



An Overview of the Gastroretentive Drug Delivery System

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ABSTRACT

Recent years have seen numerous advancements to increase the bioavailability of drugs when taken orally. A prominent example is the development of gastroretentive drug delivery systems, which were created to increase the bioavailability and potency of medication using a limited absorption window in the upper GI tract and stimulate local activity in the duodenum and the stomach. A system that remains in the stomach for a sufficiently long period while overcoming all physiological obstacles releases the active portion in a regulated manner and is ultimately easily digested by the body is considered an ideal GRDF system. Developing an effective GRDF is hampered by physiological constraints, including stomach motility and gastric retention time (GRT). Different technologies can be designed to increase gastro retention, including high-density systems, floating drug delivery systems (FDDS), bioadhesive systems, expandable systems, super porous systems, and magnetic systems. These systems each have benefits and drawbacks of their own. This review concentrated on several GRDF development-related elements, which included the most current developments and trends.

Keywords: Gastroretentive drug delivery systems; floating drug delivery systems; mucoadhesive systems; expandable systems; super porous systems; magnetic systems; raft forming; current trends in GRDDS.

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1. INTRODUCTION

Due to its well-known benefits, the oral administration route has long played a prominent role in therapy. Patients favor this technique for several reasons, such as formulations are more affordable, convenient to transport and store, adaptable in terms of the ingredients, and ready to use; there is no need for specialized medical staff to administer.¹

However, because of the diversity of the gastrointestinal system, oral administration is subject to some physiological limitations. Additionally, many factors alter the gastrointestinal tract and significantly impact drug absorption. The most significant of them are pH, commensal flora, gastrointestinal transit time, enzyme activity, and surface area.²

Conventional solutions cannot fully address the limitations imposed by the digestive system. For instance, because traditional formulations cannot deal with gastric emptying, they are inappropriate for drugs that are absorbed preferentially in the upper portion of the digestive tract.³

Drugs' stomach residence times can be significantly extended by gastro retentive systems since they can stay in the gastric region for several hours. For medications that are less soluble in environments with high pH, prolonged stomach retention increases bioavailability, lowers drug waste, and enhances solubility.⁴

Gastro retentive drug delivery systems (GRDDS) are intended to confine and localize the drug delivery device in the stomach or within the upper portions of the small intestine until all the drug is released. They are created based on delayed gastric emptying and CR principles.⁵

GRDFs are created using one of several methods, such as formulating low-density dosage forms that float above gastric fluid (FDDS) or high-density dosage forms that are retained at the bottom of the stomach, imparting bioadhesion to the stomach mucosa, reducing GIT motility through simultaneous administration of drugs or pharmaceutical excipients, expanding the dosage form by expanding or unfolding to a restrictive size the escaping of the drug, super porous hydrogels, magnetic systems or any combination of these methods.⁶

Drugs targeting the stomach can also be attractive for several other reasons:

- It is possible to induce a prolonged local action on the gastroduodenal wall, e.g., medicines used to eradicate *H. pylori* infection, like amoxicillin.⁷
- For weakly basic drugs with poor solubility in an essential environment.



- For drugs that may not stay stable in the colon.
- For drugs with a narrow window for absorption⁸

GRDDS can either function as intrinsic controlled-release systems or in conjunction with such technologies to ensure a controlled release of drugs. Although they require less frequent administration and have fewer side effects, controlled-release applications encourage improved patient compliance and therapeutic efficacy.⁹⁻¹³

Various formulation-related factors can impact the quality and effectiveness of the gastroretentive dosage form in terms of stomach retention and controlled drug release. These include the molecular weight of the polymer(s) employed in the formulation, the type of polymer (non-ionic, cationic, and anionic polymers), the composition of the polymer in dosage form, the viscosity grade, and the solubility of the drug.¹⁴

2. ANATOMY & PHYSIOLOGY

For the development of gastroretentive dosage forms to be successful, understanding the physiological and anatomical structure of the stomach is necessary.¹⁵ (Refer to Fig 1)

The primary role of the stomach is to temporarily store food, grind it, and then gently release it into the duodenum.¹⁶

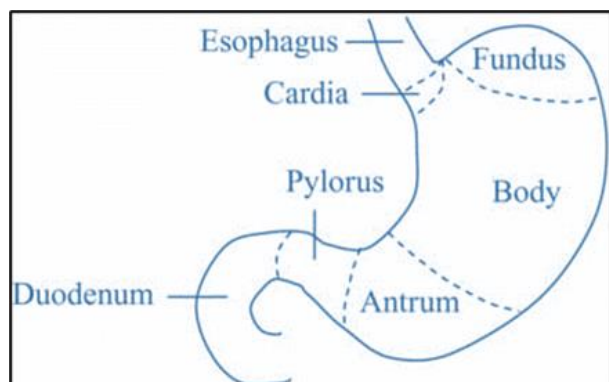


Figure 1: Schematic diagram of the stomach: Shows the anatomy of the stomach.

The stomach is located just beneath the diaphragm in the left upper portion of the abdominal cavity. Its size varies depending on the degree of distension: after a meal, it can be up to 1500 ml; however, once the stomach has emptied, a collapsed state is attained with a resting capacity of 25 to 50 ml.¹⁷

Anatomically, the stomach is divided into three sections: the fundus, which is closest to the esophagus; the body, which stores ingested food; and the antrum, the final section that joins the body to the small intestine. Antrum aids in stomach emptying and churning movement.¹⁵

Both fed and fasting states result in stomach emptying, yet the two conditions have very different fundamental gastric emptying patterns.¹⁶

The bioavailability of medications taken orally will change depending on the feeding stage. The inter-digestive series of electrical events and cycles, which pass through the stomach and small intestine every 2-3 hours, is what distinguishes the fasted state from other states.⁸

The term "inter digestive myoelectric cycle" or "migrating motor complex" refers to this process (MMC). The four phases of MMC are frequently referred to as basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals as given in Fig 2.⁸

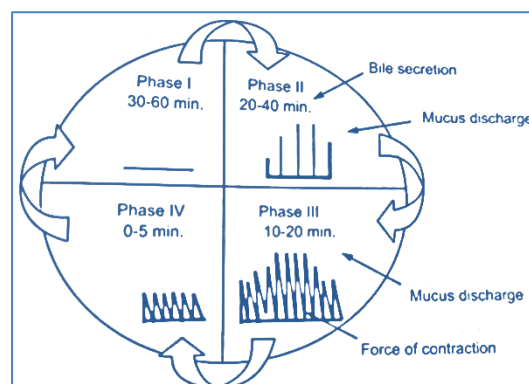


Figure 2: Phases of gastric retention: Shows the four phases during gastric residence.

The different phases are: (See table no.1)

1. Phase I (basal phase)
2. Phase II (pre-burst phase)
3. Phase III (burst phase)
4. Phase IV

The size of the pylorus increases to about 19 mm during the inner digestive phase. Particles that are smaller than the diameter of the pyloric sphincter can, therefore, quickly evacuate from the pylorus and travel to the duodenum during the inner digestive phase.¹⁶

As long as the food is still in the stomach, the fed state's motor activity is triggered 5 to 10 minutes after a meal. With average periods of 2–6 h, but more frequently 3–4 h, and phasic contractions similar to Phase II of MMC, fed activity tends to last longer the more food is consumed.⁸

3. FACTORS AFFECTING GRDDS

Pharmaceutical factor:

1] Density of dosage form

The physical parameter density affects the gastric retention time through the opposing behaviors of floating and sinking.³

To allow dosage form floats in the stomach, low-density systems should have a density less than the estimated gastric fluid density, i.e. 1.004 g/cm^3 . To ensure effective sinking in the stomach's bottom and resistance to peristaltic movements, high-density systems should have densities more significant than the gastric contents, i.e. 2.5 ,

g/cm³ is thought to be essential for a prolonged GRT of this formulation.⁷

2] Size and Shape of dosage form

Another crucial factor impacting GRDDS efficacy is the size and shape of the dosage form. The pyloric sphincter, which has a reported diameter of 12.8 7 mm, is responsible for gastric emptying. It is broadly accepted that dosage forms greater than 15 mm are required for efficient stomach retention.^{20,21}

Tetrahedron-shaped dosage forms and rings with flexural moduli of 48 and 22.5-kilo pounds per square inch (KSI) are said to have improved GRT, with 90 to 100% retention at 24 hours, compared to other designs.²²

3] Single and Multiple unit formulation

Compared to single-unit dosage forms, multiple-unit formulations have a higher margin of safety against dosage form failure, a more predictable release profile, and minimal performance impairment due to unit failure. They also allow the co-administration of units with different release profiles or containing incompatible substances.²³

Physiological Factors:

1] Fasting vs Fed state

In the fasting state, gastrointestinal tract (GI) motility is characterized by episodes of vigorous motor activity or migrating myoelectric complexes (MMC), which happen every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach, and if the timing of administration of the unit's formulation is similar to the MMC's, a short GRT can be expected.²⁴

Food prolongs the residence time of the dosage form because it decreases the rate of stomach emptying, which increases the absorption of drugs in the upper digestive system.³

2] Type of food

Administration of fatty acid salts or indigestible polymers, such as cellulose, starch, and polydextrose, can alter the stomach's motility pattern by delaying the MMC, which lowers the rate at which the stomach empties and prolongs digestion.⁶

3] Caloric content

GRT can be increased between 4 to 10 hours with a meal high in proteins and fats.²⁵

4] Posture

whereas non-floating systems tend to settle near the pylorus, the upright position encourages gastric retention since the system floats on top of the gastric contents. Non-floating systems have a longer stomach retention time when sitting down.³

5] Viscosity of polymer

The Viscosity of polymers has a measurable impact on floating time and drug release. It has been discovered that low-viscosity polymers are more beneficial than high-viscosity polymers for improving floating properties.²²

6] Frequency of meals

The administration of successive meals can increase gastric retention by 6-7 h, compared to a single meal intake, due to the low frequency of MMC.⁷

Biological factors:

1] Age

People over 65 generally exhibit longer GRTs for the dosage forms.²²

2] Gender

According to research by Wang et al., gender can significantly affect gastric emptying time and luminal pH, with women having slower gastric emptying rates than men.²⁶

Generally, females have a slower gastric emptying rate than males.²⁷

3] Disease conditions

Different disease conditions can have varying effects on the GRT of dosage forms. Longer GRTs and possible constipation are common in Parkinson's disease patients.²⁸

In patients with diabetes mellitus, the gastric emptying rate is significantly slower compared to nondiabetic patients.²⁶

4] Emotional state

Since it has been found that there is a decrease in the gastric emptying rate when the patient is in a depressed emotional state, and the inverse is observed in people feeling anxiety, the patient's emotional state also appears to have a part in determining the gastric residence time.²⁶

Stress increases gastric emptying rate while depression slows it down.²⁷

4. DRUG SELECTION CRITERIA FOR GRDDS

1] Drugs acting locally in the stomach are suitable candidates for drugs.

Ex. Nizatidine, piroxicam, Cefixime trihydrate²⁹

2] Drugs poorly soluble at alkaline PH, i.e., insoluble drugs in the intestine.

Ex. Cinnarizine, Quinidine⁶

3] Drugs that disturb normal colonic microbes are good candidates.

Ex. Tetracycline, Clarithromycin, Amoxicillin³⁰

4] Drugs that have a narrow absorption window in the gastrointestinal tract.



Ex. Repaglinide, Paraaminobenzoic acid⁸⁷

5] Drugs locally active in the stomach are suitable for drugs.³¹

Ex. Antacid, Misoprostol

6] Drugs that are unstable in the intestinal or colonic environment.³²

Ex. Captopril, Ranitidine, HCl

7] To treat particular conditions, the stomach, and proximal small intestine via local or sustained drug delivery are utilized.³³

8] Primarily absorbed in the stomach.³³

5. TECHNIQUES

5.1. Floating Drug Delivery System

Low-density systems with enough buoyancy to float above the stomach's contents and stay there for a considerable time are known as floating systems. Davis initially characterized them in 1968. Increased GRT and less fluctuation in plasma drug concentration occur from the drug delivered slowly and at the desirable rate while the system floats over the gastric contents.^[34] Such formulations have a bulk density of less than 1.004 g/cm³, which allows them to float in stomach juices.³⁵(Refer to Fig 3)

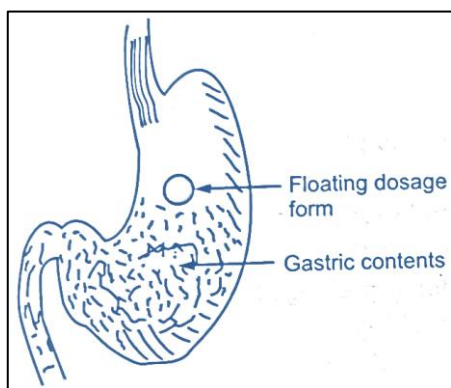


Figure 3: Floating System: Floating of dosage form on gastric fluid.

Merits of FDDS

- Decreases dosage frequency to increase patient compliance.
- Drugs with short half-lives can have improved therapeutic benefits.
- Because of buoyancy, the gastric retention period is prolonged.
- Over an extended period, the drug is released gradually and under control.
- It is possible to administer drugs to the stomach in a targeted manner.
- Increased absorption of drugs that only absorb in the stomach.

- Superior to single-unit floating dosage forms because they consistently release the drug and reduce the chance of dose dumping.

Demerits of FDDS

- For the dose form to float effectively and maintain buoyancy, a high quantity of fluids must be present in the stomach.
- Not feasible with drugs that have complications with solubility or stability in stomach fluid.
- Since slow gastric emptying may result in decreased systemic bioavailability, drugs like nifedipine, which is highly absorbed along the whole GIT and undergoes extensive first-pass metabolism, may not be ideal candidates for FDDS.
- Restrictions on the use of FDDS for drugs that irritate the stomach mucosa.⁸

Approaches to gastric retention

5.1.1. Effervescent system:

This system produces in-situ carbon dioxide (CO₂) using carbonates, such as sodium bicarbonate. To hasten the reaction, organic acids (such as citric and tartaric acid) are added, causing the dosage form to become less dense and float in the stomach.^{6,14} It is categorized into two classes:

a) Volatile liquid/vacuum type: These are divided into three more categories

- Inflatable system:** It is mainly composed of a pull-out system with a compartment loaded with flammable liquids that evaporate at body temperature. Therefore, the chamber expands, and the system floats when these systems are placed inside the stomach. A bio-erodible polymer filament consisting of polymers like polyvinyl alcohol and polyethylene is used in the inflated chamber. The polymer slowly breaks down and releases the drug as the inflated chamber floats in the digestive juice. After some time, the inflatable part collapses due to polymer disintegration.^{6,14}
- Intragastric floating system:** It has a vacuum-filled chamber and a microporous compartment that acts as a drug reservoir.¹⁴ Utilizing the gel-forming substances hydroxypropyl methylcellulose (HPMC), Carbopol, and xanthan gum, Patel et al.³⁶ created intragastric floating tablets containing verapamil HCl. Adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid produced buoyancy. A short buoyancy lag time of 36 seconds, a total buoyant time of at least 24 hours and controlled drug release for up to 24 hours were all features of the optimized formulation that produced good results.
- Intragastric-osmotically controlled system:** A biodegradable capsule that combines an osmotic

pressure-controlled drug delivery system with an inflatable floating support congestion can accomplish osmotic control.^{37,38} Zhao et al.³⁹ created an oral push-pull osmotic pump using mesoporous silica nanoparticles loaded with fenofibrate. As expanding and suspending agents, polyethylene oxide (100,000,000) and polyethylene oxide (600,000,000) were chosen, respectively. As a semipermeable membrane, cellulose acetate was combined with polyethylene glycol 6,000 to promote flexibility and regulate membrane permeability. The prepared system is said to deliver the drug for 24 hours in almost zero-order and stay in the stomach for a duration of 21.72 h compared to the 12.48 h of the reference tablet.

- b) Matrix tablets:** They are available in single-layer matrix tablets and bilayer matrix tablets. The drug and hydrocolloid-forming gel is used to create single-layer matrix tablets. In contrast, the bilayer matrix tablet has two layers: immediate release and sustained release.⁴⁰ Utilizing varying ratios of HPMC-K4M and karaya gum as retarding polymers and sodium bicarbonate as an effervescent agent by direct compression technique, Saisivam et al. developed single-layer floating matrix tablets containing losartan potassium. Results of an in vivo trial of an optimized formulation showed that the tablet floated in the gastric content and that the GRT was extended to about 12 hours. X-ray imaging research on albino rabbits revealed that the tablet continued to remain in the stomach even after 12 hours.⁴¹
- c) Gas-generating systems:** Hydrophilic polymers and effervescent chemicals create gas-generating devices.⁴⁰
- i) Floating capsules:** The drugs used in these dosage forms are encapsulated in hydrophilic polymers such as ethyl cellulose and eudragit RS-100. Containing effervescent additives, such as calcium carbonate, sodium bicarbonate, etc. Nifedipine hydrochloride and hydrocolloids were used to create a hydrodynamically balanced capsule by Moursy et al.⁴² When the capsule shell comes into touch with stomach fluid, it dissolves and swells, creating a gelatinous barrier that floats in the gastric juice for a long time.
- ii) Floating pills:** Utilising an effervescent ingredient in the inner layer and a hydrophilic polymer in the outer layer, numerous unit types of oral floating dosage forms have been created. The outer layer of hydrophilic polymer expands and sinks when it touches gastric fluid. Still, as soon as the effervescent agent contacts gastric content, it releases CO₂, which causes the system to float.^{43,44} Meka et al.⁴⁵ created multiple-unit captopril mini tabs using a gas formation approach to extend the GRT and boost the drug's overall bioavailability.
- iii) Ion exchange resins:** These are used in these floating systems were primarily created to increase the gastric retention time of drug-delivery systems that use ion

exchange resin. They are composed of hydrophilic polymer-coated drug resin complex beads loaded with bicarbonate ions.⁴⁶ The beads float because it causes the production of CO₂ gas when it comes into contact with gastric juice. Ion exchange resin comprises resin beads loaded with bicarbonate and a negatively charged medication bound to the resin, which is the foundation of the floating system that Atyabi et al.⁴⁶ created. Using a standardized approach, it was identified that each of the two resins, Dowex 2 x 10 and Amberlite IRA-400, had in vitro floating periods of more than 24 hours. The coated dosage form showed a significantly higher retention rate than the conventional formulation, remaining in the stomach for more than 3 hours with the non-coated method.

5.1.2. Non-effervescent systems One of the ways to create these dosage forms is by mixing the drug with a gel that, after being taken orally, swells when it comes into contact with gastric fluid while maintaining relative shape integrity and a bulk density of less than one inside the outer gelatinous barrier.⁴⁸ These dosage forms float due to the air trapped by the inflated polymer.

After swallowing, this system swells impulsively from ingesting gastric fluid to the point when it obstructs its exit from the stomach. Excipients include hydroxypropyl methylcellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates are most frequently utilized in these systems.⁶

This system can be further divided into four sub-types:

- i) Hydrodynamically balanced system:** Sheth and Tossounian developed the initial version of the hydrodynamically balanced system (HBS), also known as the colloidal gel barrier system. HBS is a medication that produces gel-forming hydrocolloids to keep the stomach contents buoyant.⁴⁹ These single-unit dose forms incorporate one or more hydrophilic polymers that can gel. Excipients are frequently employed in the development of these systems, including hydroxypropyl methylcellulose, hydroxyethyl cellulose, agar, carrageenans, etc.^{50,51} and the matrix-forming polymer used in either tablets or capsules, such as polycarbophil, polyacrylates, and polystyrene.⁵² (Refer to Fig 4)

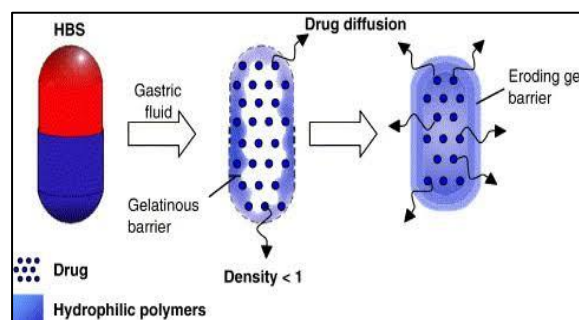


Figure 4: Hydrodynamically balanced system: Produces gel-forming hydrocolloids to remain buoyant in the stomach.

ii) Microballon: The most effective floating drug delivery technique is this one. It is a multiunit system that floats for a considerable amount of time. The microsphere has a hollow interior. And polymers are used to coat the drug's outside. The polymers eudragit, cellulose acetate, acrylic, and PVA are frequently utilized.

Solvent evaporation and emulsion-solvent diffusion are methods used to create hollow micro balloons.

Modifying polymer concentration and plasticizer ratio can alter drug release. This system's capacity to float depends on the kinds of polymers, plasticizers, solvents, and formulation techniques used. A unique approach employs ethanol: dichloromethane medication and acrylic polymer solution.⁵³

Baclofen micro balloons were developed by Dube et al. (2014) utilizing ethyl cellulose and hydroxypropyl methylcellulose K4M to create a floating oral controlled drug delivery system. X-rays revealed that barium sulfate-labeled floating microspheres successfully retained stomach contents for at least 10 hours.⁵⁴

iii) Alginate beads: Multiunit floating dosage forms have been made using a dried calcium alginate complex. Calcium alginate precipitates when sodium alginate solution is added to a calcium chloride aqueous solution, producing spherical beads with a diameter of about 2.5 mm. After the beads are separated, they are snap-frozen in liquid nitrogen and 24 hours of freeze drying at 40°C, creating a porous structure that can sustain a floating force for more than 12 hours.⁵⁴

Using the emulsion gelation approach, trimetazidine calcium alginate floating beads were created by Ghareeb and Radhi⁵⁵ using sodium alginate solution (2,3, and 4%w/v), HPMC, and peppermint oil (15,20, and 25%v/v). They discovered that oil-entrapped floating beads had favorable outcomes for extending the drug's release for ten hours.⁵⁵

iv) Layered tablets: Due to their simplicity in preparation, low cost, and excellent stability, they are more widely used.⁴⁰

a. Single-layered floating tablets: These were made by blending gas-producing substances with drugs within the matrix tablet. Due to their lower bulk Density than gastric fluid, these formulations maintain their buoyancy in the stomach via raising GRT.⁵⁶ Kim et al.⁵⁶ developed non-effervescent gastroretentive tablets of pregabalin once a day using wet granulation and compaction. They found that the amounts of HPMC and crospovidone were found to be critical factors affecting in vitro dissolution and floating properties of the prepared tablets.

b. Double-layered floating tablets: These consist of two formulations with two different release profiles that are layered on top of the other and separated by stacking.⁵⁷ Kuldeep et al.⁴⁰ By using the direct compression method, a bilayer floating tablet

containing the drugs metoprolol succinate (sustained-release layer) and rosuvastatin calcium (immediate-release layer) was formulated. HPMC K100, K4M, and K15M were employed as gel-forming agents. As a super disintegrant, cross-carmellose sodium, sodium starch glycolate, and crospovidone were employed. The effervescent agent used in beverages is sodium bicarbonate. The in vitro buoyancy study revealed that floating lag time decreases as gas-generating agent concentration rises. Additionally, it was identified that the polymer gas-producing agent ratio affected both the floating lag time and the overall floating duration.

5.2. Raft forming system

Gastric esophageal reflux disease (GERD) has been treated with floating rafts, and the mechanism of raft formation comprises the formation of viscous cohesive gel when in contact with gastric fluids. A continuous layer known as a raft is formed as each liquid portion swells. It has a low bulk density because the system's constituents contain a gel-forming material, such as alkaline bicarbonates or carbonates, which causes the system to become less dense by generating CO₂.

The system includes a gel-forming component, such as sodium alginate, which, when it comes in contact with the gastric, creates a swelling sodium alginate gel (raft), which stops the reflux of gastric contents into the esophagus.^{58,59,60} (Refer to Fig 5)

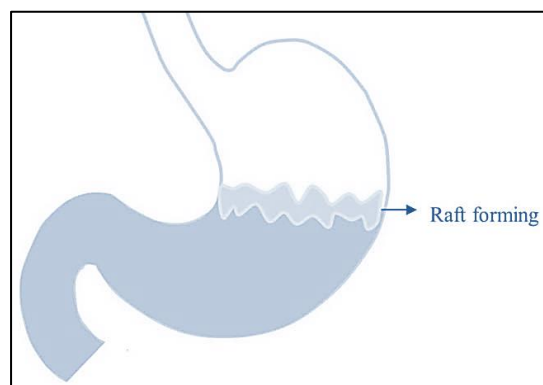


Figure 5: Raft forming system: Formation of viscous cohesive gel on coming in contact with gastric fluid.

A patent assigned to Reckitt and Colman Products Ltd. describes a raft-forming formulation for treating *Helicobacter pylori* (H. Pylori) infections in the GIT.^{61,62}

5.3. Bioadhesive / mucoadhesive system

Bioadhesion is adherence to a biological surface, such as mucus or the mucosal surface. The term "mucoadhesion" refers to instances where the polymeric system solely interacts with the mucus layer.²³ These systems enable incorporating a specific drug delivery system with bio/mucoadhesive substances, allowing the device to stick to the gastric (or other gastrointestinal) walls and obstruct gastric emptying.⁸ Mucoadhesive systems prolong drug interaction with biological membranes and promote its intimacy to extend the gastric residency time. The ability

of bioadhesive polymers to adhere to biological tissues can be either natural or synthetic.³

The mucoadhesive polymer and mucosal surface improve a connection that promotes mucoadhesion. The contact and consolidation stages are the two primary steps in this process.²⁶

Various processes allow the delivery system to adhere to the mucosal surface. Among these mechanisms is:⁶³

1. Wetting theory- The wetting theory based on mucoadhesive polymers has the capacity to spread and make contact with the mucous layers.

2. Diffusion theory- The diffusion theory is based on mucin stands interacting with the porous polymer substrate's structure.

3. Absorption theory- According to the absorption theory, hydrogen bonds and Vander Waals forces cause bioadhesion.

4. Electronic theory- The electronic theory is based on attractive electrostatic forces between the bioadhesive materials and the glycoprotein mucin network.⁶³

Natural polymers (sodium alginate, guar gum, gelatin, etc.), semi-synthetic polymers, and natural polymers are the most frequently used materials in the formation of mucoadhesive (Carbopol, HPMC, Sodium CMC). When a dosage form is taken orally, it dissolves in gastric fluids and sticks to the mucosal surface.²⁹

Examples of polymers frequently used for bioadhesion include poly (acrylic acid), chitosan, cholestyramine, tragacanth, sodium alginate, Carbopol, hydroxy propyl methyl cellulose, Sephadex, sucralfate, polyethylene glycol, dextran, poly (alkyl cyanoacrylate), and polylactic acid.²⁰

The bio-adhesion systems offer several significant benefits. Adhesion to the epithelial surface will not only help the drug reach its intended area and be mobilized but will also help it form a more potent, longer-lasting interaction with the local microenvironment. These properties improve the drug's residence time in the target area and allow a controlled, predictable release, which reduces the amount of medication needed.³

The fundamental disadvantage of such systems is that they cannot resist stomach turnover, the continuous renewal of the mucus layer, and the high stomach hydration that reduces the adhesion of polymers.²⁰ Another consideration is the possibility of adhesion to the esophagus, which could lead to collateral lesions.

5.4. Swelling & expandable system

An expandable system achieves a longer stomach residence time by altering its volume and form, as its name implies. Interestingly, these technologies were first intended for veterinary usage before being quickly investigated for use in human applications.⁶

Due to their mechanical characteristics, swellable systems are maintained in the stomach. After being in contact with stomach fluids or upon hydration, these systems expand in size. Hydrophilic polymers, such as Carbopol, polyethylene oxide, and hydroxypropyl methylcellulose, are the only ones that make this procedure possible since they draw water from the gastric secretions.⁶⁴

Polymer swelling, participation, erosion, and a reduction in the glass transition temperature are just a few of the changes the polymer undergoes due to absorbing water. These changes enable the release of drugs (due to polymer disentanglement).⁶⁴

Other dose forms that enlarge after ingestion and eventually become too large to pass via the pylorus are swelling and expanding systems.⁶⁵ (Refer to Fig 6)

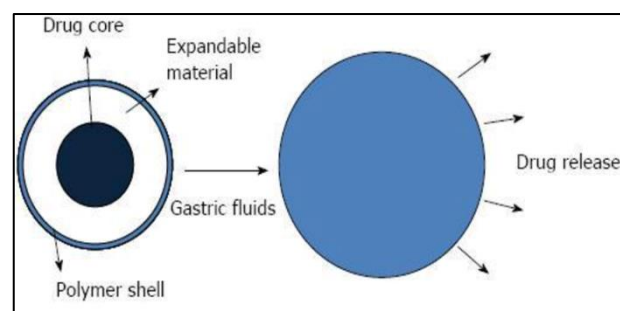


Figure 6: Swelling and expandable system: Polymer swells and releases the drug from the core.

Because of this, the dosage form spends much time inside the stomach. Because they frequently also log at the pyloric sphincter, these devices are called "plug-type systems".¹⁶

Regardless of how comprehensive the system is, three essential components must always be present for these systems to operate correctly. The first is that they need to be simple to swallow because patients won't be eager to take medications if the pharmaceutical dosage form isn't the right size to eat. Once it enters the stomach, the system's size must be larger than the pyloric sphincter. This is the second factor. Last but not least, it can be guaranteed that the remaining structure shrinks to a size that permits its elimination when the medicine is released on schedule.⁶⁶

Swelling and unfolding systems, which allow for volume and shape alteration, are the two tactics used by expandable systems to maintain their position in the stomach compartment.³

Typically, unfoldable systems are made of biodegradable polymers that are folded and contained in a carrier that is broken down in the stomach. Drug release from the pharmaceutical approach is made possible by carrier degradation as the drug unfolds and regains its original geometric form.⁶⁷

When the medication delivery system comes into contact with stomach contents, the polymer swells due to the water it collects and releases a controlled drug.¹⁶

The amount of cross-linking in the hydrophilic polymer network is a significant factor in a polymer's propensity to swell. While a low cross-linking level results in significant swelling and quick polymer disintegration, a high cross-linking level preserves the system's integrity.⁶⁸

The bulk prevents housekeeping waves from occurring while allowing for gastric retention and keeping the stomach "fed".⁶⁶

Hydrogel-coated balloons that swell and medicated polymer sheets are examples of such delivery systems.⁶⁹

The expandable GRDF typically comes in three configurations: a trim (or "collapsed") configuration for easy oral intake; an expanded form obtained in the stomach that prevents passage through the pyloric sphincter; and finally, another small form accomplished in the stomach when retention is no longer necessary, or after the GRDF has released its active ingredient, enabling withdrawal.⁷⁰

Expandable systems have shortcomings despite having some intriguing features. It is challenging to store polymers that are so easily hydrolyzed and biodegradable.⁷¹

The mechanical shape memory is relatively long-lived for the unfolding systems.

Additionally, it may not be economical to use this dosage form, which is the most challenging to industrialize. Expandable systems must also be readily biodegradable, free of sharp edges, and incapable of causing local injury during prolonged retention. They must also not impair stomach motility.⁷²

5.5. High density

These systems, which are kept in the lining epithelium of the stomach and can endure its peristaltic movements, have a density of about 3g/cm^3 . Such systems can be retained in the lower region of the stomach when their Density rises to about 2.4 and 2.8g/cm^3 .^[73]

The pyloric region of the stomach, which is the lowest part of the organ when it is upright, has been employed as a retention mechanism for pellets that are small enough to be held in the folds of the stomach body.⁷⁴ (Refer to Fig 7)

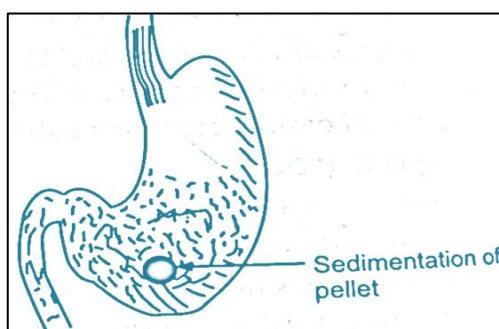


Figure 7: High Density: Due to the high-density dosage form retained in the stomach bottom for a prolonged period.

The average GI transit time with pellets can be prolonged from 5.8 to 25 hours.¹⁶

Among the excipients frequently used are barium sulfate, zinc oxide, titanium dioxide, and iron powder. These materials can potentially improve Density by $1.5\text{--}2.4\text{g/cm}^3$.¹⁶

According to the findings of a clinical trial, enteric-coated sinking ursodeoxycholic acid (UDCA) tablets have a higher bioavailability than enteric-coated floating tablets and hard gelatin capsules in 12 healthy people.⁷⁵

After oral administration of enteric-coated, sinking UDCA, the area under the curve (AUC, mol/l (8h)) was significantly larger (39.0 ± 8.5) than those obtained after both conventional UDCA (30.5 ± 4.9) and floating enteric-coated UDCA (29.3 ± 3.4).⁷⁵

Drawbacks

The main disadvantage of such systems is that it is technically challenging to produce formulations with high drug content ($>50\%$) and achieve a density of approximately 2.8g/cm^3 .^{76,77}

Because the dry substance that makes up the tablet gradually reacts or interacts with the gastric fluid to release the medicine contained within it. There is currently no such system on the market.⁷⁸

5.6. Magnetic systems

In this approach, the movement of the controlled gastroretentive formulation includes a tiny internal magnet by applying a strong appeal with a solid magnetic field onto the body surface.⁴⁰

As they are based on the attraction between two magnets, magnetic systems represent a method extremely distinct from any other gastroretentive delivery forms previously disclosed.⁷⁹

These systems consist of two parts: an external magnet that is attached to a device that is put under the belly, close to the stomach, and the medication dosage form itself, which has a small internal magnet.⁷⁹

The extra-corporal and small internal magnets regulate the dosage form's gastrointestinal transit in the magnetic dosage forms.⁸⁰(Refer to Fig 8)

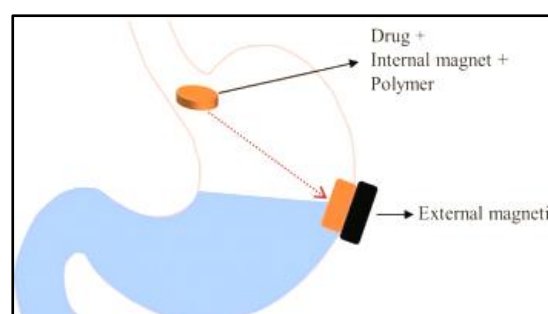


Figure 8: Magnetic system: Attraction between the internal magnet and external magnet.

Even though these systems appear, the external appeal needs to be positioned to function. A level of accuracy that could endanger patients' compliance.⁸

An extracorporeal magnet is implanted above the stomach to regulate where the dosage form is placed. The extracorporeal magnet's position and magnetic intensity can impact how the magnetic systems behave during gastric retention.⁸¹

The capacity of acyclovir magnetic depot tablets to remain in the stomach was examined by Gröning et al. in human volunteers both with and without using an external magnetic field.²⁶

In the presence of the extracorporeal magnet, the tablets were kept in the stomach for a considerable amount of time, and the values of the area under the concentration curve dramatically increased.⁸⁰

To create microbubbles that would cause cavitation when ultrasound energy from an external device was applied, Zhou et al. made gastroretentive adhesive tablets with superparamagnetic iron oxide nanoparticles (SPIONPs).⁸²

The difficulty of precisely locating the magnet and the potential for low patient adherence are two significant issues with magnetic devices.⁸¹

Therefore, clinical importance must be the main focus of future research on these gastroretentive systems.²⁶

Drawbacks: Accurate positioning of the external magnet is required. Uncooperative patients. Hardly ever utilized.^{83,84}

5.7. Self-unfolding system

The self-unfolding structures can mechanically expand beyond their original dimensions.

This increase makes its prolonged stay in the stomach possible by stopping the system from flowing through the pylorus.

A medicine can be integrated into the gastroretentive system's polymeric composition or to be used separately.

The self-unfolding effect must be achieved through a variety of techniques:

- (1) Using hydrogels causes swelling when they come into touch with stomach fluid.
- (2) Osmotic systems have a membrane that is semipermeable to an osmotic medium.
- (3) Devices based on the idea that low-boiling liquids will turn into gases at body temperature.²³

5.8. Super porous hydrogel system

These formulations, which have excellent mechanical strength and elastic properties, are becoming increasingly popular as controlled-release drugs. Highly cross-linked polymers, known as super porous hydrogels, can absorb large amounts of aqueous fluids and expand rapidly to produce a stable gel. The pore size in such systems is more

significant than 100 m. Due to capillary wetting, they can rapidly absorb water and quickly swell to their equilibrium size.²⁶ Highly expandable polymers, such as sodium croscarmellose and alginate, are utilized in these systems.^{85,86}

These hydrogels have a density of less than 1 g/cm³, allowing them to float in hydrochloric acid.²⁶

There are some drawbacks to using super porous hydrogels for gastric retention. Because ionic polymers are often used in developing these systems, their swelling behavior can be highly dependent on gastric pH and hence reversible with any pH change. Furthermore, they exhibit inadequate mechanical strength, which is a barrier to effective gastric retention.⁸⁵

6. CURRENT TRENDS IN GRDDS

6.1. Dual working system

These systems are based on floating, bioadhesive, swelling, and bio-adhesion working principles. The therapeutic efficacy of the medicine would be significantly improved by a dual-functioning system, which would overcome the limitations of bioadhesive, swelling, and floating systems. Using rosiglitazone maleate as a model medication created a bilayer and floating-bioadhesive drug delivery system that exhibited a particular combination of flotation and bioadhesion to extend residence in the stomach.⁸

6.2. Floating osmotic system

A floating osmotic drug delivery system floats on gastrointestinal fluid using the osmotic pressure principle. These systems are composed of three parts: an osmotic core, a shape-retaining semipermeable membrane, and an outside compression coating composed of gas-generating and gel-forming substances. The drug's delivery is wholly dependent on the osmotic pressure generated within the core.

First, a saturated solution of the drug is formed due to fluid flow through the semipermeable membrane, and then, due to osmotic pressure, the drug is released from the orifice within the osmotic core.⁸

6.3. Floating pulsatile system

Drugs are rapidly and wholly released from pulsatile drug delivery devices after a certain period. However, due to lag time, such systems may remove from the body without releasing drug content. To address this issue, floating pulsatile devices have been developed, and interest in them for a variety of drug therapies has grown recently.

Hollow calcium pectinate beads with pulsatile floating release diclofenac sodium were created by Badve et al. in 2007.⁸



CONCLUSION

Since these delivery systems limit the drug's absorption in the upper GIT and may transport them effectively, improving absorption and enhancing absolute bioavailability, GRDDS can offer many benefits for medications with limited bioavailability.

These days, several medication delivery systems are being created to deliver the drug in the upper GIT or stomach region so that whatever medication is provided can be absorbed, increasing the bioavailability of the medicine.

According to the systems and dosage forms in which they are available—tablet, bead, gel, or capsule forms—many formulations are on the market.

Considering this, several researchers are striving to optimize the use of this approach, some with success and others failing due to the unpredictable nature of the human GIT. Thus, it is essential to evaluate the physiological event in the GIT, choose the ideal mixtures of medications and excipients, and develop suitable formulation procedures to create a successful GRDDS.

Although many GRDDS, such as low or high Density, bio or mucoadhesive, and magnetic systems, have been documented in the literature, more investigation is needed to determine their effectiveness or clinical relevance.

LIST OF ABBREVIATIONS

GRDF	Gastro Retentive Dosage Form
GRT	Gastric Retention Time
FDDS	Floating
GRDDS	Gastro Retentive Drug Delivery Systems
GIT	Gastro-Intestinal Tract
MMC	Migrating Motor Complex
KSI	Kilo Pounds Per Square Inch
CO ₂	Carbon Dioxide
HPMC	Hydroxypropyl Methylcellulose
HBS	Hydrodynamically Balanced System
GERD	Gastric Esophageal Reflux Disease
H. Pylori	Helicobacter Pylori
UDCA	Ursodeoxycholic Acid
AUC	Area Under Curve
SPIONPs	Superparamagnetic Iron Oxide Nanoparticles

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