GASTRO RETENTIVE DRUG DELIVERY SYSTEM: CURRENT STATE AND FUTURE PERCEPTION

Abstract

Gastroretentive drug delivery systems (GRDDS) have emerged as a vital branch of pharmaceutical research, focusing on improving drug delivery efficiency, patient compliance, and therapeutic outcomes. The current state of GRDDS reveals a diverse array of approaches and technologies, including floating systems, mucoadhesive systems, expandable systems, and magnetic systems. These technologies have found applications in drugs with limited solubility, sensitivity to gastric conditions, or narrow absorption windows in the upper gastrointestinal tract. In addition, superporous hydrogel, magnetic, ion-exchange resin, bio/mucoadhesive, low- and high-density systems, and expandable systems have all been employed recently in gastrointestinal technologies. Several GRDDS-based products have already been introduced to the market or are under clinical development, underscoring the practicality and effectiveness of these systems. Looking ahead to the future, GRDDS are poised for continued innovation and refinement. Anticipated trends include advanced formulations, personalized medicine approaches, the integration of biotechnology and nanotechnology, smart drug delivery systems, and a focus on regulatory considerations and environmental sustainability.

Keywords: Gastroretentive drug delivery, Superporous hydrogel, ion-exchange resin.

Authors

Yashkumar Ashok Meshram
Associate Professor
Jagadambha Institute of Pharmacy and Research, Kalamb Yavatmal.
yashkumarmeshram@gmail.com

Laximikant N. Barde
Jagadambha Institute of Pharmacy and Research, Kalamb, Yavatmal, M.S.
chetanbarde21@gmail.com

Mukesh M. Nikhade
Jagadambha Institute of Pharmacy and Research, Kalamb, Yavatmal, M.S.

Shrikant V. Kamle
Jagadambha Institute of Pharmacy and Research, Kalamb, Yavatmal, M.S.

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I. INTRODUCTION

The most common and practical method of medication delivery is oral. Because oral drug delivery is more flexible than other modes of administration in terms of dosage form design, it has garnered increased attention in the pharmaceutical industry.[1] Due to its simplicity of administration, this route has a high level of patient acceptance. As controlled release drug delivery systems (CRDDS) have developed throughout time, oral dosage forms have advanced as well.[2]

Targeting the specific part of gastro intestinal (GI) tract and designing controlled release devices for good absorption and bioavailability is challenging task. GI absorption of drug is a complex process and that relies on a several variables. The longer the drug remain in contact with GI tract the higher is absorption.[3] Therefore, for drugs that are only partially absorbed, the short intestinal transit time is essential. Extend the time that drugs are kept in the stomach since gastroretentive systems might remain there for several hours. Long-term retention in the stomach increases the solubility of the medication, reduces drug waste, and increases the bioavailability of pharmaceuticals that are less soluble in high pH conditions. It can be used to provide medications locally to the stomach and small intestine. The availability of new medications with innovative treatment possibilities and considerable patient benefits is improved with the help of gastro retention.[3,4]

The gastro retentive drug delivery system (GRDDS), a form of CRDDS with the ability to be held in the stomach, can enhance the oral controlled administration of pharmaceuticals by constantly releasing the medication prior to the "absorption window" over a prolonged period of time. Long-term retention in the stomach increases the solubility of the medication, reduces drug waste, and increases the bioavailability of pharmaceuticals that are less soluble in high pH conditions.[1]

II. GASTROINTESTINAL TRACT PHYSIOLOGY

With the duodenum at the pyloric sphincter and the neck at the cardiac sphincter, the stomach is persistent. Two ebbs and flows occur in it. The smaller ebb and flow is swift, located on the rear of the stomach, and continues the back divider of the throat downward. The pyloric sphincter has been bending upward for some time recently to complete the J form. Where the esophagus meets the stomach, the front region bends downward to form the larger ebb and flow before pointing slightly upwards toward the pyloric sphincter.

The stomach is divided into the fundus, body, and antrum. At the greater curvature lies the pyloric sphincter, that protects the opening between the stomach and the duodenum. When the stomach is bloated with food, the sphincter closes.[5]

Figure 1: Physiology of Stomach.[5]

III. GASTRIC EMPTYING

Gastric purging can happen both after eating and after fasting. Anyhow, the motility is specifically designed for each of the two states. During the fasting state, an interdigestive arrangement of electrical events cycles through the stomach and digestive tract every two to three hours. This process is usually referred to as the moving myloelectric cycle (MMC), sometimes known as the interdigestive myloelectric cycle. Usually, there are four pieces to it.

1. Phase I (basal phase) consists of infrequent contractions and lasts for 40 to 60 minutes.
2. Phase II (preburst phase) has sporadic contractions and action potential that continue for 40 to 60 minutes. The intensity and frequency steadily rise as the phase goes on.
3. Phase III (burst phase) is 4 to 6 minutes long. It contains brief, recurring contractions that are strong and frequent that assist in pushing the food to small intetsine. Another name for it is the housekeeping wave.
4. Phase IV between phases III and I of two successive cycles, lasting 0 to 5 minutes.

After consuming a blended supper, the withdrawal pattern switches from a fasting to a fed condition. This is also frequently referred to as a stomach-related motility design and involves ongoing withdrawals similar to those in stage II of a fasting condition. As a result of these compressions, the size of the food particles that are propelled toward the pylorus in a suspension frame is reduced (to less than 1 mm). The delayed onset of MMC occurs when the pace of stomach purging slows down during the boosted state.[4]

Figure 2: Patterns Gastrointestinal Motility.[6]

IV. NEED FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

Certain drugs have the most beneficial effects when delivered into the stomach, especially when the release is constant and controlled. Drugs released in this manner have fewer side effects and provide their beneficial effects without the need for repeated doses or a high dosage rate. Because it increases the specialist's contact time within the stomach where retention occurs. Cloth, for example, can be digested by the tiny digestive system in as little as 1-3 hours under average or normal conditions.[7]

V. FACTORS AFFECTING PERFORMANCE OF GRDDS [2]

1. Formulation Factors

- **Density:** Ideals of their drifting tendency, for which their thickness ought to be smaller than that of the gastric material, hold FDDS inside the stomach.

- **Shape:** Different geometrical forms' effects on the measuring frame's GRT have been carefully examined. The potential for stomach maintenance of six forms (ring, tetrahedron, clove leaf, string, pellet, and circle) was examined in vivo. At 24 hours, the tetrahedron and rings showed almost 100% maintenance. Contrarily, plates showed a range of 40% to 67%, whereas thread and pellets showed no maintenance after 24 hours.

- **Size:** Smaller pills are removed from the stomach during the stomach related stage, whilst larger tablets are removed during the housekeeping waves. Changing gastric purge times for non-disintegrating tablets of varying size were monitored.

2. Iodosyncratic Factors [2]

- Concomitant admissions of nourishment and drugs like anticholinergics, sedatives and prokinetic operators.

- Organic components like sexual orientation, age, pose, body mass record and infection state.

3. Other Factors

- **Presence of Food:** GRT increments within the nearness of nourishment, leading to the increment within the disintegration of the medicate and a longer home of the measurement shape at the foremost ideal locales of retention.

- **Nature of Food:** The GRT of the measurement form is influenced by caloric content and the frequency of nutrient intakes. The duration of gastric purge may be extended when GIT motility-decreasing medications are also used.

- **Gender Factor:** Women and older people seem to have slower stomach dumping than males. Additionally seen throughout the stomach and intestinal transit durations are intersubject and intersujective variants. Additionally, subject posture causes a range of intragastric activities. The upright position protects the floating frame from postprandial purging because it keeps constant watch on the gastric material regardless of its amount.

VI. GASTRO-RETENTIVE DRUG DELIVERY SYSTEM CLASSIFICATION

A number of procedures have been utilized to extend the GRT of measurement shapes utilizing a assortment of concept such as coasting, swelling, swelling and attachment. These frameworks have been classified agreeing to their essential guideline of gastric maintenance as underneath.

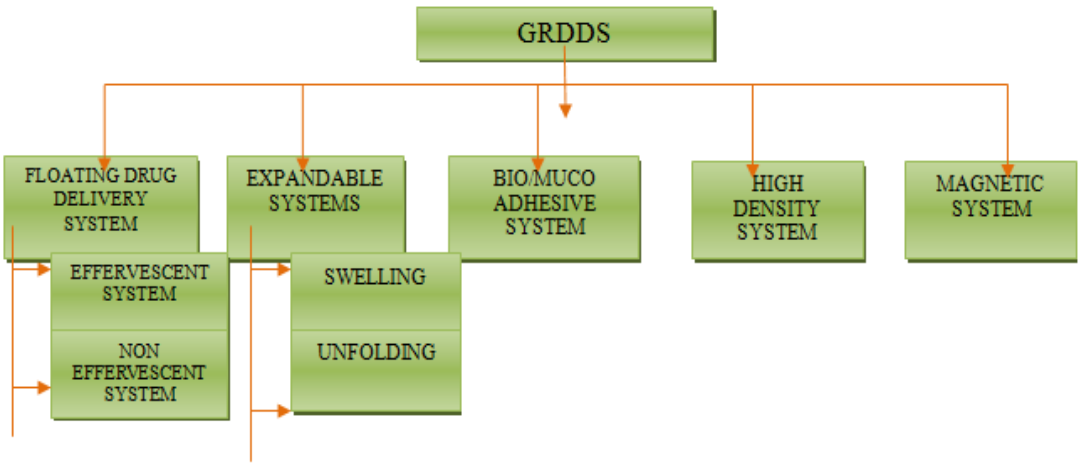

Figure 3: Gastro-Retentive Drug Delivery System Classification.[2]

Floating Drug Delivery System: Drifting frameworks, to begin with portrayed by davis in 1968, have lower than gastric liquid, and hence remains buoyant in stomach for a delayed period. Whereas the framework is coasting on the gastric substance, the sedate is discharged gradually at a craved rate. This result in an increment within the GRT and distant better; a much better;a higher;a stronger;an improved"a much better control of flocculation within the

plasma medicate concentrations. Drifting frameworks can be classified into two unmistakably diverse categories, they are,

- Effervescent System
- Non- Effervescent System [2]

1. **Effervescent System:** Carbonates (such as sodium bicarbonate) and other organic acids (such as citric acid and tartaric acid) in the formulation are employed in effervescent systems to generate carbon dioxide (CO2) gas, which decreases the density of the system and allows it to float atop the stomach juiceThere are two types of effervescent systems.[8]

    - Vacuum/volatile liquid containment systems
    - Gas generation systems

    - **Volatile Liquid/Vacuum Containing Systems:** A drug delivery system's GRT can be maintained by incorporating an inflatable chamber that carries a liquid, such as ether or cyclopentane, that gasifies at body temperature to produce the inflation of the chamber in the stomach. These devices are osmotically controlled floating systems that feature hollow deformable components that may shift from a collapsed to an expanded condition and then return to the collapsed position after a significant length of time. The deformable system's two chambers are linked by an impermeable, pressure-responsive, movable bladder. The drug is kept in the first chamber, while the volatile liquid is kept in the second. When the device is inflated, the medicine from the reservoir is continually distributed into the stomach fluid.

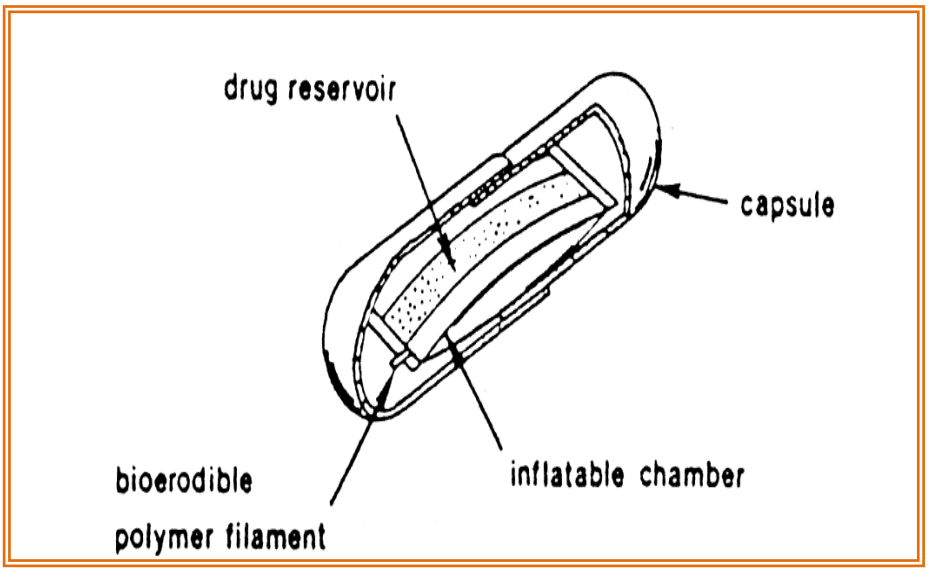

Figure 4: Osmotically Controlled Drug Delivery System. [9]

- **Gas Generating Systems:** This buoyant conveyance framework uses a foaming reaction between carbonate/bicarbonate salts and citric/tartaric corrosive to release CO_2. This freed CO_2 is subsequently confined inside the framework's gellified hydrocolloid layer, where it loses specific gravity and floats over time. These tablets can be single- or bilayered, with the gas-producing components crushed in one layer of hydrocolloid and the sedate in another layer designed for SR impact. The CO_2

producing components can be manually combined inside the tablet structure with single-layered tablets. [2]

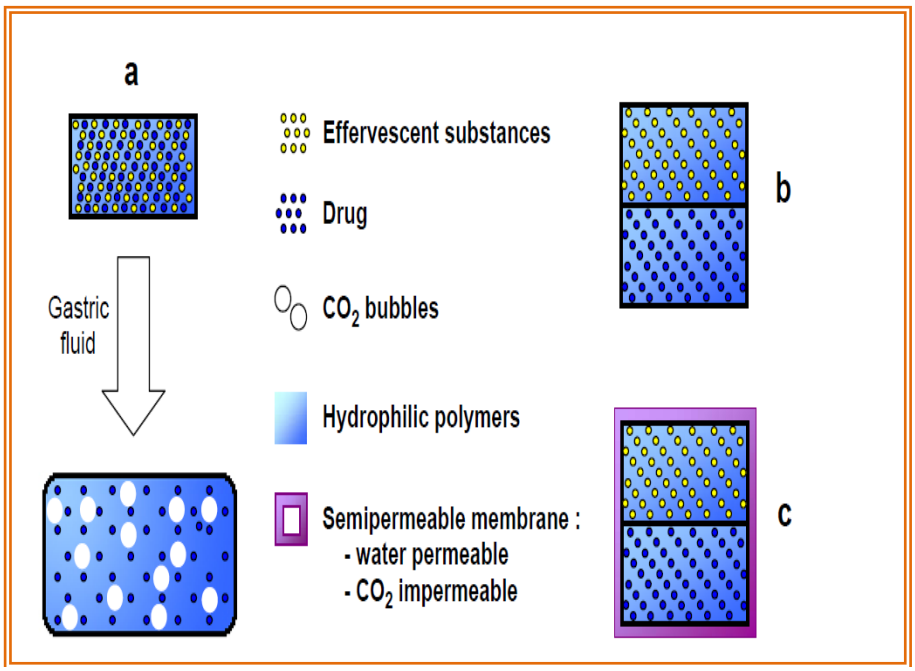

Figure 5: Gas generating System: Monolayer Drug Delivery System (a) Bilayer Gas Generating System, with (c) or without (b) Semipermeable Membrane.[10]

- **Raft-Forming Systems:** When in contact with stomach fluid, a gel-forming solution (such as a sodium alginate solution containing carbonates or bicarbonates) swells and solidifies into a thick, cohesive gel with trapped carbon dioxide bubbles. Antiacids like calcium carbonate or aluminum hydroxide are frequently used in formulations to lessen stomach acidity. Raft-forming devices are frequently used to treat gastroesophageal reflux because they create a layer on top of stomach fluids. [10]

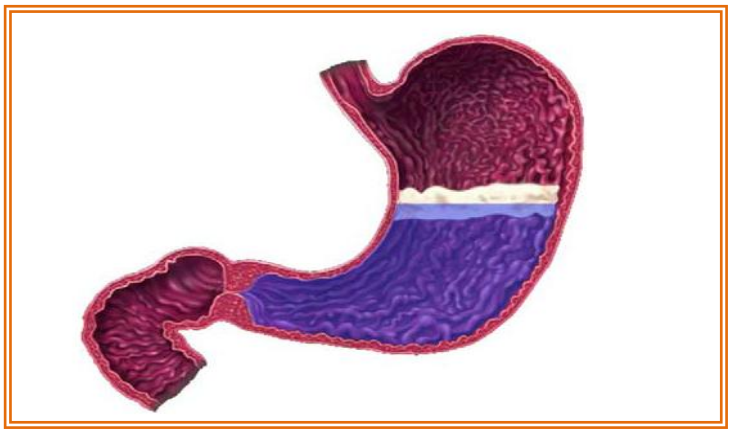

Figure 6: Barrier Formed by a Raft-Forming System.[10]

- **Non-Effervescent Floating Dosage Form:** The matrix-forming polymers polycarbonate, polyacrylate, polymethacrylate, and polystyrene, as well as gel-

forming or highly swellable cellulose type hydrocolloids, are the excipients most typically used in no effervescent FDDS. One technique for making these floating dose forms includes thoroughly combining the medication with a hydrocolloid that, following oral delivery, gels when it comes into contact with stomach fluid. Inside the outer gelatinous barrier, this hydrocolloid preserves relative form integrity and a bulk density that is less than unity. Due to the air that the expanded polymer has captured, these dosage forms float. Additionally, the gel structure acts as a reservoir for long-lasting drug release since the medication is gradually released via a controlled diffusion across the gelatinous barrier.10

- **Hydrodynamically Balanced Systems:** Colloidal gel barrier system is another name for it. Sheth & Tossounian created this technique for the first time in 1975. Such systems include medications that create gels with hydrocolloids and are intended to float on the contents of the stomach. This extends the GI residence time and increases the amount of medication that reaches the absorption site in the solution, making it suitable for absorption. These formulations contain high concentrations of one or more readily gelling cellulose-type hydrocolloids, such as sodium carboxymethylcellulose (NaCMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and hydroxypropyl methyl cellulose (HPMC), as well as polysaccharides and matrix-forming polymers such as polycarbophil, polyacrylates, and polystyrene. When the system's hydrocolloid comes into touch with the fluid on the stomach's outside, it hydrates and forms a colloidal gel barrier. This gel barrier regulates the rate at which fluids enter the device and hence release the drug. When the dosage form's external surface dissolves in the solution, the adjacent hydrocolloid layer hydrates to retain the gel layer in place. These dose forms have buoyancy because of the air trapped within by the inflated polymer, which maintains a density below unity.

  Three fundamental conditions must be met by the hydrodynamically balanced system:
  - It needs to have enough structure to create a cohesive gel barrier.
  - It must continue to have a total specific density that is lower than gastric content.
  - It ought to disintegrate gradually enough to act as a reservoir for the delivery system.[2]

  The operation's main weakness is its inactivity. After the gelatinous surface layer has hydrated, the characteristics and amount of polymer rely on the air that has been sealed inside the dry mass center. Effective medicine delivery is determined by the balance of drug loading and the effect of the polymer on the release profile. The effectiveness of the floating HBS has been increased through a variety of strategies. Bilayer formulations were developed where one layer controlled the buoyancy and the other the medication release. [10]

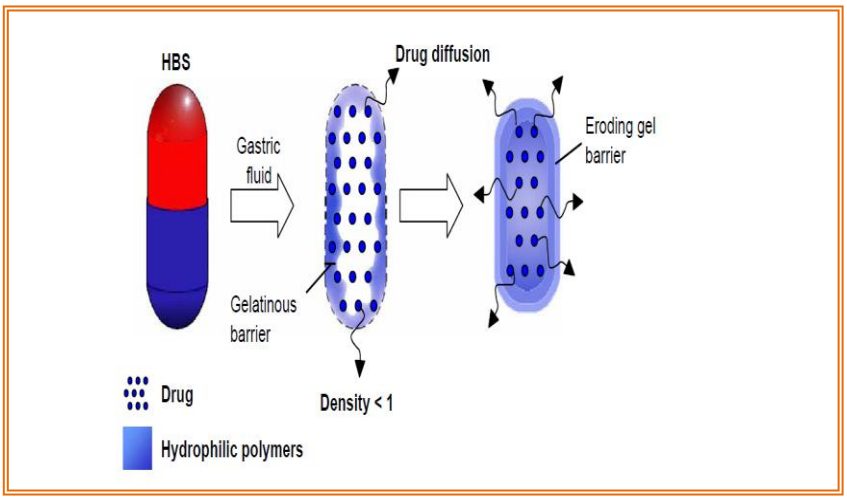

Figure 7: Hydrodynamically Balanced System (HBS).[10]

- **Expandable System:** These dose forms inflate after being ingested, preventing them from passing through the pylorus. Three configurations serve as the foundation for extendable GRDFs:

- A compact, collapsible design that allows for enough oral intake.
- Expanded shape that develops in the stomach and obstructs pyloric sphincter passage.
- A smaller version that is produced in the stomach after retention is no longer necessary, i.e., after the GRDF has released its active component and allowed evacuation.

The expansion can be achieved by,

- **Swelling System:** These are the dose forms that enlarge after consumption and become impossible to pass via the pylorus. As a result, the dose form remains in the stomach for an extended period of time. These systems are known as "plug type systems" because if their diameter exceeds 12 to 18 mm, they tend to remain blocked at the pyloric sphincter. The drug is delivered into the gastrointestinal cavity under carefully controlled settings and with stomach retention in mind. Even when fed, such polymeric matrices can remain in the stomach cavity for several hours. [8]

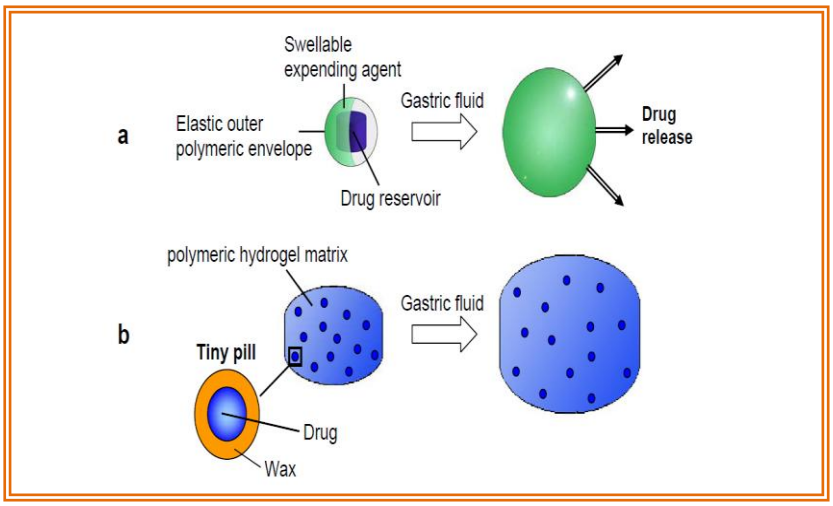

Figure 8: Swellable System.[10]

- **Superporous Hydrogels:** Although these systems can expand, they vary from more common variants in a way that necessitates a distinct classification. Traditional hydrogels absorb water relatively slowly and may take many hours to reach an equilibrium condition, at which time the dosage form may prematurely evacuate. Their pores range in size from 10 nm to 10 Am. Superporous hydrogels with an average pore size of >100 Am grow to equilibrium size in under a minute as a result of rapid water absorption by capillary wetting through many connected open pores. Additionally, they swell considerably (swelling ratio of 100 or above) (Fig. 8) and are made to be mechanically robust enough to withstand pressure from stomach contraction. This is made up of various chemicals and the hydrophilic particle material Ac-Di-Sol (croscarmellose sodium). In vivo tests with dogs revealed that the superporous hydrogel composite (i.e., one containing Ac-Di-Sol) remained in the stomach for 2-3 hours when fasting. The fed condition was only maintained for a brief period of time, although that period lasted for more than 24 hours. Fragmentation occurred after around 30 hours, and the composite soon cleared.[10]

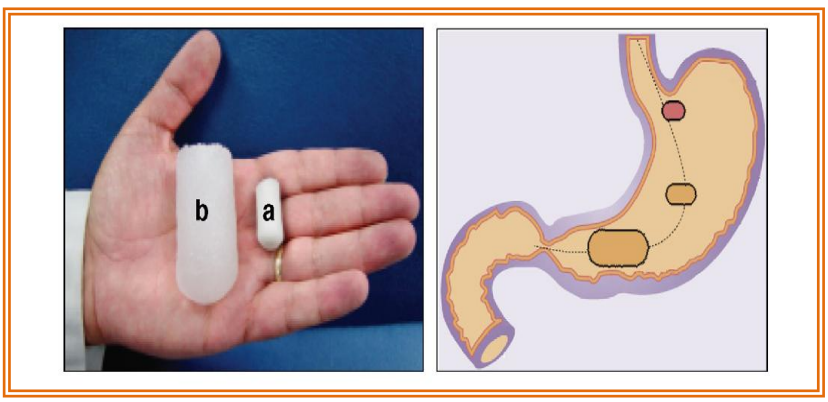

Figure 9: Superporous Hydrogels in its Dry (a) and Water-Swollen (b) State. On the Right, Schematic Illustration of the Transit of Superporous Hydrogel.[10]

- **Unfolding System:** Biodegradable polymers are used to create foldable systems. The idea is to develop a carrier with a compressed mechanism that expands like a capsule in the stomach. Caldwell et al. offered a tetrahedron, ring, or planar membrane [4-lobed, disc, or 4-limbed cross shape] as a geometric form of bioerodible polymer compacted inside a capsule. 10 points based on Figure 10.

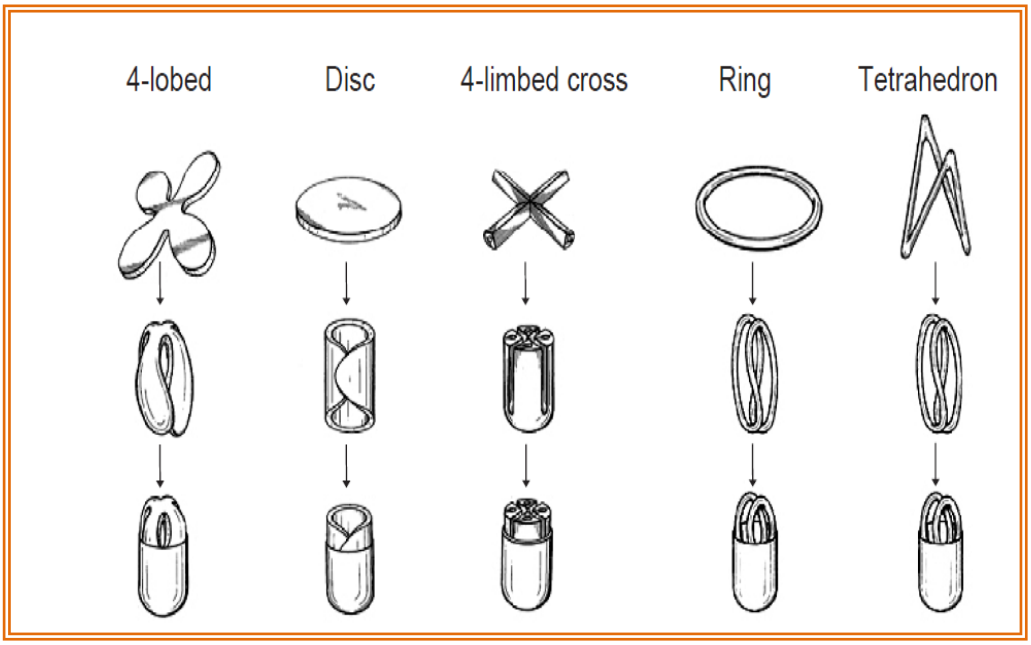

Figure 10: Different Geometric Shapes of Unfolding Systems.

- **Bio/Muco Adhesive Systems:** The surface epithelium of the stomach and intestine is known to maintain its integrity throughout the course of its existence despite being continuously exposed to hydrochloric acid at a high concentration and potent protein-splitting enzymes like pepsin. The specialized goblet cells of the stomach, duodenum, and transverse colon continually release a significant amount of mucus that adheres tightly to the surface epithelium, which is the cause of this self-protective mechanism. The epithelial cell membrane is protected by mucin, an oligosaccharide chain containing terminal salicylic acid that may neutralize hydrochloric acid and survive the action of pepsin. A polymer that may form an adhesive bond with a biological membrane is referred to as a biomucoadhesive polymer. This is thus referred to as a bioadhesive polymer, or with the GI mucosal membrane's mucus lining, which is referred to as a mucoadhesive polymer. It is understood that a biomucoadhesive polymer possesses the following molecular features:

  - Its molecules are flexible.
  - Functional groups that are hydrophilic are present.
  - It demands a certain chain length, molecular weight, and conformation.[11]

Figure 11 illustrates the idea of employing mucoadhesive polymer to prolong GI transit time.

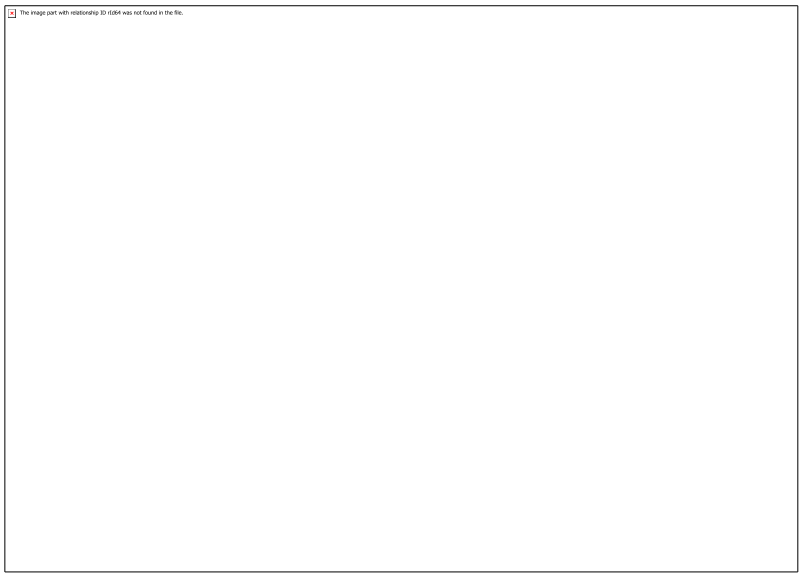

Figure 11: Interaction between a Mucus Layer on the Gastrointestinal Surface Epithelium and a Mucoadhesive Medication Delivery Mechanism. [11]

- **High Density System:** The high-density system is another GRDDS variant. Because they are retained in the rugae of the stomach and have a density of roughly 3g/cm3, these systems can endure peristaltic motions. Systems with a density threshold of 2.6-2.8 g/cm3 can be kept in the lower region of the stomach.

The system's one main limitation is the difficulty in producing formulations with a high drug concentration (>50%) and a density of about 2.8.[2]

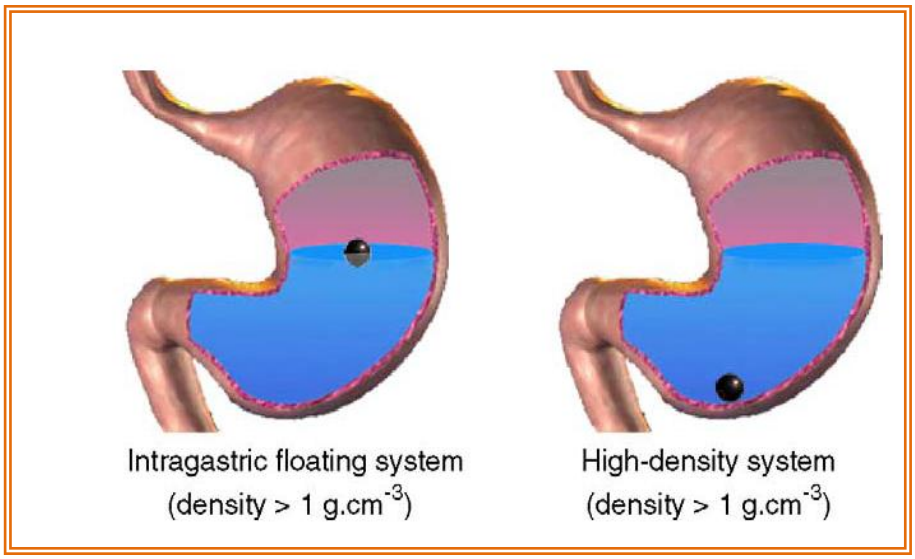

Figure 12: An Intragastric Floating and High Density System Form in the Stomach.[10]

- **Magnetic Systems:** This device is based on a simple concept: a small internal magnet is inserted in the dose form, and a magnet is attached to the abdomen above the stomach site. Ito et al. used bioadhesives granules containing ultrafine ferrite (g-Fe2O3) to apply this approach to rabbits. They used an external magnet (1700 G) to drive the granules to the oesophagus for the first two minutes, and virtually all of them were remained there after two hours. Despite the fact that these technologies appear to operate, positioning the external magnet with such accuracy risks compromising patient compliance.[10]

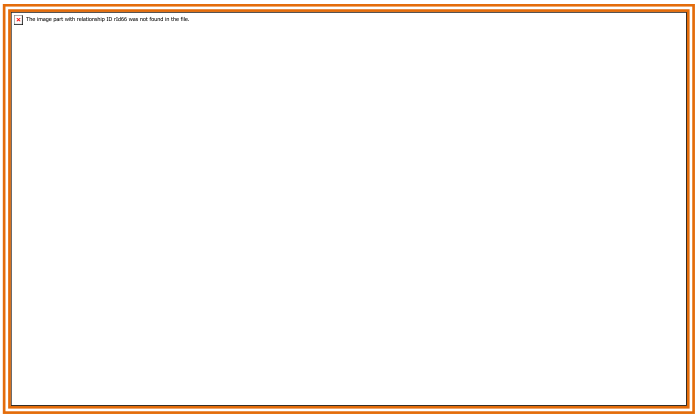

Figure 13: The Various Mechanisms used for Development of Gastroretentive Drug Delivery Systems.[2]

VII. PARAMETERS FOR THE DEVELOPMENT OF FLOATING ORAL SUSTAINED RELEASE SYSTEMS FOR DRUGS

Molecules with limited intestinal absorption but enhanced absorption in the higher regions of the GIT are frequently suitable CRGRDF candidates:

- Riboflavin and levodopa have a narrow window of absorption in the GI tract.
- Calcium supplements, chlordiazepoxide, and cinnarizine are mostly absorbed from the stomach and upper GI tract.
- Antacids and misoprostol are examples of drugs that only have a limited effect on the stomach.
- Metronidazole and ranitidine HCl are examples of drugs that degrade in the colon.
- Amoxicillin trihydrate and other antibiotics that alter the normal balance of bacteria in the colon. [12]

1. **Limitations of Gastroretentive Drug Delivery System:** Gastroretentive drug delivery systems are designed to prolong the residence time of orally administered drugs in the stomach, which can be beneficial for drugs that have specific absorption or release requirements. However, like any drug delivery system, gastroretentive systems have their limitations. Some of these limitations include.

2. **Interpatient Variability:** The gastric emptying time can vary significantly among individuals, which can make it challenging to design a one-size-fits-all gastroretentive system. What works for one person may not work as effectively for another.

3. **Food Interference:** The presence of food in the stomach can affect the gastric emptying rate. Gastroretentive systems may not work as intended if the patient has recently eaten, as the system may be pushed out of the stomach more quickly.

4. **Gastrointestinal Disorders:** Patients with certain gastrointestinal disorders, such as gastroparesis (delayed gastric emptying) or gastric motility disorders, may not benefit from gastroretentive systems because their stomach emptying is already impaired.

5. **Limited Drug Compatibility:** Not all drugs are suitable for gastroretentive delivery. Some drugs may degrade or lose efficacy in the acidic environment of the stomach, limiting their use in this type of drug delivery system.

6. **Risk of Bezoar Formation:** Gastroretentive systems may increase the risk of bezoar formation, which are solid masses of undigested material that can accumulate in the stomach and cause gastrointestinal obstruction.

7. **Patient Compliance:** Gastroretentive systems often require patients to take large tablets or capsules, which may be challenging for some individuals, especially those with difficulty swallowing.

8. **Design Complexity:** Developing an effective gastroretentive system can be technically challenging and may require specialized formulations or technologies, which can increase development costs.

9. **Safety Concerns:** There can be safety concerns associated with gastroretentive systems, such as the potential for device malfunction or complications related to prolonged gastric residence time.

10. **Drug Release Variability:** Achieving consistent drug release from gastroretentive systems can be difficult, especially if the system is sensitive to factors like pH or agitation within the stomach.

11. **Limited Applicability:** Gastroretentive systems are not suitable for all types of drugs or therapeutic applications. They are typically reserved for drugs that benefit from prolonged gastric residence or those with specific absorption requirements.

12. **Regulatory Approval:** Developing and gaining regulatory approval for gastroretentive drug delivery systems can be a lengthy and complex process, which may deter some pharmaceutical companies from pursuing this technology.[13,14]

VIII. FUTURE PERSPECTIVES

The future of gastroretentive drug delivery systems holds promise, with ongoing research and innovation aimed at addressing some of the limitations and expanding their applications. Here are some key future perspectives for gastroretentive drug delivery systems:

1. **Personalized Medicine:** Advances in pharmaceutical science and technology may allow for the development of personalized gastroretentive systems tailored to individual patient

needs. This could involve the use of patient-specific formulations or technologies to optimize drug delivery based on factors such as gastric emptying rates and gastrointestinal health.

2. **Improved Drug Compatibility:** Researchers are working on improving the compatibility of a wider range of drugs with gastroretentive systems. This includes developing new drug formulations and protective coatings to ensure drug stability in the acidic gastric environment.

3. **Multi-Drug Delivery:** Gastroretentive systems may be designed to deliver multiple drugs simultaneously, which could be beneficial for combination therapies targeting various conditions. This can improve patient compliance and treatment outcomes.

4. **Biodegradable and Eco-Friendly Materials:** Research is ongoing to develop biodegradable and environmentally friendly materials for gastroretentive systems. This is important for reducing the environmental impact of pharmaceutical waste.

5. **Nanotechnology:** Nanotechnology-based approaches, such as nanoparticles and nanocarriers, hold potential for improving drug delivery to the stomach and enhancing drug absorption. These systems can provide controlled and sustained drug release.

6. **3D Printing:** 3D printing technology can be used to customize and manufacture gastroretentive devices with intricate designs and tailored drug release profiles. This allows for greater flexibility in design and formulation.

IX. CONCLUSION

In summary, the future perception of gastroretentive drug delivery systems is one of continued growth, evolution, and adaptation to meet the evolving needs of patients and the pharmaceutical industry. These systems hold the promise of revolutionizing drug delivery, providing more targeted and efficient therapies, and ultimately improving the quality of healthcare for patients around the world. However, achieving these goals will require ongoing research, regulatory support, and a commitment to addressing the challenges and opportunities in this dynamic field.

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