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Review On Gastroretentive Drug Delivery Systems

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ABSTRACT

GRDDS represents a pioneering approach within the pharmaceutical sector, aimed at enhancing therapeutic outcomes through several key advantages such as simplified dosage administration, enhanced patient compliance, and increased formulation adaptability. This comprehensive review focuses on oral drug delivery systems, particularly Gastro Retentive Drug Delivery Systems (GRDDS), which serve as reservoirs for drugs and facilitate controlled release over a defined period. The primary objective of GRDDS is to augment the bioavailability of drugs. The review encompasses a detailed examination of the fundamental anatomy and physiology of the gastrointestinal tract, the prerequisites for gastroretention drugs, the rationale behind gastro retention, the factors influencing gastro retentive time, as well as an analysis of the merits and drawbacks associated with GRDDS. Additionally, it delves into recent advancements in Gastro-Retentive Drug Delivery Systems.

Keywords :- GRDDS; Approaches; Floating Drug Delivery System; Effervescent System; Raft Forming system; Factors Affecting Gastro Retentive Time

INTRODUCTION [1,2,3]

Traditionally, oral medication has been the preferred method of drug delivery. Over time, various systems have been developed to enhance this route, including controlled release systems. This review focuses on a specific type of controlled release system: the Gastroretentive Drug Delivery System (GRDDS).

GRDDS formulations aim to extend the time a medication resides in the stomach (gastric residence time, GRT) to achieve a prolonged and controlled release of the drug. These systems employ various mechanisms, such as magnetic attraction, mucoadhesion, bioadhesion, floating properties, swelling behavior, high density, and expandable structures, to improve drug bioavailability over an extended period.

The development of GRDDS specifically addresses the limitations of certain medications that exhibit poor bioavailability due to incomplete absorption or degradation within the gastrointestinal tract.

Ideal Properties of GRDDS [4]

- Localized action in the stomach
- Compatibility with the intestinal environment
- Drugs with a narrow absorption window in the gastrointestinal tract (GIT)
- Poor solubility in the high pH environment of the lower GIT

GRDDS technology offers a valuable tool for controlled drug release in the stomach and intestines. By delivering medication in a controlled and sustained manner to targeted areas like the stomach, duodenum, or intestines, GRDDS can optimize therapeutic outcomes.

Basic Anatomy and Physiology of the Gastrointestinal Tract [5, 6]

The gastrointestinal tract (GIT) can be divided into three main sections:

1) Stomach
i) Proximal Stomach: Fundus, Body
ii) Distal Stomach: Antrum (Pylorus)
2) Small Intestine
3) Large Intestine

The gastrointestinal tract (GIT) is essentially a muscular tube stretching about 9 meters from the mouth to the anus. Its primary functions include the storage of food, its mechanical breakdown, nutrient absorption, and the gradual release of digested contents into the duodenum, as well as the elimination of waste materials. A deep understanding of the stomach's anatomy and physiology is crucial for the effective development of Gastroretentive Drug Delivery Systems (GRDDS).[7,8]

The stomach typically holds about 50 ml of gastric fluid, primarily composed of hydrochloric acid (HCl), with a pH ranging from 1 to 3. This acidic environment is produced by the parietal cells located in the stomach's epithelial lining. These cells regulate the secretion of gastric acid. Additionally, the zymogenic cells in the stomach release pepsinogen, an enzyme precursor that is essential for the digestion and absorption of nutrients.[9]

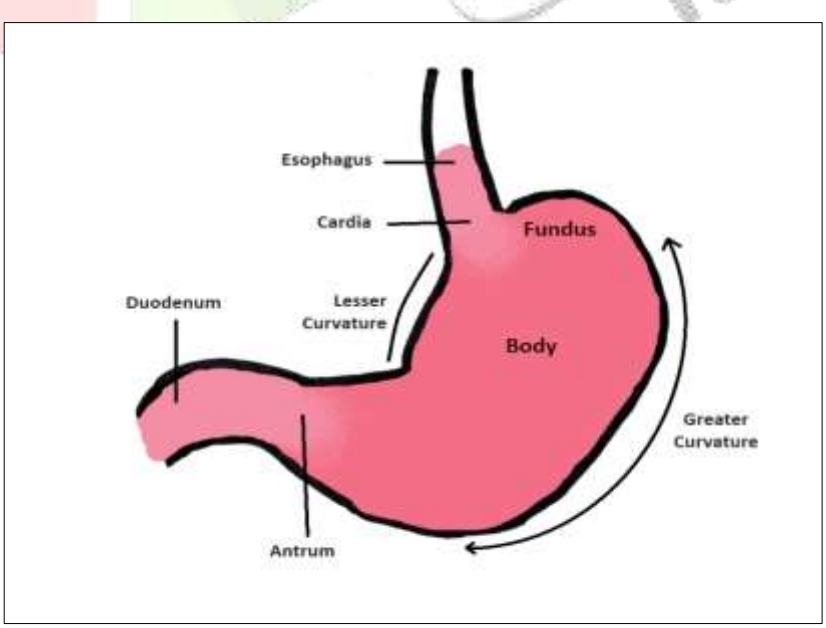

Figure 1: Anatomy of stomach

The stomach's anatomical structure is characterized by its J shape, divided into three distinct regions: the Body, Fundus, and Pylorus (Antrum), each consisting of three layers of muscle. The first layer, situated at the proximal part of the stomach, is the oblique muscle, while the second layer is located near the fundus and branches into the third layer in the higher region of the stomach. The proximal tube, comprising the fundus and body, serves to store undigested material, whereas the pylorus facilitates elimination and acts as the site for mixing motions that propel gastric emptying through pumping actions.

Gastric emptying is a regulated process comprising various phases and occurs in both fed and fasting states. However, the mobility pattern of the stomach, known as the Migrating Myoelectric Complex (MMC), varies between these states. During the fasting state, an interdigestive series of electrical events occurs. This series operates in cycles, with each cycle lasting approximately 90 to 120 minutes and encompassing four stages. The MMC cycle initiates from the lower esophagus and concludes at the ileum.[10]

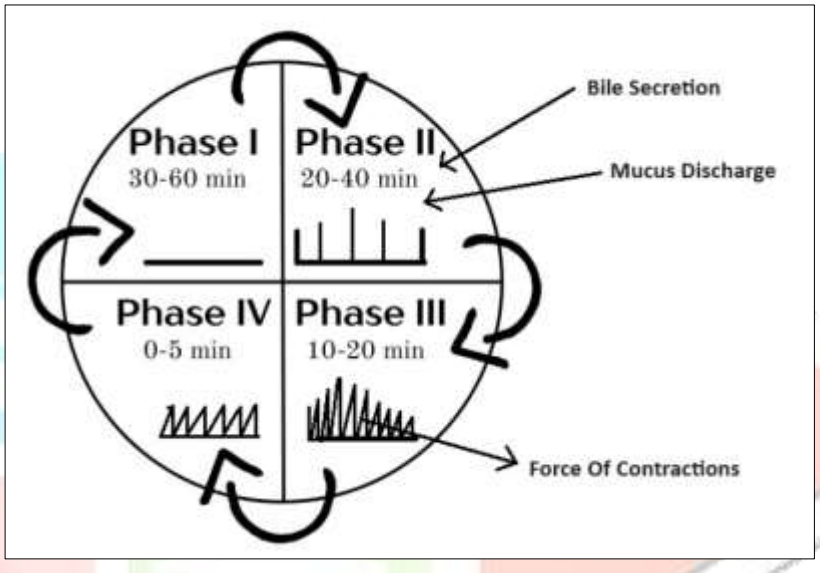

Figure 2: Phage of Migeating Myoelectric Complex

Requirements for Gastroretention Drug

Based on the anatomy and physiology of the stomach, a gastroretentive dosage form must meet specific criteria to be effective. These include uniform drug distribution within the gastrointestinal tract, extended retention in the stomach, high bioavailability, and controlled drug release. A key challenge for gastroretentive dosage forms is maintaining stability against the mechanical forces of stomach peristalsis.[11,12]

The primary goal of Gastroretentive Drug Delivery Systems (GRDDS) is to enhance the bioavailability of drugs. Drugs with a narrow absorption window in the gastrointestinal tract typically exhibit poor absorption but can benefit from prolonged retention at the target site, whether in the stomach, other parts of the GIT, or the intestines. Essential conditions for extended gastric retention include:

- Gradual dissolution of the drug.
- Delayed drug absorption in the stomach.
- Localized drug action within the stomach.
- Targeted drug delivery.
- pH-sensitive drug release.
- Enhancement of drug absorption by the presence of food.

- Gastric fluids aiding in the drug's disintegration and dissolution.
- Uniform drug absorption across the gastrointestinal tract. [13]

Need for Gastro Retention

The oral route remains the preferred method of drug delivery in the pharmaceutical industry due to its advantages, including ease of administration, cost-effectiveness, production simplicity, and design flexibility. However, low bioavailability poses a significant challenge for oral dosage forms, primarily due to rapid gastric transit. This issue is particularly pronounced when drugs have low solubility at alkaline pH levels in the intestine. Consequently, such drugs tend to exert their effects locally in the stomach before being quickly eliminated, resulting in inadequate residence time for absorption. [14]

To address this limitation, Gastroretentive Drug Delivery Systems (GRDDS) have been developed to enhance drug bioavailability by prolonging their residence time in the stomach, thereby facilitating absorption. Gastroretentive delivery systems represent a site-specific approach to drug delivery, wherein the absorption of the drug depends on the targeted site within the gastrointestinal tract. Formulations used in gastroretentive drug delivery systems are typically less soluble or slow to dissolve under alkaline pH conditions, thereby ensuring prolonged absorbance and improved bioavailability. [15]

Influential Factors on Gastro Retentive Time [16]

1. **Particle Size:** Particles with a size of 1 – 2 micrometers are likely to move on to the intestinal membrane.
2. **Density:** Gastric emptying speed is impacted by the dosage form's density.
3. **Dosage Size:** For optimal GRT, dosage forms should exceed 7.5 mm in diameter.
4. **Dosage Shape:** Certain shapes, such as tetrahedrons and rings, significantly enhance GRT, achieving retention effectiveness of 90 to 100%.
5. **Food Composition:** The physical nature of the food, particularly indigestible polymers, can influence stomach motility.
6. **Food Temperature:** Cooler food temperatures slow down gastric emptying.
7. **Caloric Content:** High-calorie foods, especially those rich in proteins or fats, can extend GRT to between 4 and 10 hours.
8. **Feeding Frequency:** More frequent eating sessions can lengthen the GRT up to 400 minutes.
9. **Gender Differences:** Females generally experience longer GRTs of 4-6 hours, influenced by physical metrics such as height and weight, whereas males typically have GRTs of 3-4 hours.
10. **Age:** Individuals older than 70 years tend to have longer GRTs.
11. **Posture:** The posture of a patient can affect the GRT.
12. **Drug Interactions:** Certain drugs, including antacids like Aluminum hydroxide, anticholinergics such as atropine, and narcotics like codeine, can enhance and extend GRT.

Advantages of Gastro Retentive Drug Delivery Systems (GRDDS) [17]

1. **Enhanced Bioavailability:** Improves absorption and effectiveness of drugs processed in the upper GIT.
2. **Reduced Frequency of Dosing:** Helps maintain therapeutic levels of drugs with shorter half-lives, enhancing patient compliance.
3. **Extended Drug Release:** Provides a sustained therapeutic effect, particularly in the upper GIT regions like the small intestine and stomach.
4. **Controlled Release:** Ensures a consistent and effective drug concentration at the target site.

5. **Stable Drug Levels:** Minimizes the peaks and troughs in drug concentration, reducing the risk of side effects related to dosage fluctuations.
6. **Selective Targeting:** By stabilizing drug levels, it's possible to achieve more targeted receptor activation.

Disadvantages of GRDDS [18,19]

1. **Limited Drug Suitability:** Not appropriate for drugs with issues related to stability or solubility in the stomach.
2. **Dependence on Gastric Fluid Levels:** Floating systems need a substantial amount of gastric fluid to float and function effectively.
3. **Challenges with Mucoadhesive Systems:** The rapid turnover and variability of the gastric mucosal layer can impede effectiveness.
4. **Variable Retention Factors:** Factors like stomach motility, pH levels, and the presence of food make predicting buoyancy and retention challenging.
5. **Pre-Activation Swelling:** Swelling agents might expand prematurely before reaching the stomach.
6. **Delayed Activation:** Hydrogel-based systems may need significant time to swell, potentially delaying their therapeutic effect.

Recent Advances in Gastroretentive Drug Delivery Systems [20,21]

Significant advancements have been made in the development of oral controlled-release and sustained-release drug delivery systems targeting gastrointestinal ailments. These systems enhance the bioavailability of drugs within the gastroretentive tract and maintain effective drug concentrations over extended periods in the stomach (GIT).

Oral dosage forms such as tablets, capsules, and pellets are designed to retain the drug within the stomach and release it in a controlled manner. This approach ensures a steady supply of the drug to its absorption or target site. It incorporates pH-sensitive mechanisms where the drug is released at specific pH levels. This is often achieved through a robust metallic coating that protects the drug from stomach acids but allows it to dissolve at the intended site.

This review explores various contemporary gastroretentive drug delivery strategies that have recently emerged as forefront techniques in the domain of site-specific and controlled release drug delivery.

Approaches of GRDDS

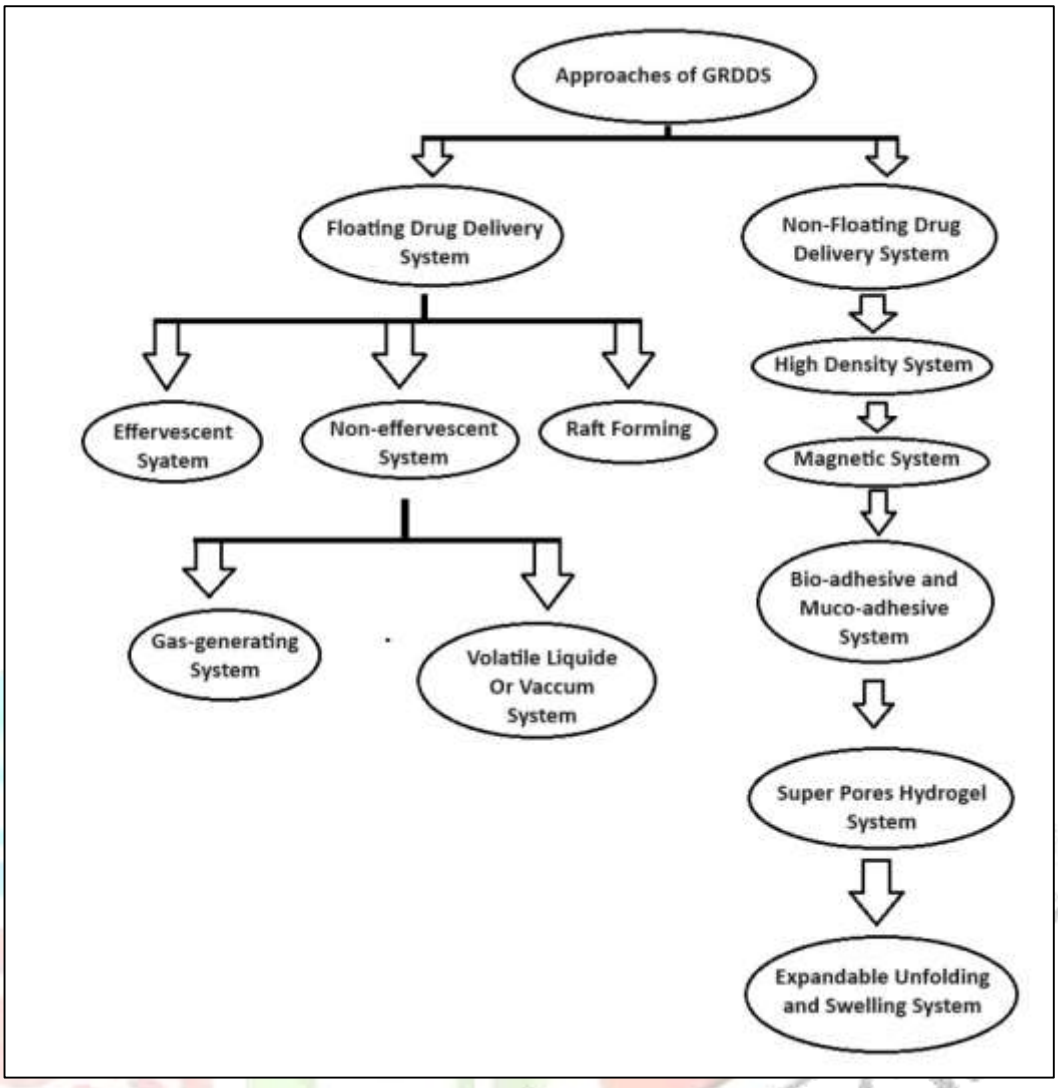

Figure 3: Approaches of GRDDS

1. **Floating Drug Delivery System (FDDS)** [22,23]

Introduced in 1968 by Sir Davis, the Floating Drug Delivery System (FDDS) features a formulation with a bulk density lower than gastric fluids. This allows it to remain in the stomach for extended periods without influencing the rate of gastric emptying. As a result, it continuously releases medication in a controlled manner, enhancing both bioavailability and gastric retention time.

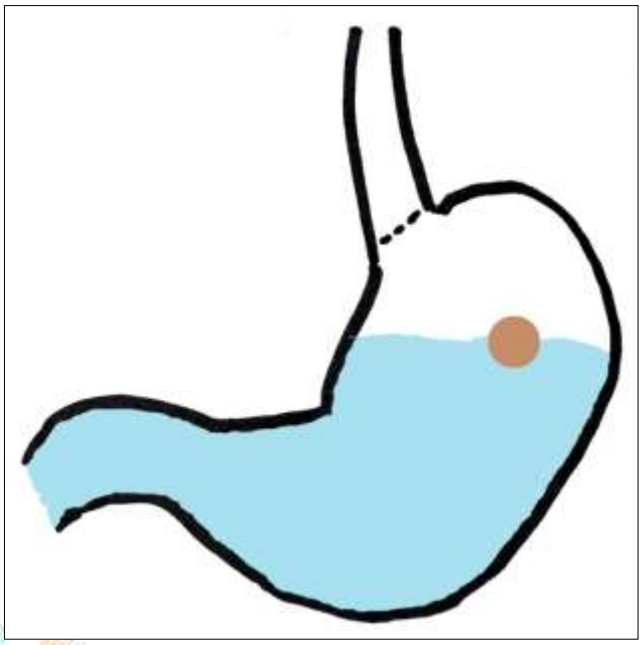

Figure 4: Floating Drug Delivery System

Properties of FDDS

- Ensures prolonged drug release.
- Functions as a reservoir for the drug.
- Maintains a bulk density less than that of gastric fluids (approximately 1.004 – 1.0 gm/cm^3).
- Forms a cohesive gel barrier to control release rates.

i) Effervescent System [24]

Composed of a matrix that includes swellable polymers such as Tartaric acid, HPMC, and chitosan, along with effervescent compounds like sodium bicarbonate and citric acid.

The effervescent action enhances drug absorption and modifies gastric pH, improving the bioavailability compared to standard tablets.

On reaction in the stomach, the effervescent agents produce carbon dioxide, reducing the tablet's density and enabling it to float in the gastric fluid. This reaction typically involves a mixture of sodium bicarbonate and citric acid in a specific ratio to optimize gas production.

In this system, the drug is stored in a reservoir, with controlled or sustained release triggered by the production of effervescence.

a) **Gas Generating System** [25]

A subset of the effervescent system, this method involves a reaction between sodium bicarbonate and citric acid to release carbon dioxide.

The released gases reduce the specific gravity and density of the drug formulation, allowing it to float on gastric contents.

b) **Volatile Liquid or Vacuum System** [26]

Recent innovations in gastroretentive drug delivery include the use of inflatable chambers filled with volatile liquids like ether or cyclopentane, which gasify at body temperature, aiding in drug release.

Alternatively, the chamber may be filled with a bio-erodible polymer plug, such as poly vinyl alcohol or polyethylene, facilitating controlled release as the chamber inflates and eventually erodes.

ii) **Non-Effervescent Systems** [27]

Non-effervescent systems utilize matrix-forming polymers like polymethacrylate, polyacrylate, and polystyrene, along with highly swellable and gel-forming substances such as polysaccharides and hydrocolloids. When administered orally, these forms (tablets, capsules, pellets) interact with the gastric fluids, which have a pH of 1 to 3, causing them to swell and become buoyant as their density drops below 1.

The gel structure that forms acts as a drug reservoir, facilitating controlled and prolonged release. A distinctive feature of non-effervescent systems is the porous surface that creates osmotic conditions, causing the dosage form to expand significantly more than typical oral forms upon contact with gastric fluids.

This expansion prevents the dosage form from moving towards the pylorus by increasing in size and creating a counter pressure that keeps it floating at the top of the gastric fluid, thus enhancing slow drug release and absorption.

iii) **Raft-Forming Systems** [28]

Raft-forming systems are primarily used in the management of gastroesophageal reflux disease (GERD). These systems work by forming a viscous, cohesive gel upon contact with gastric fluids. This gel then swells and forms a protective layer, or "raft," that floats on the surface of the stomach contents.

Typically incorporating agents like carbonate or bicarbonate, raft-forming systems increase in bulk and release carbon dioxide, which decreases their density. The primary gel-forming agent in these systems is sodium alginate, which transforms into a raft in reaction to gastric fluids and aids in preventing the backflow of gastric contents into the esophagus.

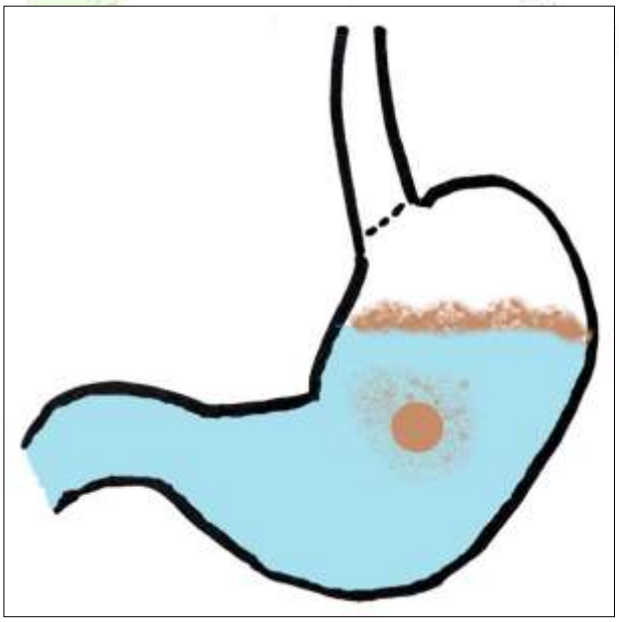

Figure 5: Raft Forming in Stomach

2. Non-Floating Drug Delivery Systems [29,30]

Non-floating drug delivery systems retain the dosage form in the stomach through various mechanisms, rather than relying on buoyancy. These systems ensure sustained drug release and can be pH-dependent, releasing the drug at specific pH levels.

i) High Density System [31]

In this approach, high-density dosage forms (capsules, tablets, pellets) sink to the bottom of the stomach, entrapped in the antrum, and resist peristaltic waves. Formulations include heavy metal coatings or inert materials like zinc oxide or barium sulfate, increasing density to exceed that of gastric contents. Transit time ranges from 6 to 24 hours, but this method is still under research due to its limited efficacy in humans.

ii) Magnetic System [32]

Magnets incorporated into both the dosage form and the abdomen enhance gastric residence time, facilitating prolonged drug absorption. Initial experiments involved bioadhesive granules containing ultra-fine ferrite, demonstrating retention in the stomach region for up to 10 hours.

iii) Bioadhesive / Mucoadhesive System [33,34]

Bioadhesive systems use adhesive polymers to adhere to the stomach epithelial surface, promoting prolonged drug absorption. Mucoadhesive systems, although less adhesive due to frequent mucous release, require stomach content dilution for complete adherence. Excipients like lectins, Carbopol, and chitosan enhance absorption and enable site-specific drug delivery.

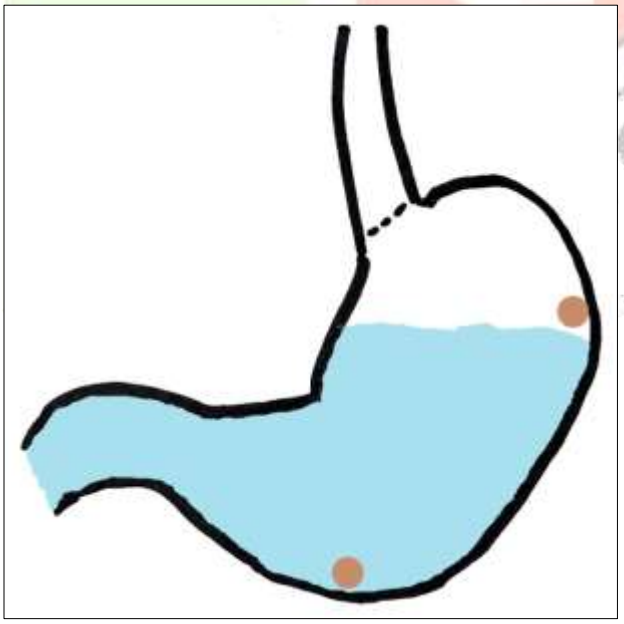

Figure 6: Bioadhesive System

iv) Super Pores Hydrogel System [35,36]

This system features interconnected microscopic pores within a hydrogel network, facilitating rapid water absorption. Ingredients like crosslinkers, stabilizers, and foaming agents contribute to its high swelling capacity, stability in acidic conditions, and mechanical strength, enhancing gastroretention time.

v) **Expandable Unfolding and Swelling System** [37,38]

Dosage forms increase in size upon contact with gastric fluid due to swelling agents like gel, cellulose, or HPMC. The swelling, driven by osmotic absorption, allows the dosage form to float on the stomach surface. These systems are promising for gastroretentive drug delivery, though challenges like hydro stability and industrial scalability persist.

To develop an effective expandable system, it must maintain a small oral dosage form size, expand in the stomach without causing gastric damage, and revert to its original size after drug release.

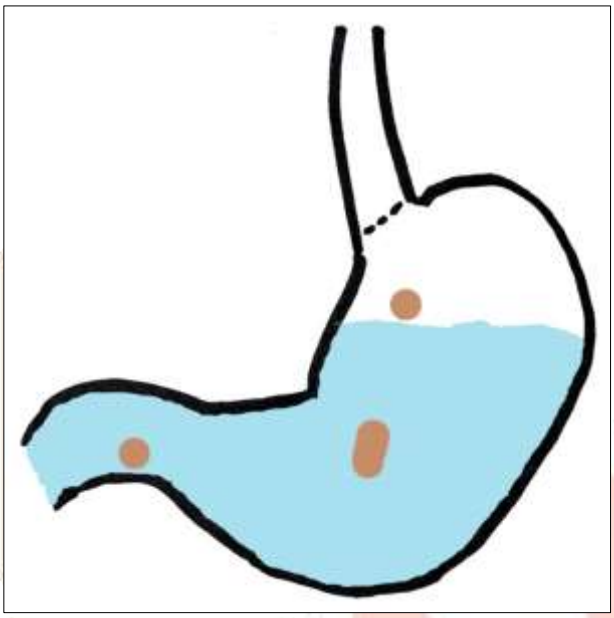

Figure 7: Expendable Swelling System

CONCLUSION

In conclusion, gastroretentive drug delivery systems represent a significant advancement in oral drug delivery, offering numerous potential advantages such as enhanced bioavailability and absorption. These systems allow for controlled solubility and absorption of orally administered drugs, ultimately improving their effectiveness.

Through the use of gastroretentive drug delivery systems, it becomes feasible to optimize the bioavailability of drugs with site-specific absorption characteristics. Extensive literature surveys indicate that GRDDS holds a specific niche in the pharmaceutical industry, and the market for GRDDS products is expected to expand significantly, leading to improved patient compliance and therapeutic outcomes.

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