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Review Article

A Systemic Review on: FORMULATION AND EVALUATION OF GASTRORETENTIVE TABLET

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ABSTRACT:
The development of gastroretentive tablets marks a significant step forward in oral drug delivery methods, particularly for medicines having limited absorption windows in the upper gastrointestinal tract, low solubility in alkaline pH, or local stomach activity. Gastroretentive drug delivery systems (GRDDS) are intended to increase the gastrointestinal residence duration of dose forms, boosting bioavailability, lowering dosing frequency, and increasing patient compliance. This comprehensive review focuses on the many formulation options for gastroretentive tablets, including floating, mucoadhesive, swelling, high-density, and magnetic systems. The selection of suitable polymers, excipients, and technologies is crucial to achieve the necessary gastroretentive characteristics. The review also delves into assessment characteristics such as floating lag time, total floating duration, swelling index, hardness, friability, medication content, and in vitro release tests. Furthermore, in vivo imaging and pharmacokinetic investigations are critical for determining gastroretentive behavior and treatment effectiveness. This study seeks to give a complete understanding of the current methodologies and assessment methods used in the creation of successful gastroretentive tablets, ultimately leading to superior therapeutic outcomes for targeted drug administration in the stomach.

INTRODUCTION

With advancements in drug delivery, the oral route is the most prevalent route to systemic circulation due to its ease of administration, cheap cost, patient compliance, and formulation versatility. Approximately 90% of all medications are taken orally. Although the medications are taken orally, solid oral dose forms are the most prevalent type of product. Tablets are the most prevalent solid dosage form in use, and they are classed according to the drug release pattern, which includes immediate and modified release. The instant release pills have several disadvantages, including non-site specific medication release. However, many medications are absorbed from particular locations and must be released exclusively at those sites for optimal absorption. Drug absorption in the GI tract is a highly variable process that is determined by factors such as stomach emptying, gastrointestinal transit duration of dosage forms, drug release from the dosage form, and drug absorption location. Drugs that are easily absorbed from the gastrointestinal tract and have short half-lives are rapidly removed from the systemic circulation. A frequent dosage is necessary to establish appropriate therapeutic action. Gastroretentive medication administration is one method for extending gastric residence duration and targeting site-specific drug release in the stomach for local or systemic effects. These dose forms can stay in the gastrointestinal area for extended periods of time, considerably increasing the drug's gastric retention. It will release the medicine in the stomach in a regulated manner, so that the drug may be administered constantly to the absorption location in the GIT, i.e. stomach.[1]

Devices for administering controlled-release medications orally have been developed. These drug delivery methods spread the medication in a specific, predictable, and controlled manner. They are not suitable for drugs with limited bioavailability due to issues with stability or absorption[2]. For more than a half-century, pharmaceutical experts have focused on developing approaches for increasing the stomach residence duration of dose forms. The prolonged residency of dose forms in the stomach, known as gastro retention, can provide a variety of therapeutic and pharmacological effects.

These include increased local drug activity in the stomach, lower variations in drug concentration in the plasma, increased patient compliance due to reduced dose frequency, and better bioavailability for specific medicines with absorption windows in the upper small intestine[3]. Modern approaches, which aim to keep such drugs in the stomach for a prolonged length of time, can help with these issues. Such drug delivery devices are known as Gastroretentive Drug Delivery devices (GRDDS).

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GRDDS is a process that retains chemicals in the stomach for a long period before releasing the active fraction in a controlled manner and finally metabolizing them throughout the body. Gastro retentive drug delivery is a method of extending stomach residence duration, resulting in site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can stay in the gastrointestinal area for extended periods of time, considerably increasing drug retention time (GRT).

Over the last few decades, several gastroretentive drug delivery approaches have been designed and developed, including high-density (sinking) systems that are retained in the bottom of the stomach, low-density (floating) systems that cause buoyancy in gastric fluid, mucoadhesive systems that cause bio adhesion to stomach mucosa, unfoldable, extendible, or swellable systems that limit emptying of the dosage forms through the pyloric sphincter of the stomach, super porous hydro[4].

GRDDS is advantageous for such medications by enhancing their:

1. Bioavailability
2. The efficacy of therapy.
3. A potential dose reduction.
4. Maintaining a constant therapeutic level over an extended length of time results in reduced therapeutic level volatility.
5. Minimize unneeded medicines.
6. Makes less-soluble drugs more soluble at low temperatures.
7. High pH conditions (e.g., papaverine, domperidone, or other weakly basic medicines) [5]

Aside from these benefits, these systems provide a variety of pharmacokinetic benefits, such as the preservation of stable therapeutic levels over an extended length of time, resulting in a reduction in therapeutic level fluctuations. Drugs that are easily absorbed from the gastrointestinal tract and have short half-lives are rapidly removed from the systemic circulation. To obtain the desired therapeutic efficacy, these medicines must be dosed often. To overcome this constraint, the development of oral sustained controlled release formulations aims to slowly release the medication into the GIT while maintaining an effective drug concentration in the systemic circulation for an extended period of time. After oral administration, such a drug delivery would remain in the stomach and release the medication in a regulated way, allowing the drug to be delivered continually to its absorption sites in the GIT.

Benefits of Gastro-Retentive Drug Delivery Systems

1. Improved bioavailability profile

GRRDS provides a means to increase the bioavailability profile. Riboflavin bioavailability has been significantly increased in CR-GRDF compared to non-GRDF CR polymeric formulations after oral treatment, for example. Several factors influence medicine absorption through the digestive system[6].

2. Medication administration with accuracy

Gastric retention using a floating device is one way to provide a focused impact, particularly for drugs with limited proximal small intestine absorption. Because of restricted absorption, systemic effects of the medication are avoided by slow and regulated delivery of the pharmaceuticals to the stomach, which allows sufficient amounts of the drug to induce local effects[7].

3. Patient compliance has improved.

GRDDS may prolong the effects of drugs, which is especially relevant for therapies with short half-lives since it reduces the frequency of doses, which improves patient compliance. [8].

4. Avoiding the large bowl's activities.

GRDDS allows for stomach retention, which limits the quantity of medicine that enters the colon while also preventing drug activity in the big bowl. This may be critical in some cases, such as when beta-lactam antibiotics are administered to the colon, causing the formation of microbial resistance. The use of beta-lactam antibiotics in gastro-retentive formulations prevents microorganism resistance from developing.

5. Improves clinical outcomes.

Rather than the peak concentration, the length of time the medicine remains above the critical concentration might define the agent's pharmacodynamics. The goal of GRDDS is to achieve sustained mode concentration, which increases the period of time the drug is above the critical concentration. This trait has a substantial impact on the pharmacological effects and enhances treatment outcomes.

The disadvantages of gastroretentive medication delivery methods

- Not recommended for medications that might cause stomach lesions, such as non-steroidal anti-inflammatory drugs.
- Medicines can become unstable in very acidic or basic environments.
- Ensure consistent and predictable floating properties under harsh gastrointestinal conditions.
- To ensure intestinal retention, the dose form must pass through the stomach intact, which might be challenging.
- Not suitable for unstable drugs in acidic or basic environments.

- Compared to traditional dose forms for gastrointestinal absorption, these systems do not offer significant benefits. [9,10].

Factors influencing gastric retention

- **Density:** Lower-density dose forms float and stay in the stomach longer than higher-density ones.
- **Size of dosage form:** Larger dose forms cannot pass past the pyloric sphincter quickly to reach the intestine, resulting in an extended gastric residence time in most circumstances[11].
- **Shape of dosage form:** Tetrahedron and ring-shaped devices are reported to have better GRT and ~ 90% to 100% retention at 24 hours compared with other shapes[12].
- **Single or multiple-unit formulation:** Formulations containing numerous components have a more regulated release profile, co-admiration of different units, and a greater safety margin.
- **Fed or unfed state:** Typically, the presence of food in the stomach raises the GRT of the dose form and promotes medication absorption by allowing it to remain at the absorption site for longer periods of time.
- **Nature of meal:** By converting the stomach's motility pattern to a fed state by feeding indigestible polymers or fatty acid salts, the pace at which the stomach empties its contents can be delayed, lengthening the period that medications stay active non the body.
- **Calorie content and frequency of food intake:** A high-protein, high-fat meal can increase GRT by 4-10 hours. Because of the low frequency of MMC, giving consecutive meals instead of a single meal can boost GRT by over 400 minutes.
- **Posture:** The floating medication will be directed toward the pyloric antrum while the patient is lying on their left side. If the patient lies on its right side, it will face the other way. GRT can vary between the supine and upright ambulatory states of the patient.
- **Age and gender:** Elderly people and women have a slower stomach emptying rate. It was discovered that stomach emptying is slower in women than in males, regardless of height, weight, or body surface area. Regardless of weight, height, or body surface, males have a lower mean ambulatory GRT (3.4 plus or minus 0.6 hours) than females of the same age and race (4.6 plus or minus 1.2 hours).

DIFFERENT APPROACHES OF THE GRDDS

Various measures have been taken to improve the retention of oral dose forms in the stomach. Some are designed with a single component, while others include many components. GRDDS are widely classified into floating and non-floating systems.

A. Non-floating system: These GDDS do not float in the stomach, but are kept there by several means. Non-floating systems are further classified as:

a. High density (sinking) drug delivery system
b. Bioadhsive or mucoadhesive system
c. Magnetic system
d. Unfoldable system

B. Floating drug delivery system (FDDS): Unlike high-density drug delivery systems, floating systems have a lower density than the gastric content, allowing the system to remain in the stomach for an extended length of time without influencing the gastric contents. Floating medication delivery systems are sometimes called low density systems.

Floating medication delivery systems can be classified as:

1. **Effervescent system**
2. **Noneffervescent system**
1. **Hydrodynamically balanced system**
2. **Microbaloons or hollow microspheres**
3. **Alginate beads**
4. **Microporous compartment**
5. **Layered tablets**

A. Non-floating system

a. High Density (Sinking) Drug Delivery System

In this method, formulations are created by coating a medicine on a heavy core or mixing it with inert ingredients such as iron powder, barium sulfate, zinc oxide, and titanium oxide, so that the formulation's density surpasses that of typical stomach contents. These materials improve the density by 1.5-2.4 gm/cm3. Depending on density, pellets' GI transit time might range from 5.8 to 25 hours on average. However, the usefulness of this approach in humans has not been demonstrated 13, and no formulation has been released.

b. Bioadhsive or mucoadhesive system

The stomach retention period is increased by sticking the bioadhesive system to the gastric mucosa membrane. The delivery system's adhesion to the stomach wall increases residence time, which improves bioavailability. Polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose, gliadin, and other compounds are used to promote mucoadhesion. Novel adhesive materials produced from bacterial fimbrae or synthetic counterparts

have also been tested for gut attachment. However, the gastric mucoadhesive force is often insufficient to resist the propulsion force of the stomach wall. Another shortcoming of such a system is the continual creation of mucus and the diluting of stomach content. Many researchers have attempted a synergistic approach combining floating and bioadhesion systems.

The premise of adhesion is that a dose form can adhere to the mucosal surface via several ways. The mechanisms are:

- The wetting idea is based on bioadhesive polymers' capacity to spread and form close contact with mucosal layers.
- The diffusion theory suggests that mucin strands are physically entangled with flexible polymer chains or penetrate the substrate's porous structure.
- According to the absorption hypothesis, bio attachment relies on secondary forces such Vander Waal forces and hydrogen bonding.
- The electron theory suggests electrostatic interactions between the glycoprotein mucin network and bioadhesive substance[14].

c. Magnetic system

In this approach, the dose form contains a tiny magnet, and another magnet is put on the abdomen above the stomach. The external magnet should be set with accuracy, which might reduce patient compliance.

d. Unfoldable system

The medication delivery system expands and becomes caught in the sphincter, preventing it from exiting the stomach. For this, the system should be small enough to swallow but expand when it comes into touch with stomach fluid, and after a specific amount of time, its size should decrease so that it may be readily evacuated. The unfoldable systems are composed of several biodegradable polymers.

B. Floating Drug Delivery System

i. Effervescent System

This system is made up of swellable polymers such chitosan and effervescent substances such as sodium bicarbonate, disodium glycine carbonate, cytroglycine, citric acid, and tartaric acid. When the system comes into contact with gastric fluid, it emits CO2, causing the formulation to float in the stomach. The best ratio of citric acid to sodium bicarbonate for gas production is stated to be 0.76:1. This technology is further separated into single unit matrix tablets and multiple unit pills. A single unit matrix tablet can have one or more layers. A floating system using ion exchange resins has also been reported. Effervescent systems and their drug release.

ii. Non-effervescent system

In this system, gel-forming or highly swellable cellulose hydrocolloids, polysaccharides, and matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene are utilized. After oral administration, this dosage form expands in contact with stomach juices and achieves a bulk density of less than 1. The air trapped within the swelling matrix provides buoyancy to the dose form. The resulting swelling gel-like structure serves as a reservoir, allowing for continuous drug release through the gelatinous mass. Superporous hydrogels are a great illustration of this strategy. When the dosage form comes into contact with gastric fluid, it swells significantly to several times its original volume. Gastric contractions push the dosage form to the pylorus, but because the dosage form is larger, the contractions slip over the surface of the system, causing the dosage form to push back into the stomach. Non-effervescent systems are further classified into hydrodynamically balanced systems, microbaloons, alginate beads, and microporous compartments.

1. Hydrodynamically balanced system: Sheth and Tossounian built the first hydrodynamically balanced system (HBS). HBS includes hydrocolloids that form gels and remain buoyant in the stomach contents. This system comprises one or more cellulose-based hydrocolloids that produce gels, such as hydroxypropyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, agar, carrageen, or alginic acid. It also includes matrix-forming polymers including polycarbophil, polyacrylate, and polystyrene. When such a system comes into touch with stomach fluid, the hydrocolloid hydrates and forms a colloid gel barrier on its surface.

2. Microbaloons or hollow microspheres: The emulsion-solvent diffusion process is used to create hollow microspheres (microballoons) containing drugs embedded in their outer polymer shells. Figure 9 summarizes the stages used in this technique. At 40°C, an agitated aqueous solution of polyvinyl alcohol and an acrylic polymer are added to a 1:1 ethanol: dichloromethane solution. The gas phase formed in the dispersed polymer droplet by dichloromethane evaporation creates an interior cavity in the polymer microsphere containing the medicine. For almost 12 hours, the microballoons float constantly on the surface of acidic dissolving fluid containing surfactant.

3. Alginate beads: Freeze-dried calcium alginates were employed to create multi-unit floating dosage forms. Spherical beads with a diameter of about 2.5 mm can be made by dropping a sodium alginate solution into an aqueous calcium chloride solution. The beads are separated and air-dried. This causes the creation of an aporous system, which remains buoyant in the stomach.

4. Microporous compartment: In this technique, the drug reservoir is enclosed within a microporous compartment with pores on its top and bottom surfaces. The flotation chamber, which contains trapped air,

causes the delivery system to float above the stomach contents. Gastric fluid enters the aperture, dissolves the medicine, and transports it to the stomach and the proximal section of the small intestine for absorption.

5. Layered tablets: Because of their great stability, affordability, and convenience of preparation, layered tablets are becoming more and more popular.

These are of two types:

Single-layered floating tablets:

Narcotics and gasses were combined in the matrix tablet to create these pills. The formulations retain their buoyancy in the stomach by increasing GRT30 because their bulk density is lower than that of gastric fluid. Kim et al.[15] employed compaction and wet granulation. to produce once-daily, non-effervescent, gastroretentive pregabalin tablets. The in vitro dissolving and floating properties of the generated tablets were shown to be significantly influenced by the amounts of crospovidone and HPMC.

Double-layered floating tablets:

Stacking separates the two formulations with distinct release profiles that are placed one on top of the other. Kuldeep et al.33 used the direct compression method. Metoprolol succinate (sustained-release layer) and rosuvastatin calcium (immediate-release layer) were combined to create a bilayer floating tablet. HPMC K100, K4M, and K15M were used as gel-forming agents. Crospovidone, sodium starch glycolate, and cross-carmellose sodium were used as super disintegrants. Sodium bicarbonate is the effervescent agent used in drinks. The in vitro buoyancy investigation showed that when the concentration of the gas-generating agent increases, the floating lag time reduces. It was also demonstrated that the ratio of polymer gas-producing agents affected the floating lag time and total floating duration.

METHODS OF PREPARATUON

The wet granulation process was used to create floating tablets utilizing lactose, sodium bicarbonate, carbopol 934P, and hydroxyl propyl methyl cellulose (HPMC K4MCR).

Preparation of granules:- The wet granulation process was used to create the granules. Every component was precisely weighed. Then, using a glass crusher and pestle, precisely weighed amounts of medication, lactose, HPMC K4MCR, and sodium bicarbonate were combined uniformly. 95% ethanol was used during the wet granulation process. The wet bulk was dried overnight at 40°C in a hot air oven after being run through a 40-mesh screen. After being sieved through 40/60 mesh, the dry granules were mixed with 1% w/w magnesium stearate. Lactose served as a channeling agent and filler. Here, ethanol is employed as a granulating agent, while sodium bicarbonate was used as a gas-generating agent.

Preparation of floating tablet:- A single punch tablet compression machine was then used to compress the uniformly lubricated granules with magnesium stearate (1% w/w) into tablets. With a Monsanto tablet hardness tester, the compression force was changed to produce a tablet with a hardness between 6.2 and 6.9 kg/cm2. Blends are evaluated prior to compression. The direct compression approach can be used to create floating tablets. Here, the pure medication was geometrically combined in a mortar and pestle for ten minutes with the necessary amounts of HPMC K4M, sodium CMC, carbopol 934P, sodium bicarbonate, and lactose. For two minutes, magnesium stearate was used to lubricate the aforementioned powder in a mortar and pestle. The CLIT Pilot Press rotary tablet machine was used to compress the lubricated mix into tablets using 12 mm flat face round tooling. The slugging technique of dry granulation On powerful tablet machines, the formulation's contents are carefully combined and precompressed. The resulting slug is squeezed into the final tablet after being ground to a consistent size.

EVALUATION PARAMETERS OF GRDDS:

The following are typical GRDDS evaluation parameters:

- **Bulk density**

It is the mass of the powder divided by the volume of the bulk. The size distribution, shape, and cohesion of the particles all affect the bulk density. The initial bulk volume was determined after a precisely weighed amount of powder was carefully poured via a huge funnel into a graduated measuring cylinder. It has the following formula and is stated in gm/ml:

$$\textbf{Bulk density} = M/Vo$$

Where,

M = mass of the powder

Vo = bulk volume of the powder

- **Tapped density**

A 100 ml measuring cylinder that had been cleaned and dried was filled with 10 g of powder. The tapped volume was then measured after the cylinder was tapped 100 times from a fixed height. It is provided by and expressed in gm/ml:

$$\textbf{Tapped density} = M/Vt$$

Where,

M = mass of the powder

Vt = final tapping volume of the powder.

- **Angle of repose (θ)**

It is the greatest angle that can exist between the powder pile's surface and the horizontal plane. The fixed funnel approach was applied. A graph paper was laid on top of a flat, horizontal surface, and a funnel was secured with its tip at a specific height "h." A funnel was used to delicately pour powder until the conical pile's peak barely touched the funnel's tip. The following formula was then used to get the angle of repose:

Angle of repose Ø = tan1(h/r)

Where,
h=height of the pile
r=radius of the pile.

- **Compressibilty Index (carr'sIndex)**

Compressibilty Index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristic. Carr's index can be represented by equation:

Carr's index = [(Tapped density-Bulk density)/Tapped density]*100

- **Hausner's ratio**

The powders' ability to flow is predicted using Hausner's ratio. The compressibility index is comparable to this approach. The following equation can be used to express Hausner's ratio:

Hausner's ratio = Tapped density / bulk density

- **Drug-excipient interaction**

FTIR and HPLC are used in this process. The drug-excipient interaction is indicated by the emergence of a new peak and/or the loss of the original drug or excipient peaks.

- **Floating lag time**

It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds.

- **In vitro drug release and duration of floating**

It is ascertained by churning a simulated gastric fluid with a pH of 1.2 at 37±2oC with a USP II equipment (paddle) at 50 or 100 rpm. Samples are taken in aliquots, and their drug content is examined. The floating time is the amount of time that the medicine stays afloat on the medium's surface.

- **In vivo evaluation of gastric retention**
  - Imaging methods like γ-scintigraphy and X-ray are used to analyze the dosage form's location in the GIT.
  - When γ-scintigraphy is being prepared, a little quantity of stable isotope is combined in the dosage forms. A γ-camera or scinti scanner can be used for indirect external observation when a γ-emitting radio-nuclide is included in a formulation.
  - Barium sulfate is used as a contrast agent for x-rays. Finding the dose form in the GIT aids in predicting and correlating the passage of the dosage form with the time it takes for the stomach to empty.
  - The in vivo assessment of GRDDS may also involve gastroscopy and ultrasound investigations. Gastroscopy includes peroral endoscopy, which is performed using video and fibereoptic equipment. It is not common practice to evaluate GRDDS with ultrasound. By doing the investigation in an appropriate animal model, an in vivo plasma profile may also be produced.

Water uptake study

This is accomplished by submerging the dosage form in 37°C simulated stomach fluid and monitoring changes in dimensions, such thickness and diameter, at regular intervals. Following the allotted time, the enlarged tablets are weighed, and the percentage weight gain that results from water absorption is calculated as follows:

WU= (Wt-Wo) X100/Wo;

To achieve this, the dosage form is submerged in 37OC simulated stomach fluid, and the dimensional changes—such as thickness and diameter—are measured at regular intervals. The enlarged pills are weighed after the allotted period, and the percentage weight gain that results from water absorption is calculated as follows:

- Morphological and dimensional analysis is carried out with the use of optical and scanning electron microscopy.
- The microsphere's yield percentage.

Ingredients used for the preparation of GRDDS:

GRDDS makes use of a variety of chemicals. HPMC K4 M, HPMC K15, HPMC K4, HPMC 4000, HPMC 100, calcium alginate, sodium alginate, Eudragit S100, Eudragit RL, Eudragit S, Eudragit RS, propylene foam, ethyl cellulose, polymethyl methacrylate, methodical K4M, polyethylene oxide, cyclodextrin, CMC, HPC, metolose, PVP, PVA, HPCH, HPC-M, acrylic polymer E4 M, polyethylene glycol, and carbopol have all been used extensively in the production of floating drugs. Hydrophilic gums, acacia, pectin, agar, alginates, gelatin, casein, bentonite, and veegum, as well as modified cellulose derivatives like MC, HPC, HEC, and NaCMC, are examples of synthetic, anionic, or nonionic hydrocolloids that can be used in GRDDS.

Other chemicals used in GRDDS include effervescent substances like citric acid, tartaric acid, sodium bicarbonate, citroglycine (CG), and di-sodium glycine carbonate (DiSGC). Mannitol and lactose both increase release rates. Dicalcium phosphate, magnesium stearate, and talc are examples of release rate inhibitors. materials with a low density, like powdered Acurel MP 1000® polypropylene foam. Examples of surfactants used as emulsifiers or stabilizers that simultaneously function as microsphere hardeners are Tween 80, span 80, and SLS. Hardening agents are used to help the microspheres formed in the processing media harden, and cross-linking agents such as formaldehyde, glutaraldehyde, or diacid chlorides like terephthaloyl chloride are used to make microspheres. For example, n-hexane and petroleum ether. Combinational strategies for gastro retention in recent years: Currently following combination approaches used in GRDDS[16,17]:

A. Swellable and floating
B. Bioadhesive and floating
C. Bio adhesion and swelling
D. Bio adhesion and High-density
E. Floating pulsatile system

CONCLUSION:

A promising method for improving the bioavailability and therapeutic effectiveness of medications that are mostly absorbed in the stomach or upper small intestine is the use of gastroretentive tablet formulations. These tablets may successfully extend the stomach residence duration by a variety of formulation techniques, including floating, swelling, mucoadhesion, and high-density systems, which improves drug absorption and produces sustained release profiles. The effectiveness of gastroretentive systems is largely dependent on the selection of polymers and excipients as well as the meticulous assessment of critical factors including floating lag time, drug release, and mechanical strength. In order to guarantee the effectiveness and dependability of gastroretentive tablets, this review emphasizes the need of combining in vitro and in vivo assessments. Optimized gastroretentive drug delivery systems will be made possible by ongoing research and technical progress in this field, especially for medications with site-specific action and low bioavailability.

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