remain in the stomach for longer than eight hours. Extended stomach availability improves medication absorption. In addition to improving patient compliance, the tablet offers a combination of rapid and sustained drug release characteristics. dosage form fabrication using a multilayer coating In orderto distribute medication in a controlled manner during the period of severe stomach movements, GRID maintains its shape. Consequently, this mode of dosing can be employed as a "Once-a-day" technique because drug plasma concentrations are sustained in the therapeutic range for longer. This innovative medicine form allows forthe customization of drug anticipated release to achieve both instantaneous and gradual release pairings.

For many oral medications, keeping the medicine type close to the absorption site mighthelp reduce the dose and consequently the negative effects[23].

Excipients used in floating systems:

(1). 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.

(2). Release rate accelerants: It is an agent that increases the rate of drug release e.g.,lactose, mannitol.

(3). Release rate retardant: It is an agent that uses substances such as calcium phosphate, magnesium striate, and talc to decrease the solubility of the medication, hence delaying its release effect.

(4). Buoyancy increasing agent: For increasing or enhancing the buoyancy by using the low-density materials like ethylcellulose.

(5). Effervescent agent: These are the substances that, upon coming into touch with anacidic medium, release carbon dioxide.Gas-generating agents like sodium bicarbonateand citric acid are employed in floating systems[24,25].

Conclusion: GRDDS are distinct systems that have grown in significance during thepast thirty years. It has a number of benefits, including the ability to release medications from various gastroretentive dosage forms in a site-specific, regulated, and gradual manner. This increases patient compliance and lowers side effects by lowering the frequency of doses. As a result, it is anticipated that more pharmaceutical companies will step forward in the future to pioneer the use

of gastroretentive drug delivery technology in order to provide superior benefits, extend patents, and improve the performance of their commercial formulations. The variability in gastric emptying, the potential for local irritation, gastrointestinal side effects, and complex formulation and manufacturing processes are significant drawbacks. Regulatory hurdles and the potential risk of aspiration further underscore the need for meticulous design, thoroughtesting, and a clear understanding of patient variability to ensure safety and effectiveness.

While gastroretentive systems hold great promise, addressing these limitations iscrucial for their successful application. Continued research, innovative design approaches, and a comprehensive understanding of patient physiology will be instrumental in optimizing these systems, making them safer, more effective, and widely applicable in clinical settings.

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