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GASTRORETENTIVE DRUG DELIVERY SYSTEMS: A MODERN INSIGHTS ON APPROACHES AND APPLICATIONS

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GASTRORETENTIVE DRUG DELIVERY SYSTEMS: A MODERN INSIGHTS ON APPROACHES AND APPLICATIONS

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ABSTRACT: The pharmaceutical research sector is very interested in oral gastro-retentive dose formulations. The importance of gastro-retentive drug delivery systems (GRDDS) was boosted by these systems, which also improved patient compliance with higher medication therapeutic indices. The use of different technical advancements in the design and production of gastroretentive dosage forms can alleviate a number of physiological restrictions associated with these forms, such as short gastric retentive time and fluctuations in stomach emptying time. Medication having shorter half-lives, unstable or poorly soluble at alkaline pH, or poor absorption in the lower gastrointestinal tract can benefit greatly from GRDDS. In order to achieve the required retention period and release pattern, the system may be built using a range of innovative methods, including magnetic, bioadhesive, expandable, and floating systems. The use of gastro-retentive drug delivery systems (GRDDS) for the oral administration of medications has significantly increased in recent years. A number of innovative design strategies, including the widely used floating drug delivery system (FDDS), have been used to create effective GRDDS. GRDDS has a number of advantages, including the capacity to provide drugs with a narrow window for absorption, improve pharmacological effects, lower dose frequency, increase bioavailability, and extend the duration of the drug's residency in the stomach for local effects like the treatment of peptic ulcer disease. The purpose of this study is to give a brief introduction to gastro retentive drug delivery (GRDD), including its need, advantages, disadvantages, factors affecting, approach and also its applications.

KEYWORDS: Gastroretentive, GRDDS, bioadhesive, bioavailability, gastrointestinal tract, floating drug delivery system.

INTRODUCTION

Drug delivery techniques that are novel include gastroretentive systems. These systems' major objective is to prolong the time a medication stays in the stomach, guaranteeing site-specific release in the upper gastrointestinal tract for effects that might be local or systemic. The gastric retention time (GRT) of drug formulations intended for gastroretentive administration is greatly

increased by their prolonged stomach residence. Over the past few decades, a variety of techniques for gastroretentive medication administration have been developed. The most practical and recommended way to get medicine into the systemic circulation is by oral means. [1] The pharmaceutical industry has recently shown an increasing amount of interest in oral controlled release drug delivery systems because of their potential for improved therapeutic outcomes. Dosing simplicity, increased patient compliance, and formulation flexibility are some of these advantages. Drugs with short half-lives and fast absorption from the gastrointestinal tract (GIT) are quickly eliminated from the body, requiring regular dosage to keep therapeutic levels attained. In order to tackle this problem, oral sustained-release formulations have been created that progressively release medications into the gastrointestinal tract, keeping the systemic circulation's effective drug concentrations stable for a longer amount of time. [2] These delivery systems are made to stay in the stomach after oral administration, releasing the medication in a regulated way that enables a steady supply of the medication to the GIT's absorption sites. Short gastric retention time (GRT) and irregular gastric emptying time (GET) are two issues these systems must deal with. These issues might result in partial medication release in the absorption zone (the stomach or upper portion of the small intestine) and decreased dosage effectiveness. [3] A longer stomach residence period is ideal for improving site-specific controlled release dose formulations. Prolonged stomach retention has the potential to increase drug solubility, decrease drug waste, extend the period of drug release, and improve bioavailability of medications that are less soluble in high pH conditions. Furthermore, prolonged stomach retention times may be advantageous for local actions in the upper section of the small intestine, such as peptic ulcer therapy. [4]

ADVANTAGES

Several advantages are provided by the gastroretentive drug delivery system (GRDDS): Boosts the therapeutic efficacy and bioavailability of drugs.

- Makes the most cost-effective use of doses. [3]
- Reduces the possibility of antibiotic resistance by preventing changes in therapeutic levels and keeping them constant. [4]
- Increases the effectiveness of drug release, particularly for medications with brief half-lives. [1]
- Affects pharmacokinetic characteristics. [1]
- Encourages patient compliance by lowering dosage frequency. [2]

- Because stomach fluid has lower bulk density than other fluids, it stays buoyant in it, which helps to overcome problems with gastric emptying time (GET) and retention time (GRT). [2]

DISADVANTAGES

GRDDS have a number of drawbacks.

- They require more stomach juices to be produced. [3]
- Drugs that induce gastrointestinal irritation, are inefficient in acidic settings, have a low solubility in gastric fluids, or are intended for selective release in the colon should not be used with GRDDS. [2]
- The efficiency of GRDDS can vary depending on whether they are taken before or after a meal, as the drug's residence time in the stomach is impacted by the subject's digestive condition; [4]
- It is difficult to estimate the adherence of medications due to the continual renewal of the stomach's mucus layer. [3]

FACTORS AFFECTING GASTRIC RETENTION

1. Density: The density of the dosage form (1.004g/ml) should be less than the density of the stomach contents.

2. Size: If a dosage form's diameter is more than 7.5 mm, it will stay in the stomach for a longer period of time than if it is 9.9 mm [4].

3. Dosage form shape: A diameter remained in the stomach for a longer period of time than other devices of a similar size. Multiple unit formulations have a more predictable release profile than single unit dosage forms, allow a greater margin of safety against dosage form failure, and demonstrate minimal performance impairment from the failure of units with incompatible substances or different release profiles.

4. Fed or unfed state: GI motility during a fast is determined by strong motor activity, or the migrating myoelectric cycle (MMC), which occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach, and the formulation's GRT is affected if the formulation's delivery period coincides with the MMC. In the fed state, MMC is delayed and GRT is much longer [5].

5. Meal type: By feeding indigestible polymers or fatty acid salts, the stomach's motility pattern can be changed to a fed state, which slows down the rate of gastric emptying and lengthens the amount of time that medications escape from the stomach.

6. Caloric content: Eating a meal heavy in fat and protein can increase GRT by 4–10 hours.

7. Meal frequency: Because MMC has a low frequency. When comparing successive meals to a single meal, feeding rises by more than 400 minutes [6, 7].

8. Gender: The mean ambulatory GRT in males (3,4 hours) is lower than that of their age- and race-matched female counterparts (4,6 hours) [8], regardless of height, weight, or body surface area.

9. Age: The GRT is notably longer in those over 70.

10. Taking medications at the same time: GRT may be prolonged by anticholinergics like propantheline and opioids like codeine and atropine [9].

APPROACHES TO ACHIEVE GASTRIC RETENTION

The following tactics are used to increase the amount of time medications stay in the gastrointestinal tract:

A. Pharmacological Approach

This technique slows down the emptying of the gastrointestinal tract by employing medications or incorporating them into the dose form. To do this, for instance, antimuscarinic medications such as propantheline are employed. [12]

B. Physiological Approach

This method slows stomach emptying by activating receptors in the duodenum or jejunum using natural chemicals or fat derivatives like triethanolamine myristate.

C. Use of Pharmaceuticals

Several pharmaceutical treatments are used since the first two procedures raise concerns about toxicity. [14]These strategies include:

1. Floating or Low Density Drug Delivery Systems

This system can remain buoyant in the stomach because its bulk density is lower than that of gastric fluids. [13] These systems, also known as Hydrodynamically Balanced Systems (HBS), can be further classified into:

i. Effervescent Systems: These comprise systems that contain volatile liquids and those that generate gas.

ii. Non-Effervescent Systems: These include systems that are low density by nature and those that may swell or expand.

2. Sinking or High Density Drug Delivery System

The medication is guaranteed to stay at the stomach's bottom thanks to this mechanism.

• **Changed Form or Unfolding Mechanism:** This structure permits the medication to enlarge, obstructing its excessive passage through the pyloric sphincter. [11]

• **Mucoadhesive or bioadhesive drug delivery systems:** these systems allow the medication to adhere to the stomach mucosa.

• Magnetised System; Super Porous Hydrogel System [10]

APPROACHES IN GASTRO RETENTIVE DRUG DELIVERY SYSTEM:

1. Floating drug delivery system:

Floating systems are among the most efficient ways to maintain stomach retention among all other gastroretentive dosing systems, resulting in better drug bioavailability and longer gastric residence times. Floating systems are suitable drug delivery strategies for drugs with absorption window constraints and improved results of absorption window issues in the upper small intestine or stomach. Because these systems have a lower bulk density than gastric fluids, they can remain in the stomach for extended periods of time without slowing down the rate of gastric emptying. Because of their excellent buoyancy, which enables the dosage form to release the medicine gradually in a predetermined and regulated manner, they display good gastrointestinal retention. Once the drug has completely released, the residual system is discharged from the stomach [15, 16].

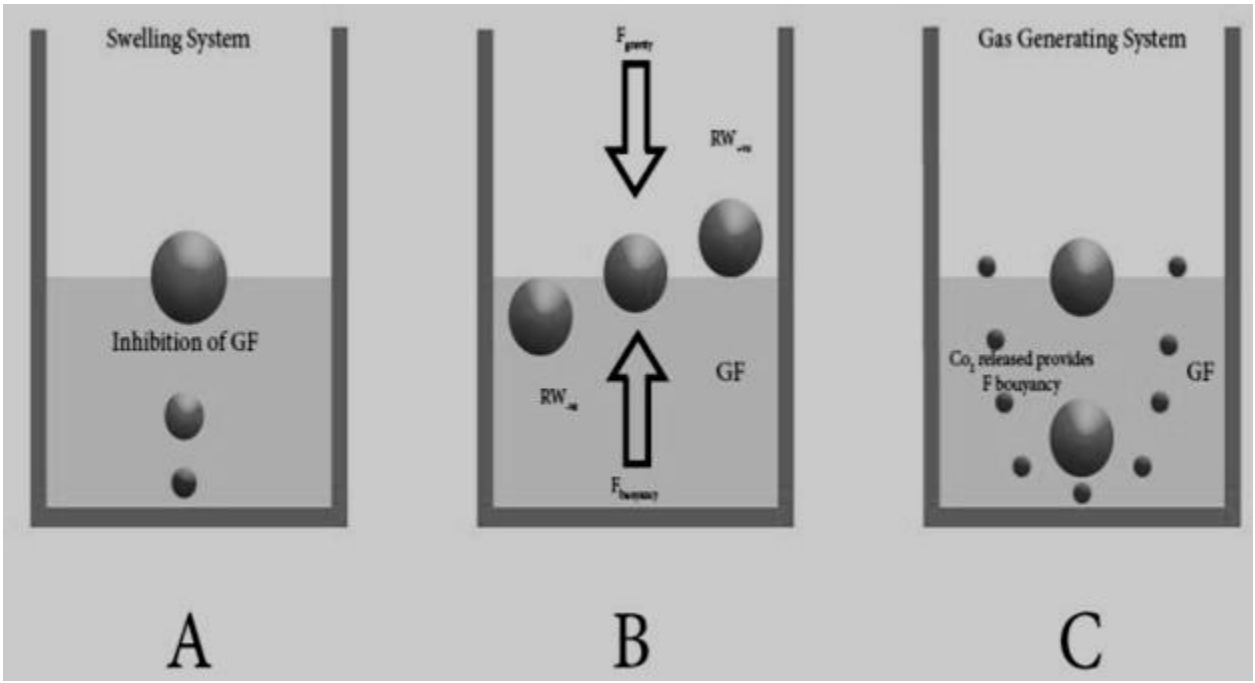

Figure 1: floating drug delivery system's mechanism

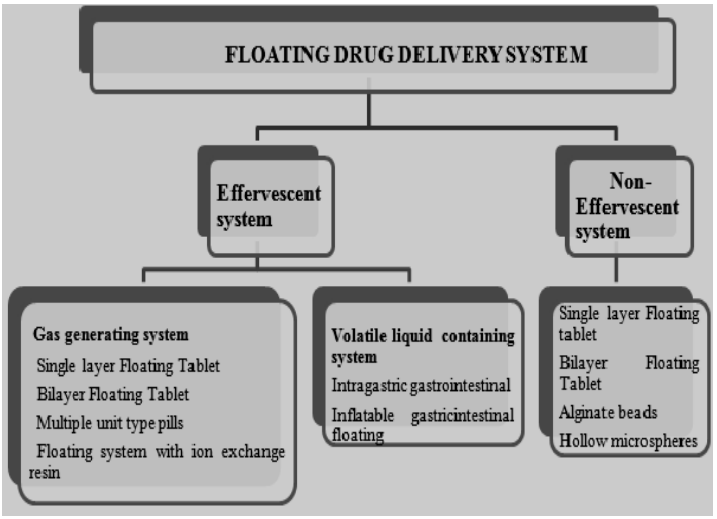

Figure 2: Classification of floating system

I. Effervescent system:

a pharmaceutical system floating in an airtight, vacuum-filled, or inert gas-filled stomach. Gas can be released into the floating chamber by volatilisation of organic solvents like cyclopentane or ether. On the other hand, gas can be produced when carbonate-bicarbonate salts and organic acids react effervescently to produce CO2. These devices allow for the spontaneous expulsion of thin, floatable systems from the stomach. They contain a hollow, pliable unit that may be stretched or constricted, but after a while, it will collapse back into its original shape. [17, 18]

A. Gas generating system:

Generating gas bubbles is another way to make anything floatable. CO2 can be created when acid (either the stomach's natural acid or acid that has been coformulated as citric or tartaric acid) is mixed with carbonates or bicarbonates. It has been found that for gas production, a stoichiometric ratio of 0.76:1 between sodium bicarbonate and citric acid is optimal. An approach is to use a matrix that contains trapped liquids that, at body temperature, transform into a gas. These techniques have been used with systems with one or more units. [19]

B. Volatile liquid containing system:

A pressurised, movable, impermeable bladder divides the two chambers in this type of system. The volatile liquid is in the second chamber, while the medication is in the first. An inflatable chamber can be filled with a liquid (such as ether or cyclopentane) that gasifies at body temperature and causes the stomach chamber to expand in order to maintain the GRT of a medication delivery system.The device may additionally incorporate a bioerodible plug made of polyethylene, polyvinyl alcohol, etc. that progressively dissolves and causes the inflated chamber to release gas and collapse after a certain length of time, enabling the inflatable

systems to be automatically ejected from the stomach. The medication is constantly released from the reservoir into the stomach fluid as the device inflates [20, 21].

II. Non effervescent system[33]:

Tablets or capsules in non-effervescent systems contain high concentrations (20–75% w/w) of gel-forming, highly swellable, cellulosic hydrocolloids (like sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose (HPMC)), polysaccharides, or matrix-forming polymers (like polycarbophil, polyacrylates, and polystyrene). When stomach fluid comes into touch with these gel formers, polysaccharides, and polymers, they hydrate and form a colloidal gel barrier that controls how quickly fluid enters the device and how soon the drug is released. When the outer surface of the dosage form dissolves, the hydrocolloid layer next to it hydrates and preserves the gel layer. By trapping air, the expanded polymer lowers the dosage form's density and increases its buoyancy. The following methods were applied in the creation of intragastric floating systems [22, 23].

A. Hydrodynamically Balanced Systems

These are single-unit dosage forms made of one or more gel-forming hydrophilic polymers. Although HPMC is the most widely utilised excipient, agar, HEC, HPC, NaCMC, and alginic acid are other viable choices. The drug and polymer are mixed together and frequently administered as gelatin capsules. The capsules dissolve rapidly in the stomach juice, and when the surface polymer expands and becomes hydrated, a floating mass is produced. Drug release is controlled by the surface formation of a hydrated barrier. Because of ongoing surface erosion, which maintains the surface wet and buoyant, water can permeate into the inner layer of the surface. Low density formulations with fatty excipients reduce erosion by limiting water penetration. The main drawback is the passivity of the operation. After the gelatinous surface layer has hydrated, it depends on the characteristics and amount of polymer as well as the air sealed in the dry mass centre. Important elements of an efficient drug delivery system are the polymer's effect on the release profile and the drug loading balance. [24, 25, 26]

B. Microporous Compartment System

The core of this method consists of enclosing a reservoir of medicine inside a microporous chamber with pores along the length of its top and bottom walls. The outside walls of the drug reservoir compartment are hermetically sealed to prevent the undissolved medication from making direct contact with the stomach surface. Owing to the restricted air space within the flotation chamber, the delivery system hovers over the contents of the stomach. When gastric fluid enters via the opening, the medication dissolves and is thereafter continually carried across the stomach for absorption. [27]

C. Alginate Beads

Calcium alginate that has been freeze-dried has been used to create floating dosage forms containing many units. Calcium alginate precipitates when sodium alginate solution is dropped into an aqueous calcium chloride solution, generating spherical beads with a diameter of around 2.5 mm. The beads are separated, freeze-dried for 24 hours at -40ºC, and then snap-frozen in liquid nitrogen. This creates a porous structure that is able to sustain a floating force for more than twelve hours.Over 5.5 hours was the extended residency length that the floating beads offered [28, 29].

D. Hollow Microspheres

By employing a simple solvent evaporation or solvent diffusion technique to produce hollow microspheres or micro balloons packed with medicine in their other polymer shelf, the GRT of the dosage form was increased. These systems are made from polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low methoxylated pectin, and other common polymers. The number of polymers, the plasticiser polymer ratio, and the formulation solvent are the three parameters that influence drug release and buoyancy from dosage forms. These small balloons were floated above the surface of an acidic dissolving liquid containing surfactant for almost 12 hours. Hollow microspheres are now thought to be among the most promising buoyant systems because they combine the advantages of multiple-unit systems with strong floating qualities [30, 31].

2. Muco/ Bio-adhesive System:

Orally given drugs can be more effectively absorbed at a specific location when gastroretentive dosage forms called bioadhesive systems are used. Bioadhesive polymeric compounds are used to achieve extended gastric residence duration and dosage form adhesion to stomach epithelial surface. Dosage forms with bioadhesive properties may be produced using several techniques, which are based on a simple mechanism in which the dosage form sticks to the mucous membrane surface. Polymeric polymers such chitosan, cholestyramine, sodium alginate, polyacrylic acid, hydroxypropyl methyl cellulose, sucralfate, tragacanth, dextrin, and polylactic acids are commonly used in bioadhesive applications. These polymeric materials do have certain limits, though, since some of them effectively produced bioadhesive characteristics, but it was challenging to maintain this adhesiveness due to the gastrointestinal tract's rapid mucus turnover rate [31, 32, 33].

3. Modified System:

These are non-disintegrating, geometric structures that are moulded from plastic elastomer or extruded from polyethylene blends. These forms can prolong the stomach retention, depending on the size, shape, and flexural modulus of the drug delivery system. [32]

4. High Density System:

These systems withstand the peristaltic motions of the stomach because the active drug molecule is retained in the rugae of the stomach. The density of the stomach contents is 1.004 gm/cm3, which is similar to that of water. Because these dosage forms comprise high-density pellets, they are resistant to the peristaltic motions of the stomach wall. The great density of the pellets, however, may cause them to sink to the bottom of the stomach and become lodged in the antrum's folds if the patient is erect. An estimated stomach content density of 2.5 gm/cm3 is sufficient to prolong the gastric stay. An effective development technique for these formulations is to combine drug-coated heavy core with innocuous substances including barium sulphate, iron powder, zinc oxide, and titanium oxide. After this point, these compounds raise the density of the dose form to 1.5–2.4 gm/cm3, which is about the same as the density of the contents of the stomach. [34, 35]

5. Magnetic System:

The fundamental concept underlying this approach to enhance the GRT is that a small internal magnet is included in the dosage form, and there is an additional magnet on the abdomen above the stomach site. The magnetic system seems to be working, although the requirement for precise placement of the external magnet could compromise patient compliance. On rabbits, the method makes use of bio adhesive granules containing ultra-fine ferrite. Nearly all of the granules remained in the same location after two hours, where they had been guided for the initial two minutes by an external magnet. [36, 37]

6. Swellable and Expandable System:

A dosage form can pass through gastric transit if it is bigger in the stomach than the pyloric sphincter. However, the dosage form must be consumed in tiny enough doses and neither when taken alone nor in conjunction with other medications, it can clog the stomach. Thus, these configurations are required to develop an expandable system that will extend GRT:

Three configurations are available:

The three forms of the medication are:

1. tiny for oral intake;
2. prolonged gastro retentive form; and

3. final small form that permits evacuation upon release of the medication from the device. Thus, the mechanical contractility of the stomach and the rigidity of a big dose form to withstand peristalsis work together to increase gastro-retention. Expandable and unfoldable systems have been studied and tried recently by researchers in an attempt to develop a functional GRDDS. Unfoldable systems are made of biodegradable polymers. These bioerodible polymers are compressed inside an elongated stomach capsule and exhibit a variety of geometric forms, including tetrahedron, ring, and planner membrane (4-label disc or 4-limbed cross form). Swellable systems are also retained in the GIT due to their mechanical properties. Typically, osmotically absorbed water causes swelling.

The extremely biodegradable and hydrolysable polymers that expandable systems must store can be difficult to store, the unfolding system's mechanical shape memory is relatively short, industrialisation is difficult, and the systems are not cost-effective. Once more, the long-term use of big, rigid, single-unit expandable drug delivery dosage forms may cause intestine adhesion, gastropathy, and temporary obstruction. [36, 37, 38]

Table 1: Drugs Used Commonly in Formulation of GRDDS [39, 40]

Dosage Forms	Drugs
Floating Microspheres	Aspirin, p-nitro aniline, Terfenadine, Tranilast, Griseofulvin, Ibuprofen.
Floating Tablets	Acetaminophen, Ampicillin, trihydrate, Atenolol, Captopril, Cinnerzine, Ciprofloxacin, Diltiazem, Amoxicillin, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, Prednisolone, Nimodipine, Theophylline, Verapamil, Acetylsalicylic acid, p Aminobenzoic acid (PABA), Chlorpheniramine maleate, Sotalol.
Floating Capsules	Diazepam, Misoprostol, Furosemide, L-DOPA and Benserazide, Nicardipine, Chlordiazepoxide HCl, Propranolol, Pepstatin.
Floating Granules	Diclofenac sodium, Prednisolone, Indomethacin.
Powders Films	Several basic drugs, Cinnerzine.

APPLICATION OF GRDDS:

1. Site Specific Drug Delivery Systems:

These systems are generally advantageous for drugs that are selectively absorbed from the stomach or the proximal region of the small intestine. A controlled, slow delivery of the medicine to the stomach reduces systemic exposure while yet supplying adequate local therapeutic dosages. This decreases the adverse effect that the drug has on blood flow. Furthermore, the extended stomach availability of a site-directed delivery method may reduce the frequency of doses. For instance, furosemide and riboflavin. [34]

2. Enhanced Bioavailability:

The bioavailability of noncontrolled release polymeric formulations is significantly reduced when riboflavin controlled release gastroretentive dosage forms are used instead. The amount of medication absorption is influenced by a multitude of concurrent activities in the GIT that are related to drug absorption and transit. [33]

3. Sustained Drug Delivery:

The gastrointestinal tract's GRT is a problem for formulations with oral controlled release. Because of their bulk density of less than 1, HBS systems can aid in situations where particles can float over the contents of the GI tract and remain in the stomach for prolonged periods of time. The systems cannot pass via the pyloric opening because to their size, which is really big. [35]

4. Minimized adverse activity at the colon:

Medication in HBS systems that is kept in the stomach reduces the amount of medication that gets to the colon. Consequently, medication usage that is considered undesirable in the colon may be prohibited. This pharmacodynamic aspect explains why beta lactam antibiotics have a gastroretentive dose form; these antibiotics are only absorbed from the small intestine, and their presence in the colon encourages the development of microorganism resistance. [38]

5. Absorption Enhancement:

Medication having limited bioavailability due to site-specific absorption from the upper gastrointestinal tract might be candidates for FDDS formulation, which would maximise absorption. [31]

6. Reduced fluctuations of drug concentration:

Following GRDF administration, blood drug concentrations decrease into a more narrow range related to immediate release dose formulations when taken continuously after controlled release. This reduces changes in the pharmacological action and may help prevent concentration-dependent adverse effects associated with peak concentrations. [35]

CONCLUSION:

More drug delivery systems will be created as our understanding of how GIT physiology affects drug delivery deepens, with the goal of optimising the administration of substances that exhibit regional variability in drug absorption. More gastro-retentive drug administration techniques will be created as delivery technologies advance in order to optimise the delivery of substances with extended half-lives, restricted bioavailability, and significant first pass metabolism. After a review of the literature, we came to the conclusion that, since the upper gastrointestinal tract is the only place where drugs can be absorbed, gastroretentive drug delivery maximises absorption and improves absolute bioavailability, which presents several potential advantages for drugs with low bioavailability. The gastroretentive medicine administration strategy maximises patient benefit and maximises patient compliance. With the growing efficacy of different pharmacotherapies, it seems sense to assume that GRDD technologies will be utilised more frequently in the future to deliver medications to the systemic circulation.

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