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OVERCOMING GASTROINTESTINAL OBSTACLES: GASTRORETENTIVE DRUG DELIVERY SYSTEMS CONTRIBUTION TO IMPROVING ORAL DRUG DELIVERY

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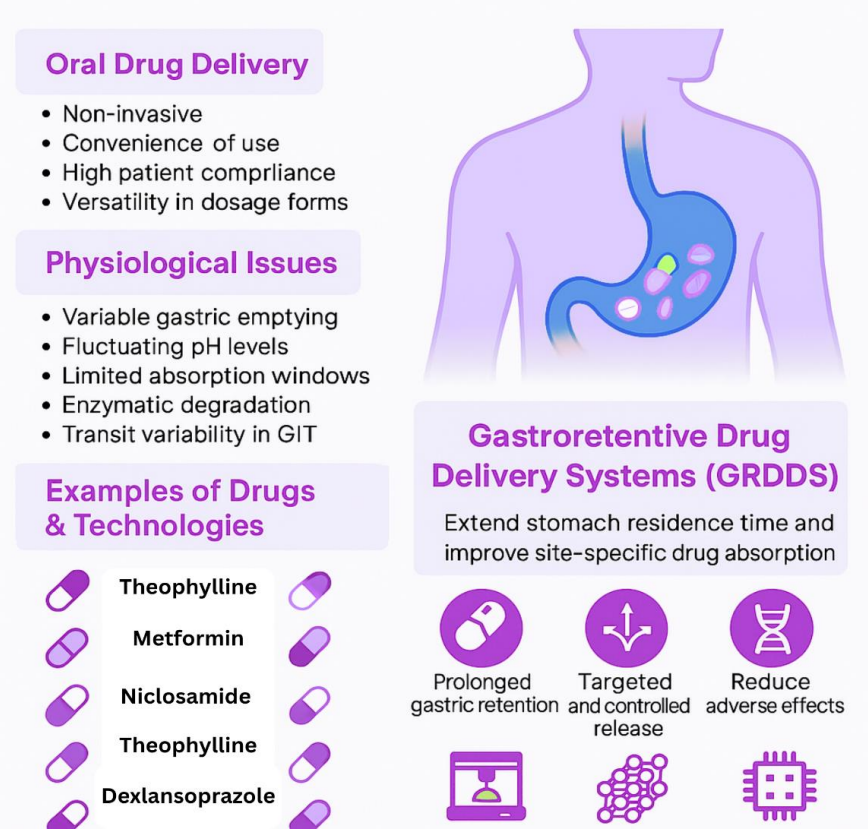
ABSTRACT

The non-invasive nature, convenience of use, high patient compliance, and versatility in dosage form design of oral medication delivery make it the most popular method. Nevertheless, a number of physiological issues can seriously impair the bioavailability and therapeutic effectiveness of many active pharmaceutical ingredients (api), including variable gastric emptying, fluctuating ph levels, limited absorption windows, enzymatic degradation, and transit variability in the gastrointestinal tract (GIT). In order to get around these restrictions, gastroretentive drug delivery systems or GRDDS, have been created to improve site-specific drug absorption and extend the stomach residence duration, especially for medications absorbed in the upper GIT. The API may be released in a targeted and regulated manner because to the GRDDS's clever design, which keeps the dose form in the stomach for extended periods of time. These methods lessen systemic adverse effects, improve therapeutic results, decrease dose frequency, and control variations in plasma drug concentrations. Drugs having limited absorption windows, low solubility at increased pH, local gastric activity, or intestinal environment instability benefit most from these systems. The behavior of dose forms and gastrointestinal retention are greatly influenced by stomach physiology and gastric motility patterns, such as the Migrating Myoelectric Complex (MMC). Additionally influencing stomach residence duration are factors such as meal composition, calorie content, patient age, sex, and co-administered medicines. In order to maximize drug delivery efficacy, modern

GRDDS technologies use biodegradable matrices, sophisticated polymers, and innovative design topologies. Notably, when administered by GRDDS, medications such as misoprostol, cyclosporine, ciprofloxacin, metformin, furosemide, and captopril have demonstrated enhanced bioavailability and therapeutic characteristics. Drug delivery has been further transformed by the incorporation of 3D printing and nanotechnology into gastroretentive systems, which allow for the creation of customized, site-specific, and programmable dosage forms.

KEYWORDS: gastroretentive drug delivery systems; magnetic retention systems; active pharmaceutical ingredients; non-invasive; biodegradable matrices.

Graphical Abstract



INTRODUCTION

Evidently many benefits when utilizing the oral administration route, such as its simplicity, high patient compliance.[1] adaptability in dosage form formulation, convenience of storage and transportation, lack of specialized staff, etc.[2,3] More than half of the medications on the market need to be taken as prescribed, according to reviews on the subject[4] The pH of the medium, the variability of absorption across the gastrointestinal tract (GIT), the variation in

surface area and enzymatic activity of different sections of the gastrointestinal tract,[5] and other physiological factors can all negatively impact the bioavailability of the API and the clinical efficacy of the drug in the majority of oral drug delivery systems transit duration through the absorption-related regions,[6,7] as well as the rate of excretion and metabolism. Targeted delivery and modulated release of API are the two primary strategic objectives for enhancing oral dosage forms, given the substantial relevance of the effects outlined on the action of many medications.[3,8,9] The following are some clinical benefits of gastroretentive systems: less variation in the therapeutic impact of medications with a concentration prolonging the maintenance duration of therapeutic concentration for medications with time-dependent pharmacodynamics, preventing the emergence of concentration-dependent adverse effects.[3,10,11] Variable gastrointestinal transit is one of the physiological limitations of most oral dose formulations, leading to non-uniform absorption characteristics as a result of reduced dosage form resident duration in the stomach, partial drug release, and variable gastric emptying.[12] Drug with an absorption window is not adequately absorbed, especially in the upper portion of the small intestine, since some of the drug is not absorbed after it passes through the absorption site.[13] Human stomach emptying of dosage forms is influenced by a wide range of factors, which causes notable variation within and between persons. In order to deliver medications in larger concentrations to the absorption location such as the upper section of the small intestine, a useful delivery system would be able to regulate and extend the stomach emptying period.

Such significant variation increases the risk of non-uniform absorption and unexpected bioavailability because many drugs are efficiently absorbed in the upper gastrointestinal tract[14] Avoiding undesired MP effects, rebound effect and tolerance, and unfavorable activation of counterregulatory systems by limiting API's entrance into other gastrointestinal tract regions. There are now a number of primary categories of gastroretentive systems,[14] including super porous hydrogels, magnetic, mucoadhesive, high-density, raft-forming, floating, and growing in size.[15]

The volume of medication released from the dosage form, the stomach's emptying rate, and the duration of the dosage form's passage through the gastrointestinal tract, as well as the site of drug absorption, can all impact the effectiveness of oral medicine administration must maintain the overall specific gravity below the amount in the stomach.[15] It needs to break down slowly enough to serve as a reservoir for the delivery mechanism.[16,17] With stomach

retentive action, floating systems are one of the important kinds of drug delivery technologies.[18] Medication that benefits from stomach retention includes cyclosporine, metformin, furosemide, ciprofloxacin, and allopurinol. It is possible to administer medications that act locally in the stomach (like misoprostol),[19,20] are less soluble in the pH of the small intestine than the stomach (like chlordiazepoxide and cinnarizine), or are prone to breakdown in the intestinal pH (like captopril) in dosage forms that retain stomach acid,[20,21] restricted to ingestion in the upper gastrointestinal tract, targeting parts of the upper gastrointestinal tract that are insoluble in water,[15] bioavailable through active transport pathways, Lower gastrointestinal mucosal sensitization, jarring, discomfort, or hazard is more effective when plasma concentrations are more constant.[22]

that are locally active in the stomach, have a window for absorption in the upper small intestine or stomach, are unstable in the intestinal or colonic environment, and are poorly soluble at high pH levels.[23]

Stomach physiology

The most dilated part of the digestive system is the stomach. This organ is situated between the small intestine, which is inferior to it, and the oesophagus, which is superior to it. The stomach is a big, hollow, muscular organ that can contain a lot of food.[24] This organ serves as a food storage and mixer, holding around two to three liters of food.[25] The four primary parts of this organ are the cardia, fundus, body, and pylorus. The area of the stomach where food initially enters is called the cardia, and it is joined to the oesophagus.[26, 27] A bulbous, dome-shaped area of the stomach, the fundus comes inferiorly after the cardia. The main part of the stomach, the body, is located distal to the fundus.[28,29] The duodenum, the highest section of the small intestine, receives food from the pylorus, which follows the body inferiorly. Following mastication and deglutition, digestion takes place in the stomach.[30,31] The stomach wall is made up of four layers: serosa, muscularis externa, submucosa, and mucosa. The mucosa, the innermost layer, is mostly made up of gastric glands that release stomach juices and is coated with epithelial tissue.[24,32,33] Gastric juices are secreted by the fundus. Mucus (Foveolar) cells cover the inner stomach mucosal wall with the protective mucus produced by the cardia. The main cells (pepsin) and parietal cells (HCl) gastric juices cannot break down the stomach wall because of mucus.[34,35] The submucosa is made up of thick connective tissue and is home to nerves, lymphatic vessels, and blood. The mucosal layer is supported by the submucosa. When food enters the stomach, this layer's many folds,

known as "rugae," which resemble accordions, allow for intraluminal distension.[36] The stomach has a robust blood supply and is a very flexible and movable organ. In order to support waves of rapid peristalsis for the second phase of digestion, this organ has many muscle layers and five distinct cell types that operate at high metabolic rates.[37,38]

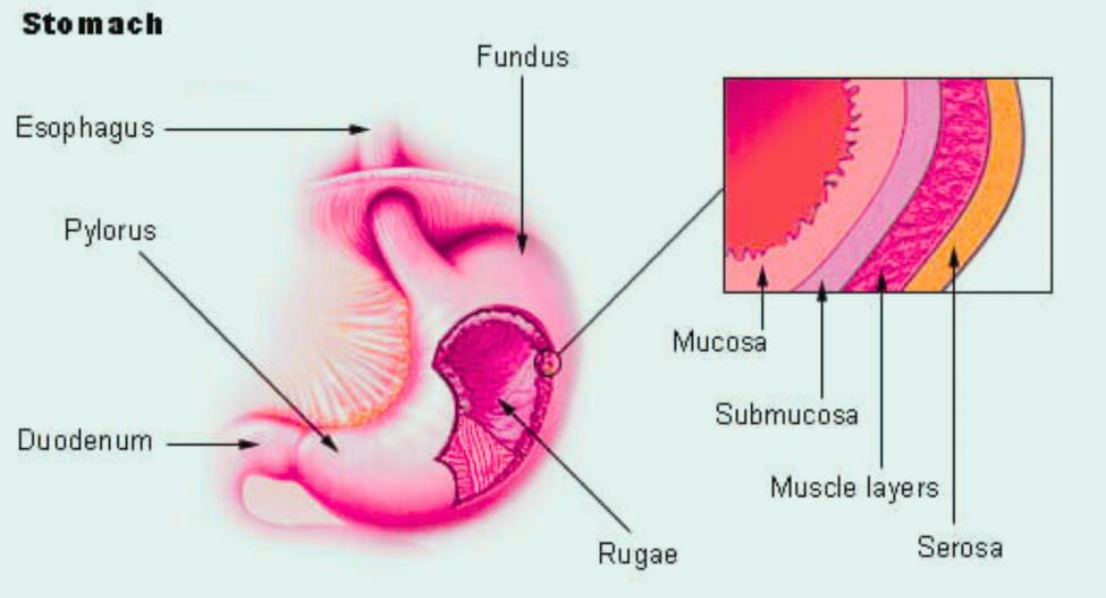


Fig. 1 Illustration of stomach and its layers.

The primary arterial supply to the stomach is provided by the celiac trunk, which branches immediately anteriorly from the aorta at the T12 spinal level. The spleen, left gastric (LGA), and common hepatic (CHA) arteries are all supplied by the celiac trunk.[39,40] The LGA's ascending branch perfuses parts of the distal esophagus, while its descending branch provides the lesser curvature proximally.[41,42] The CHA branches out as the gastroduodenal artery (GDA), passes above the pancreas, and continues as the normal hepatic artery after running to the right of the celiac trunk.[43,44] A series of electrical events known as the "inter-digestive myoelectric cycle" or "migrating myoelectric cycle" (MMC) take place during a fasting state and cycle through the stomach and intestine every two to three hours. There are four more components to the MMC.[45,46] The pattern of contractions, sometimes referred to as the digestive motility pattern, changes from the fasting condition to the fed state after consuming a mixed meal. Phase 1 (Basic phase) involves sporadic contractions and lasts 30 to 60 minutes. Phase 2, called the preburst phase, lasts 20 to 40 minutes and contractions and sporadic action potentials.[47] Phase 3 (Burst phase) lasts 10–20 minutes and is characterized by brief, strong contractions. Phase 4 takes place between phases 2 and 1 of two consecutive cycles and lasts for 0–5 minutes.[48,49]

Table 1: Some Floating formulations for GRDDS.

Drug	Disease	Key Polymers/Technique	References
Drotaverine	Antispasmodic	Floating microspheres	H. R. Bhilare et al. (2025)[50]
Dexlansoprazole	Gastroesophageal reflux disease	Effervescent floating tablets	A. Sandhya, et.al.,. (2024)[51]
Capsaicin	Peptic ulcers	Nanofiber	(Karavasili C., et al, 2024)[52]
Theophylline	Gastroesophageal reflux disease	Sublimation-based floating matrix tablet	Kriangkrai et al., 2024[53]
Propranolol Hydrochloride	Hypertension and cardiovascular disorders	3d-printed	(Mohammed AA et al 2023)[54]
Niclosamide	Antiparasitic drug being repositioned for helicobacter pylori.	3 D Printed Nanocrystals by the Melting Solidification Printing Process.	(Real JP, Real DA et al 2023)[55]
Flavonolignan Silymarin	Acute and chronic hepatic diseases	Direct compression, Floating tab	(Khan JA et al 2023)[56]
Metformin	Diabetes type ii	Three-dimensional printing	(Millán-Jiménez M et al 2023)[57]

Gastric Retention-Related Variables

Type of meal: Drug retention can be prolonged and gastric emptying slowed down by consuming indigestible polymers or fatty acid salts, which can change the stomach's motility pattern to a fed state.[58]

The number of calories: GRT may be raised by 4–10 hours by eating meals that are heavy in fat and protein.[59]

Frequency of meals: GRT can rise by more than 400 minutes in comparison to a single meal because of the infrequent MMC throughout subsequent meals.[60]

Sex: Regardless of height, weight, or body surface area, males have a lower average ambulatory GRT (about 3.4 hours) than females of the same age and race (about 4.6 hours).[61]

Age: Individuals above 70 have a noticeably longer age GRT.[62]

Taking prescription drugs simultaneously: GRT may be extended by concurrent use of opioids like codeine and anticholinergics like propantheline.[62]

Gastro-Retentive Drug Delivery System Approaches

Effervescent systems: An effervescent system is made to float in a stomach that contains inert gas, air, or vacuum. Either organic solvents like ether or cyclopentane volatilize to produce gas, or carbonate-bicarbonate salts react effervescently with organic acids to form CO2.[63] Thin, floatable systems may be expelled from the stomach more easily thanks to these technologies. Usually, they include a flexible, hollow component that may expand or shrink before returning to its original form.

Systems that generate gas: Another technique for achieving buoyancy is the creation of gas bubbles. When carbonates or bicarbonates react with acid, either the stomach's natural acid or co-formulated acids like citric or tartaric acid, CO2 is created.[64] For the formation of gas, the ideal stoichiometric ratio between sodium bicarbonate and citric acid is 0.76:1. They have also used matrices with trapped liquids that evaporate at body temperature. Both single-unit and multi-unit systems have used these strategies.[64]

Systems containing volatile liquids: In these systems, the device is divided into two chambers by a pressurized, moveable, impermeable bladder. The drug is kept in the first chamber, while a volatile liquid is kept in the second.[65] In order to preserve GRT, the liquid (such as ether or cyclopentane) vaporizes at body temperature, enlarging the chamber and the device as a whole.[66] In order to facilitate the automated ejection of the device from the stomach, the system may additionally incorporate a bioerodible plug composed of polyethylene, polyvinyl alcohol, or other materials that dissolves gradually and permits the inflated chamber to release gas and collapse after a predetermined amount of time.[67] The drug is gradually delivered from the reservoir into the stomach fluid during inflation.[68]

Floating drug delivery systems: One of the best methods for preserving stomach retention is the use of floating systems, which also improves medication bioavailability and prolongs the duration of gastric residency.[69] They work especially well for medications that have a limited window of absorption in the stomach or upper small intestine. These systems stay afloat in the stomach without impairing gastric emptying because of their reduced bulk density in comparison to gastric fluids.[59] Because to their exceptional buoyancy, the medicine may be released gradually and under control. After the drug has been fully released, the leftover system is naturally removed from the stomach.[70]

Non-effervescent systems: High concentrations (20%–75% w/w) of gel-forming, highly swellable cellulosic hydrocolloids (such as sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose [HPMC]), polysaccharides, or matrix-forming polymers (such as polycarbophil, polyacrylates, and polystyrene) are commonly found in non-effervescent systems, like tablets or capsules.[71,72] These compounds hydrate and create a colloidal gel barrier that regulates medication release and fluid entry when they come into contact with stomach fluid. The underlying hydrocolloid layer hydrates to preserve the gel barrier when the dosage form's outer surface degrades. The expanded polymer's trapped air reduces the dosage form's total density, increasing its buoyancy. Intragastric floating systems have been developed using these techniques.[73,75]

Alginate beads: Calcium alginate that has been freeze-dried has been used to create floating dosage forms with many units.[76] Calcium alginate precipitates to form spherical beads with a diameter of around 2.5 mm when a sodium alginate solution is put into an aqueous calcium chloride solution. A porous structure that can maintain buoyancy for more than 12 hours is produced by separating these beads, freeze-drying them for 24 hours at -40°C, and then snap-freezing them in liquid nitrogen.[77,78]

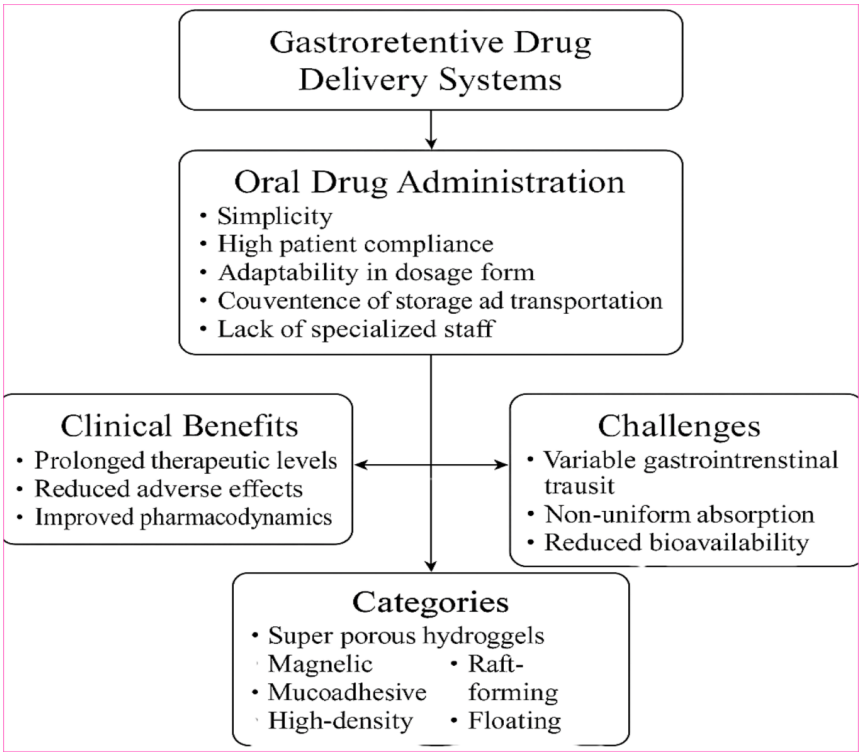


Fig. 2: Comprehensive Flowchart of GRDDS Dosage Form Approaches.

Hollow microspheres: Using solvent evaporation or solvent diffusion processes, hollow microspheres (also known as micro balloons) are created. Drugs are then placed inside their polymer shells to increase the dosage form's GRT. Polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low-methoxylated pectin, and other polymers are used to create these systems.[79] The kind and quantity of polymer, the plasticizer ratio, and the formulation solvent selection are important variables that affect drug release and buoyancy. For over 12 hours, these tiny, buoyant spheres may remain afloat in an acidic media that contains a surfactant.[80,81]

Microporous compartment systems: This technique encloses a drug reservoir in a microporous chamber with pores along the length of its upper and lower walls. To keep the undissolved medication from coming into direct touch with the stomach lining, the reservoir's outside walls are hermetically sealed. The system is able to stay suspended above the contents of the stomach because of the flotation chamber's restricted air space.[82]

Hydrodynamically-balanced systems: These systems are composed of single-unit dose forms from one or more hydrophilic polymers that form gels. The most often used excipient is HPMC, however substitutes include agar, sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose, and alginic acid are also suitable. The polymer and medication are combined, and they are frequently enclosed in gelatin capsules that quickly disintegrate in stomach acid. It creates a floating mass when the surface polymer hydrates and expands. The development of a hydrated surface barrier controls drug release.[83] Water may get through the inner layers because of the barrier's constant surface erosion, which maintains it moist and buoyant.

Systems of muco/bioadhesive: By sticking to particular areas of the gastrointestinal system, bioadhesive gastro-retentive dosage forms improve the absorption of medications taken orally. These methods stick to the stomach's epithelial surface and extend gastric residency by using bioadhesive polymers.[84] Based on the process of adherence to the mucosal membrane, a variety of approaches can be used to create dosage forms with bioadhesive qualities. Chitosan, cholestyramine, sodium alginate, polyacrylic acid, HPMC, sucralfate, tragacanth, dextrin, and polylactic acids are among the polymers frequently utilized in bioadhesive applications.[85]

Magnetic systems: A tiny internal magnet in the dose form interacts with an external magnet placed on the abdomen above the stomach as part of the magnetic system. Despite the apparent effectiveness of this approach, patient compliance may be impacted by the requirement for exact external magnet positioning at rabbit experiments, ultrafine ferrite-containing bioadhesive granules were steered by an external magnet for two minutes, and almost all of the granules stayed at the desired spot for two hours.[86,87]

3D-Printed Personalized Floating System: Customized oral dose forms made with additive manufacturing (AM) processes are known as 3D-printed floating structures. These dose forms are designed to float on stomach contents and offer individualized, controlled medication release, particularly for patients who require exact therapeutic windows.[88]

Raft-forming system: In order to help administer antacid medications and medications for gastrointestinal tract infections and disorders, raft-forming devices are gaining a lot of interest. When a gel-forming solution comes into contact with gastric fluid, the drug can be released gradually into the stomach by expanding and creating a viscous gastric fluid.[89]

CONCLUSION

Increasing a drug's bioavailability, giving it a continuous release, and avoiding many of its unfavourable side effects are now all made possible by floating tablets. It has been shown that using floating tablets to cure stomach retention is a feasible option. For medications that are mostly absorbed from the upper gastrointestinal tract, these systems provide a special advantage. A review of the literature indicates that medication absorption in the gastrointestinal tract is a very diverse process with a range of physiochemical characteristics. Numerous GRDDS platforms have demonstrated great promise in enhancing pharmacokinetic profiles and therapeutic efficacy, including floating systems, mucoadhesive/bioadhesive systems, expandable and swellable formulations, superporous hydrogels, magnetic retention systems, and 3D-printed customized dosage forms. By lowering the frequency of doses, these systems improve patient compliance, limit variations in plasma drug levels, and enable continuous drug release. The design of GRDDS has been further improved by recent developments in polymeric materials, nanotechnology, and additive manufacturing. This has made it possible to create complex drug delivery platforms with enhanced buoyancy, site-specific adherence, and adjustable release profiles.

In conclusion, GRDDS, which provide enhanced drug absorption, regulated release, and focused treatment, constitute a significant advancement in oral drug administration. The pharmacological results of difficult therapeutic drugs might be improved and their clinical applications could be expanded with further study and development in this area.

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