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Recent Overview on Gastroretentive Drug Delivery System

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ABSTRACT

The gastrointestinal barrier is an important site for gastroretentive drug delivery systems. The GIT is composed of a large amount of gastric mucus, which can replenish that which is lost during peristaltic contractions and the diluting of the stomach's contents. In order to achieve better therapeutic benefits, such as simplicity in administering doses, patient compliance, and formulation flexibility, oral controlled release drug delivery has lately attracted more attention in the pharmaceutical industry. The Gastroretentive Drug Delivery System (GRDDS) is a novel drug delivery method for oral drug administration. This system is based on the use of a bioadhesive agent that can control drug release in the stomach or intestine. It is characterized by the ability of the drug to release from a given dosage form in the gastrointestinal region. The gastrointestinal retention of oral dose forms is affected by several factors, such as food intake and type, caloric content and frequency of intake, posture, gender, and age. In this review, we will focus on the design and development of the gastroretentive drug delivery systems.

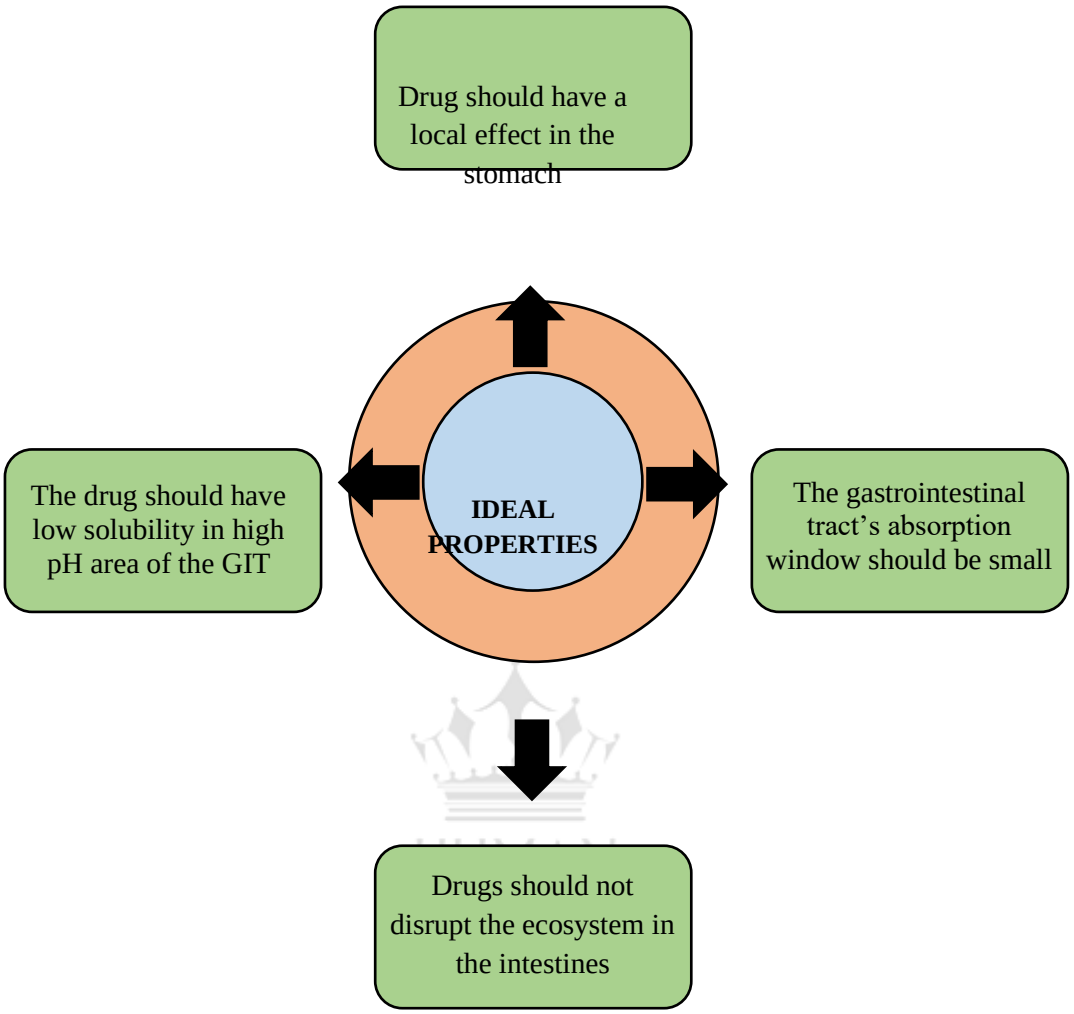
BACKGROUND

The easiest and most preferred way to administer any medication to the systemic circulation is by oral administration. In order to attain better therapeutic benefits, such as simplicity in administering doses, patient compliance, and formulation flexibility, oral controlled release drug delivery has lately attracted more attention in the pharmaceutical industry. Drugs with short half-lives and ease of gastrointestinal absorption exit the systemic circulation quickly[1]. Oral drug administration or delivery has historically been the most popular method of medicine delivery. There have been many oral medication delivery systems created in recent years. This review is also based on such oral drug delivery systems as controlled release drug delivery systems and gastroretentive drug delivery systems, which serve as drug reservoirs and release drugs in a regulated manner over a predetermined length of time (prolonged time)[2].

Gastroretentive Drug Delivery Systems are dosage forms that can be held in the stomach for an extended and predictable length of time. By constantly releasing the medication for an extended period prior to reaching its absorption site, the Gastroretentive Drug Release System can enhance the controlled delivery of drugs with an absorption window[3]. However, some rare drugs exhibit poor bioavailability as a result of inadequate absorption or gastrointestinal tract breakdown. Therefore, gastro retentive medication delivery systems are created to address this issue[4]. Gastroretentive Drug Delivery System are advantageous for such medications by enhancing their[5].

- Increases the solubility of medicines in environments with high pH levels. (e.g., weakly basic drugs like domperidone, papaverine)
- Bioavailability
- Long-term maintenance of therapeutic levels at the same level results in less variation in the therapeutic levels.
- Reduce drug wastage
- Therapeutics efficiency and
- Possibly reducing the dose

THE IDEAL PROPERTIES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS[2]



ADVANTAGES

- **Enhanced bioavailability:** When compared to the administration of non-gastroretentive drug delivery, the bioavailability of therapeutic drugs can be greatly increased, especially for those that are processed in the upper Gastrointestinal Tract. The amount of medication absorption is influenced by a number of distinct parameters that are connected to drug absorption and transit in the Gastrointestinal Tract[6].

- **Reduced fluctuation of drug concentrations:** As opposed to instant-release oral dosage forms, controlled-release gastro-retentive administration results in systemic drug concentrations within a smaller range. As a result, variations in a drug's effects are reduced,

and adverse effects that are concentration-dependent and linked to peak concentrations can be avoided.

- **Site-specific drug delivery:** Drug systemic exposure is reduced to a minimum or eliminated thanks to the regulated, gradual release of the medication in the gastroretentive dosage form, which offers appropriate local action at the sick site. The negative consequences of side effects are lessened by this site-specific medication administration. As a result, they are helpful for treating conditions that affect the stomach and small intestine (e.g., eradication of *Helicobacter pylori*).

- **Improved selectivity in receptor activation:** The significant element that affects the strength of the pharmacologic response and reduces fluctuations in blood drug concentrations is the controlled release mode of drug delivery for gastroretentive systems (i.e., between peak and trough). The impact of this property, however, varies greatly depending on the shape of the pharmacodynamic profile and the location of the particular range of concentrations on the curve of this profile due to the pronounced non-linear relationship between drug concentration and pharmacologic effect (i.e., pharmacodynamics). Drugs that can activate distinct receptors at different doses can be used to provide some selectivity in the induced pharmacological effects by minimizing variations in drug concentration.

- **Sustained drug delivery:** As mentioned earlier, the short gastric residence time available for absorption frequently restricts the absorption of drugs from oral controlled-release dosage forms. Drugs can be released from dosage forms in a continuous and prolonged manner using gastroretentive dosage forms. However, dose forms of the hydrodynamically balanced system, bioadhesive, or expandable systems type can stay in the stomach for several hours and hence greatly extend the gastric residence time of a variety of medications. Sustained release may cause flip-flop pharmacokinetics for medications with a short half-life and allow for less frequent dosages with better patient compliance[7].

DISADVANTAGES

The mucoadhesive system has limitations related to soluble mucus, a thick mucus layer, and rapid mucus layer turnover.

- Several variables, including meal presence, pH, and stomach motility, might impact gastric retention. Since these variables vary, buoyancy cannot be anticipated.

- Before the swelling formulation reaches the stomach, it may swell in the body.
- Hydrogel-based swelling systems need to swell for a longer period of time.
- These aren't the right choices for medications that have stomach stability or solubility issues.
- One drawback of the floating system is that it needs a lot of fluid in the stomach to function properly and absorb nutrients[2].

ANATOMY AND PHYSIOLOGY OF STOMACH

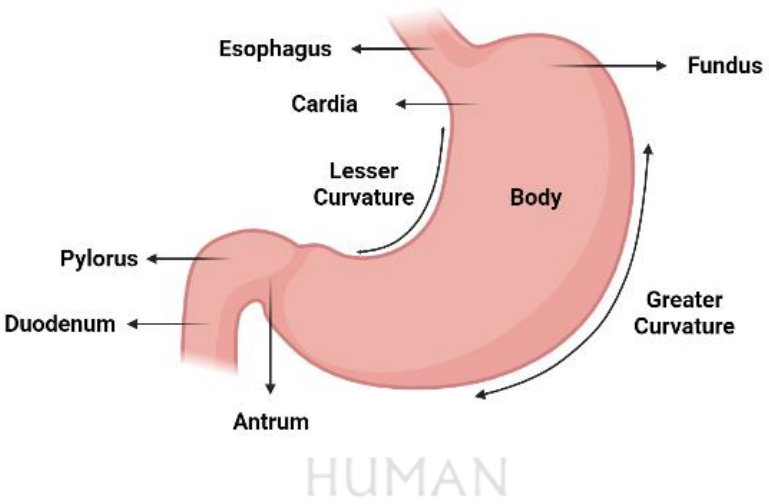


Fig. 1 Anatomy and Physiology of Stomach

The whole gastrointestinal tract, which begins at the end of the buccal cavity, is made up of the esophagus, stomach, and small intestine[8].

Oesophagus: The digestive system's esophagus, previously spelled as the esophagus and connecting the throat to the stomach, is a tubular, elongated organ[9].

Stomach Overview: The stomach is a "J" shaped expansion of the gastrointestinal system that is situated immediately under the diaphragm in the epigastric, umbilic, and left hypochondria areas of the abdomen. The stomach (the first part of the small intestine) connects the duodenum (the first part of the small intestine) and the esophagus.

Cardia: The cardia encircles the stomach's superior entrance. The area of the stomach called the cardia surrounds the cardiac orifice (the opening of the esophagus in the stomach), also known as the cardio esophageal junction[10].

Fundus: The area of the stomach that extends above the gastroesophageal junction is known as the fundus (to the left and above the cardiac orifice)[11]. The fundus relaxes its muscular fibers to compensate for the volume gain that occurs after eating. Additionally, it consistently pushes the gastric contents toward the distal stomach by applying pressure on them[1].

Body: The major central region of the stomach is known as the body or corpus[12].

Pylorus: The pylorus regulates the flow between the stomach, which serves as a reservoir for mechanical and chemical digestion, and the intestine, which serves as a conduit for nutritional absorption. In response to physiological requirements, the pylorus modifies stomach outflow resistance[10].

Gastrointestinal Utility and Emptying of Food:

Although stomach emptying happens both when you are fasting and when you're eating, there are significant differences in the two states' patterns of motility. An interdigestive series of electrical events occur during the fasting state and cycle through the stomach and intestine every two to three hours. Wilson and Washington divide the migrating myeloelectric cycle (MMC), also known as the interdigestive myeloelectric cycle, into four successive phases[7].

- Phase I (basal phase), lasts between 40 and 60 minutes and is characterized by a lack of secretory, electrical, and contractile activity.
- Phase II (Preburst phase) lasts for 40 to 60 minutes and is characterized by sporadic contractions and action potentials. The strength and frequency steadily increase as the phase goes on as well.
- Phase III (the burst phase) lasts for 4 to 6 minutes and is characterized by brief bursts of intense, voluminous, regular contractions known as "housekeeper waves" that sweep off undigested food.
- Phase IV, the interphase between phases III and I of two successive cycles, lasts 0 to 5 minutes.

Following a meal, the pattern of contractions switches from a fasting condition to a fed one. In phase II of the fasting state, constant concentrations are present in what is known as the digestive motility pattern. These contractions lead to a reduction in the size of food particles

(> 1 mm), which are then driven in suspension form into the pylorus. MMC begins later in the fed condition, slowing stomach emptying rate[13].

FACTORS INFLUENCING GASTRORETENTIVE DRUG DELIVERY SYSTEM

Density, size, and shape of the dosage form, food intake and type, caloric content and frequency of intake, posture, gender, and age are some of the crucial factors impacting the gastrointestinal retention of oral dose forms.

- **Density of dosage forms:** Gastric Residence Time is a function of dosage-form buoyancy, which is reliant on dosage-form density. While high-density systems sink to the bottom of the stomach, dosage forms with a density lower than the gastric contents might float in the gastric fluids and cause gastro-retention. The dosing system may be separated from the pylorus in either location. To demonstrate floating properties, a density of less than 1.0 g/cm3 is needed[6].

- **Effect of gender, posture and age**: In general, females empty their stomachs more quickly than males. Individuals in an upright, ambulatory, or supine condition do not significantly differ in their mean gastric residence time as a result of posture. The rate of stomach emptying is slower in older people (over 70 years old)[14].

- **Shape and size of the dosage form**: Designing indigestible, single-unit solid dosage forms require consideration of the shape and size of the dosage forms. The gastric residence time will typically increase with dosage form size since bigger dosage forms will take longer to enter the gut after passing through the pyloric antrum[15]. When compared to dosage forms with a 9.9 mm diameter, those with a diameter of more than 7.5 mm have a longer stomach residence period. Devices having a flexural modulus of 48 and 22.5-kilo pounds/inch[6], respectively, are said to have a higher gastric residence time (90%–100% at 24 hours) than those with other forms[7].

- **Food intake and its nature**: Food intake has a significant impact on the gastro retention of dose forms, as does food viscosity and volume, caloric content, and frequency of feeding. The gastric residence time of the dosage form is often improved by the presence of food in the gastrointestinal tract, and as a result, the medication absorption rises by allowing it to remain at the absorption site for a longer amount of time. A meal with a high protein and fat content can extend gastric residence time by 4 to 10 hours. Increased caloric value and acidity, once again, delay GET, which might enhance the gastro retention of dose forms[16].

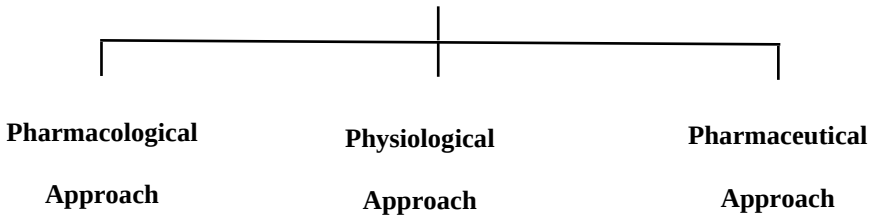
Due to the reduced frequency of MMC, gastric residence time might rise by more than 400 minutes when many meals are consumed instead of just one.

Again, factors such as sleep, body mass index (BMI), physical activity, and diseased states of the person (such as diabetes, gastrointestinal diseases, and Chron's disease), as well as the administration of medications with an impact on gastrointestinal transit time, such as atropine, propantheline, opiates like codeine, and prokinetic drugs like metclopramide and cisapride, can alter the gastro retention of oral dosage forms[4].

STRATEGIES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM[17]

Strategies for delaying drug transit through

Gastroretentive Drug Delivery System



Pharmacological Approach: It entails administering a medicine concurrently or incorporating it into the dosing form. This medication slows gastric emptying. Antimuscarinics, such as propantheline, are examples.

Physiological Approach: By stimulating the duodenal or jejunal receptors, natural substances or fat derivatives like triethanolamine myristate are used to delay stomach emptying.

Pharmaceutical Approach: The first two methods are not used because of toxicity issues. The different pharmaceutical methods include:

TYPES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

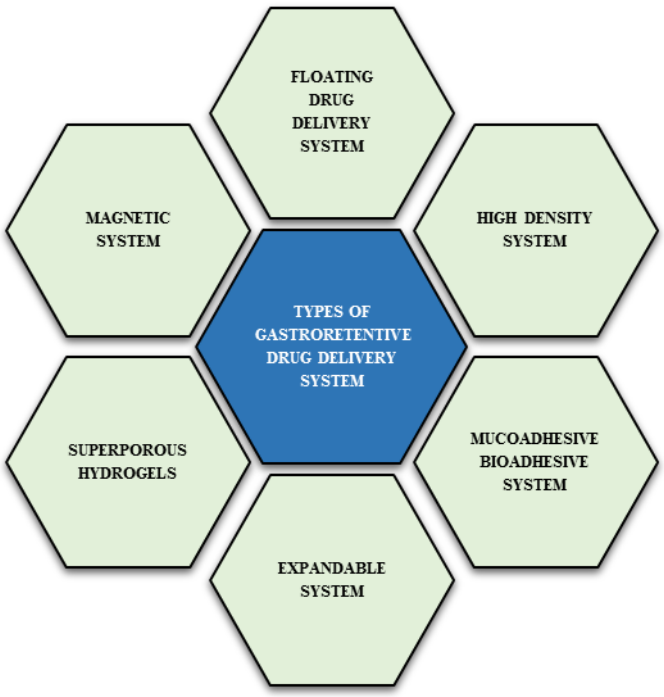
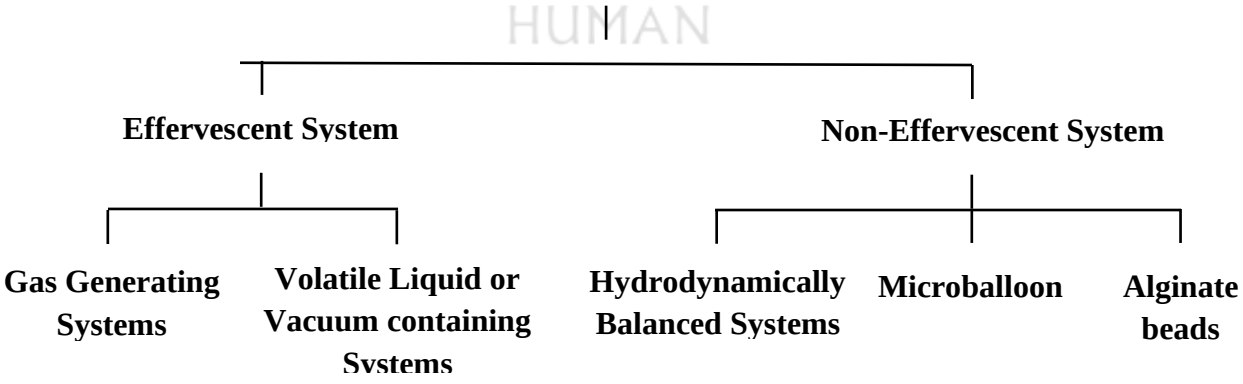


Fig. 2 Types of Gastroretentive Drug Delivery System

I. Floating drug delivery systems (FDDS)

Floating Drug Delivery System



Promising methods for boosting medication bioavailability using absorption windows in the upper small intestine include drug delivery devices that float right away upon contact with stomach juices. Since floating drug delivery systems have a lower bulk density than gastric fluids, they float in the stomach without slowing down the rate at which the stomach empties, and they are discharged from the body at a gradual, controlled rate. The stomach's residual system is emptied once the medication has been released. As a result, the gastric residence time is elevated, and the variation in plasma drug concentration is better managed[18]. To maintain the dosage form consistently buoyant on the surface of the meal, however, a certain

amount of floating force (F) is also necessary for addition to the minimal stomach content necessary to allow the appropriate attainment of the buoyancy retention principle[19]. The principal specifications for floating medication delivery systems are[17]:

- It must keep its specific gravity (1.004–1.01 g/cm3) below that of the stomach contents.
- A gel barrier that is cohesive is required.
- It should gradually discharge its contents to act as a reservoir.

Incorporating low-density elements, such as fatty substances or oils, foam powder, or hollow chambers[20], or trapping air can also contribute to the inherent low density[21,22]. Accurate control of the ensuing drug release patterns might be effectively integrated with the good floating behavior of these devices. Single-unit floating dosage forms are known to have issues including adhering to one another or being clogged in the GIT, which can cause stomach discomfort. Multiple-unit floating systems, however, would be a more appealing option because they have been demonstrated to decrease intra- and inter-subject drug availability as well as the likelihood of dosage dumping[23]. Two very different technologies, effervescent and non-effervescent, are based on the process of buoyancy[24].

A. Effervescent systems: To achieve floatability, effervescent systems use gas-producing agents (such as sodium bicarbonate, citric acid, or tartaric acid). Carbon dioxide is released from these drug delivery systems after oral administration in the GIT, which lowers the system's density and causes it to float on the stomach fluid[17]. Citric acid and sodium bicarbonate should be combined in a ratio of 0.76:1 for gas production, according to research[5,19]. Utilizing matrices made with swellable polymers such as methocel, hydroxypropyl methylcellulose (HPMC), and chitosan[19] can also provide buoyancy. The integration of the matrix's liquid-containing part yields gas that evaporates at body temperature as an alternative[25]. These effervescent systems can also be divided into systems that generate gas and systems that handle volatile liquids and vacuum.

1) Gas generating systems:

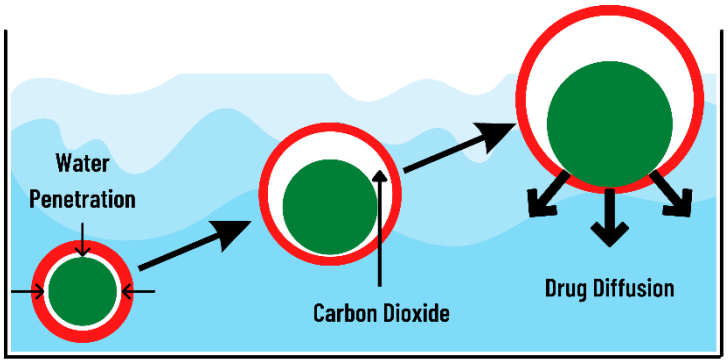


Fig. 3 Gas Generating System

Intragastric single-layered floating tablets: They are created by thoroughly combining the medication candidates and carbon dioxide-producing elements in the tablet matrix[26]. These create buoyancy in the stomach by having a bulk density that is lower than the gastric content, slowing the gastric emptying rate for an extended length of time. The medicine is continuously and at the desired rate, released from the matrix tablet. Even after the drug release has been completed, the stomach must be cleared of any leftover drugs.

Intragastric bi-layered floating tablets: Intragastric bi-layered floating tablets can be made by compacting one hydrocolloid with a sustained release layer and an instant release layer[27].

Multiple-unit type of floating pills: It has been designed to produce carbon dioxide gas in multiple-unit floating pills[28]. The technique comprises multiple layers around sustained release tablets in the form of seeds. An effervescent layer with tartaric acid and sodium bicarbonate made up the inner layer. A membrane layer that could swell made up the outer layer. Moreover, to prevent direct contact between these two gas-generating components, the effervescent layer was split into two sublayers. The inner sublayer of the layer contained sodium bicarbonate, whereas the outer layer contained tartaric acid. The system immediately sank into the solution when submerged in a buffer system at 37°C and formed bloated pills, similar to balloons (density 1 gm/ml), which float because they have a lower density. This decreased density is a result of generation and entrapment of carbon dioxide within this system.

2) Volatile Liquid or Vacuum Containing Systems:

Intra gastric osmotically controlled floating delivery systems: Two compartments a drug reservoir compartment and an osmotically active compartment—make up the osmotic pressure controlled floating devices. An impermeable to vapor and liquid pressure-responsive collapsible bag encloses the medication reservoir compartment. Water from the gastric fluid is continually absorbed into the osmotically active compartment of the stomach through the semipermeable membrane, dissolving the osmotically component. Following the creation of the osmotic pressure, the collapsible bag is forced to contract, which causes the drug reservoir compartment to release drug candidates in the form of the solution via the delivery hole. A bio-erodible plug that erodes after a certain amount of time deflates the floating support is also built into the design of the support. The stomach is subsequently emptied of the medication delivery mechanism[17].

Gas-filled floating delivery systems: A gas-filled floating delivery system is defined as the incorporation of a gas-filled flotation chamber, which may be vacuum-filled or filled with air or a safe gas and houses a drug reservoir[19], into a microporous component. The top and bottom walls have holes or apertures through which the stomach fluid can pass to dissolve the medicine. The other two walls that meet the fluid are sealed, leaving the drug undissolved within.

B. Non-effervescent systems: non-effervescent floating drug delivery systems are often made from hydrocolloids of the cellulose type that form gels or are highly swellable, polysaccharides, or matrix-forming polymers like carbopol, hydroxypropyl methylcellulose, sodium alginate, chitosan, etc. The following sub-types can be added to these systems:

1) Hydrodynamically Balanced Systems (HBS):

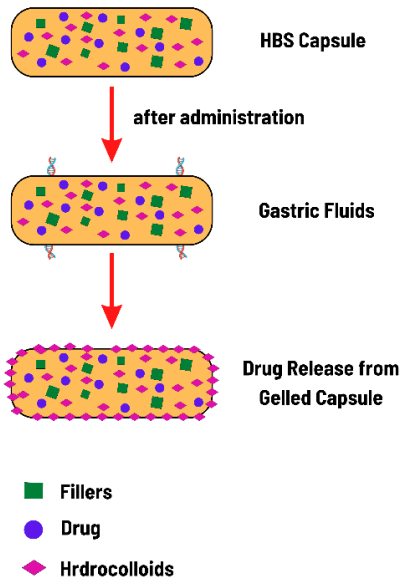


Fig. 4 Mechanism of Hydrodynamically Balanced Systems as FDDS

Sheth and Tossounian[29] coined the phrase "hydrodynamically balanced systems." hydrodynamically balanced systems have grown in significance in recent years as a means of enhancing medication absorption, particularly for substances that are absorbed from the stomach and small intestine or for substances like weak bases that dissolve more readily in the stomach's acidic environment[30]. These systems include medications containing hydrocolloids that gel and are designed to float on stomach contents. These are single-unit dose forms that incorporate one or more hydrophilic polymers that can gel. These systems are frequently developed using excipients such as HPMC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans, or alginic acid[31]. Typically, the polymer and medications are supplied together in a hydrodynamically balanced system capsule. The capsule shell dissolves, and the drug-hydrocolloid combination expands to form a gelatinous barrier when the drug-hydrocolloid mixture in the capsule comes into contact with stomach fluid. Due to the continual surface erosion, which permits water to penetrate to the interior layers, preserving surface hydration and buoyancy, the dose of Form 41 provides buoyancy in gastric juice for a prolonged duration. Fatty excipients are used to create low-density formulations that reduce erosion. Madopar LP was promoted in the 1980s[32] based on the technology. The balance of drug loading and the impact of the polymer on the release profile

are key factors in effective medication delivery. Numerous methods have been tested and researched to increase the efficiency of the floating hydrodynamically balanced system.

2) Microballoons (Hollow microspheres):

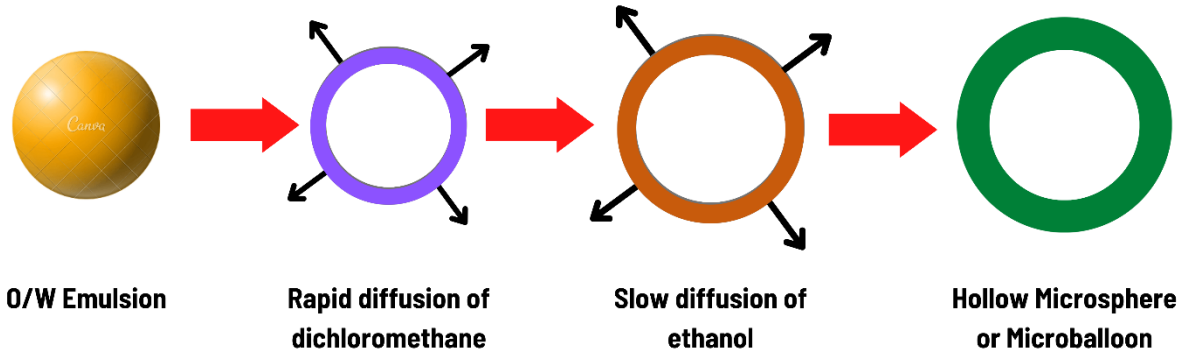


Fig. 5 Microballoons

Simple solvent evaporation or solvent diffusion/evaporation was used to construct hollow inner cores in micro balloons (hollow microspheres) that were then loaded with medications in their other polymer shelf[33]. This technique increases the dosage form's stomach residence period. Polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, and low methoxylated pectin are examples of common polymers utilized to build these systems. In the same organic solvent where the polymer is dissolved or dispersed, the drug is also dissolved or dispersed, depending on the drug's form. A stable oil-in-water emulsion is created by emulsifying the drug solution into an aqueous phase that contains polymers. The organic solvent is then evaporated either by raising the temperature under pressure or by constant stirring. In order to create hollow microspheres, the solvent is removed, which causes polymer to precipitate at the oil/water interface of the droplets. The amount of polymers used, the plasticizer-to-polymer ratio, and the formulation solvent all have an impact on buoyancy and drug release from dosage forms. For more than 12 hours, the microballoons floated constantly over the top of an acidic dissolving medium that contained surfactant[6]. Because they combine the benefits of a multiple-unit system with superior floating, hollow microspheres are now regarded as one of the most promising buoyant systems.

3) Alginate beads: A recent multiple-unit floating system based on cross-linked beads was created by Talukdar and Fassihi[34]. Ca2+, low-methoxylated pectin (anionic polysaccharide), or Ca2+, low-methoxylated pectin, and sodium alginate were used to make them. In this

method, calcium alginate is typically precipitated by dropping a sodium alginate solution into an aqueous calcium chloride solution. In a different study, freeze-dried calcium alginate was used to create multiple-unit floating alginate beads using calcium chloride as a cross-linking agent and sodium alginate as the polymer[23]. Air convection and freeze drying are used to separate and dry these beads, creating a porous structure that can sustain a floating force for more than 12 hours. These beads extend the stomach residence period by more than 5.5 hours.

II. High-Density (Sinking) System

For high-density systems that are tiny enough to be retained in the folds of the stomach body at the pyloric region, which is a section of the organ with lowest position in an upright posture, sedimentation has been used as a retention mechanism. This method calls for the development of dose forms whose density must be greater than that of the typical contents of the stomach (1.004 gm/cm3). These formulations are made by mixing the medicine with inert substances such as iron powder, barium sulphate, zinc oxide, titanium oxide, etc. or coating the drug on a dense core[35]. The materials can raise density by 1.5–2.4 gm/cm3 or more. For the stomach residence duration to be significantly prolonged, a density of close to 2.5 gm/cm3 appears to be required[36]. However, this system's usefulness in humans is constrained.

III. Expandable, Unfoldable and Swellable System:

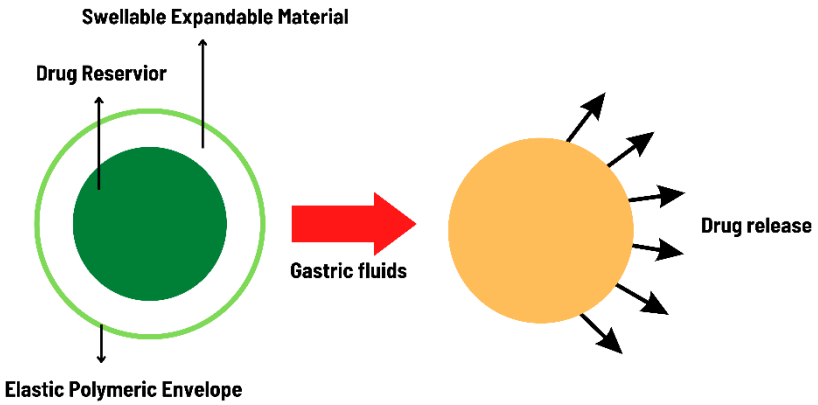


Fig. 6 Drug Release from Swellable Systems

A pharmaceutical dosage form's ability to withstand stomach acid can be improved by becoming larger than the pylorus' diameter (even in its widest state during a housekeeper wave). The gastroretentive properties of a dosage form will be achievable for a considerable amount of time if it can grow larger than the pylorus. If not, the dose form will be discharged

through the pylorus, thus it should be reached in a timely manner. Consequently, configurations needed to create an extendable system to increase gastric residency duration are:[37,38]

- a compact shape for oral ingestion
- an extended form for the stomach
- a compact form for after the medicine has been released from the device.

They should also be strong enough to endure the stomach's mechanical contraction and peristalsis. However, the cutoff size cannot be precisely calculated due to large individual variations. Recently, efforts have been made to produce effective gastroretentive medication delivery using unfoldable and swellable devices. Biodegradable polymers are used to create unfoldable systems. The idea is to create a carrier that stretches in the stomach, like a capsule. Different geometric shapes, such as a tetrahedron, ring, or planar membrane (4-lobed, disc, or 4-limbed cross form)[39] of bio-erodible polymer compacted inside a capsule, were proposed by Caldwell et al. A gastroretentive administration of levodopa based on unfolding polymer membranes that combines expanded dimensions (5 cm X 2.5 cm) with high stiffness was disclosed by Klausner et al[40]. It is compressed into a large gelatin capsule (00 or 000). According to in vitro studies, these delivery methods unfolded within 15 minutes. In 67% of human subjects, levodopa-containing drug delivery devices were kept in the stomach for 5 hours[38]. These systems' large size and low stiffness prevent them from being retained in the stomach, which can lead to gastropathy and temporary blockage. Therefore, another important factor in designing a gastroretentive delivery is the stiffness of these systems. Swellable systems are also kept in the GIT because of their mechanical characteristics. Since the dosage form is small enough to be taken by the stomach juice, the swelling is often caused by the osmotic absorption of water. In general, these size-increasing drug delivery systems may pose the risk of permanent stomach retention that may have life-threatening consequences when administered more than once. They are also not economical. The independence of these systems' performances from the stomach's filling status is a key benefit of their size-increasing abilities.

IV. Bioadhesive or Mucoadhesive Drug Delivery Systems

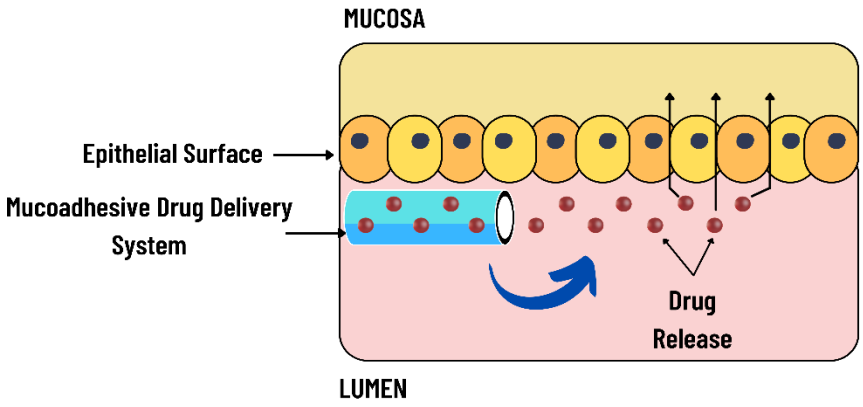


Fig. 7 Mucoadhesive Drug Delivery System

To increase medication absorption at a specific place, bioadhesive drug delivery systems are utilized to localize a delivery device inside the human body. This method uses a variety of bioadhesive polymers that may stick to the stomach's epithelial surface[41]. As a result, they lengthen the dose forms' stay in the stomach. The fundamental idea behind micro adhesion is that numerous mechanisms might cause a dosage form to adhere to the mucosal surface. These are the mechanisms[42]:

a) According to the absorption theory, bioadhesion is caused by secondary forces such as hydrogen bonds and Vander Waal forces.

b) The capacity of bioadhesive polymers to spread and form close contact with the mucosal layers is the foundation of the wetting hypothesis, which is based on this property.

c) The electron theory, postulates that the bioadhesive substance and the glycoprotein mucin network are held together by attractive electrostatic forces.

d) The diffusion theory, which suggests physical intertwining of mucin strands with flexible polymer chains or an interpenetration of mucin strands into the porous structure of the polymer substrate.

The capacity of dose forms to withstand the powerful population pressures of the stomach wall is typically not imparted through gastric mucoadhesion, which is typically not strong enough. The ability of mucoadhesion to serve as a gastroretentive force appears to be constrained by the gastric mucosa's ongoing synthesis of mucus to replenish that which is lost

during peristaltic contractions and the diluting of the stomach's contents. The rapid turnover of gastric mucus in the GIT and accompanying short retention durations provide the biggest problem for bioadhesive drug delivery methods. Additionally, it is highly challenging to use bioadhesive polymers to selectively target stomach mucus. Materials commonly used for bioadhesion include polyacrylic acid, polylactic acids, cholestyramine, HPMC, sodium CMC, chitosan, sodium alginate, sucralfate, tragacanth, dextrin, gliadin, lectin, and others.

V. Super Porous Hydrogel Systems

With pores that range in size from 10 nm to 10 m, the typical hydrogel absorption window is a very slow process, and it may take many hours to achieve an equilibrium condition at which parameter evacuation of the dosage form may happen[32]. Super porous hydrogels expand to equilibrium size in less than a minute due to fast water absorption via capillary wetting through multiple interconnected open holes with an average pore size of less than 100 m[43].

VI. Magnetic Systems

The basic idea behind this strategy to lengthen the gastric residence period is that the dosage form has a tiny internal magnet, and a magnet is applied to the abdomen above the location of the stomach. Although the magnetic method appears to work, the external magnet must be placed with enough accuracy to risk patient cooperation[44].

CHARACTERIZATION

Evaluation of Floating Drug Delivery System[45]:

1. Thickness: Thickness is primarily influenced by the filling of the die, the physical characteristics of the material being crushed, and the compression force. In every batch of tablets, there will inevitably be a little difference in thickness. To the unaided eye, though, it should not be visible. Vernier calipers were used to determine the thickness and diameter. Within 5% of the normal value, tablet thickness should be maintained.

2. Hardness: To endure the mechanical shocks of handling during manufacturing, packing, and shipping, tablets must have a specific degree of strength or hardness. During production, ten tablets were chosen at random from each formulation and tested for hardness using a Monsanto hardness tester. The measurement is in kg/cm^2. Typically, oral tablets range in hardness from 4 to 10 kg/cm^2.

3. Friability: The Roche friabilator is typically used to determine friability, a test that is closely linked to tablet hardness. Ten tablets were weighed and put into the device, where they were subjected to rolling shocks and repeated shocks as they dropped 6 inches with each spin. The tablets are then dedusted, reweighed, and their new weights are compared with the initial weight after four minutes of this treatment or 100 revolutions. A weight loss of less than 1% is regarded as acceptable.

$$F\ (\%) = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{initial weight}} \times 10$$

4. Weight Variation Test: Twenty pills were chosen at random and each one was weighed separately for the weight variation test. The weight of each pill was compared to the average weight. If no more than two tablets fall outside the % restriction and no tablet deviates by more than twice the percentage limit, the tablets pass the USP test.

5. Drug Content Uniformity: The test is used to make sure that every tablet has the right quantity of medicine and that there is little fluctuation in the drug content of tablets within a batch. The mortar was used to weigh and smash ten pills. To achieve a concentration of 250 g/ml, the powder equal to 20 mg of medication was dissolved in 6.8 pH buffer and volume was increased to 100 ml. A concentration of 50 g/ml was obtained by diluting 1 ml of this solution to 10 ml. The drug concentration was ascertained from the standard calibration curve by utilizing the regression equation and the UV Visible spectrophotometer to measure the absorbance of the produced solution.

$$\text{Concentration } (\mu g/ml) = \frac{\text{Absorbance} - \text{Intercept}}{\text{Slope}}$$

Drug Content (mg) = Concentration x Dilution Factor

$$\%\ \text{Drug Content} = \frac{\text{Drug Content}}{\text{Labelled claim}} \times 100$$

6. In-Vitro Buoyancy Studies: Floating lag time (FLT) or buoyancy lag time is the amount of time a tablet has to take to emerge from the surface after being submerged in a solution containing 100 ml of buffer with a pH of 6.8 (BLT). Additionally, the total floating time refers to the time tablet that continuously floats on the medium's surface (TFT).

7. In-vitro Dissolution Studies:

- **Dissolution for Immediate Release Tablets:** Using USP Dissolution Apparatus II, the drug release rate from Immediate Release Tablets was calculated (paddle). At 37.5°0.5°C and 50 rpm, the dissolving test was conducted using 900ml of buffer solution with a pH of 6.8. At intervals of 5, 10, 15, 20, 30, 40, 50, and 60 minutes, a sample (5ml) of the solution was removed from the dissolving equipment and replaced with new dissolution media. The samples were examined for absorbance at 236 nm wavelength.

- **In Vitro Drug Release Studies of Bilayer Tablets**: Bilayer tablets were the subject of in vitro drug release tests utilizing a USP dissolving equipment type II in 900 mL of buffer solution with a pH of 6.8 for up to 720 minutes. Samples were taken on a regular basis. At regular intervals, samples were taken and filtered. Filtered samples from the collection were examined in a UV spectrophotometer.

Evaluation of Swelling and Mucoadhesive Drug Delivery System[42]:

1. Swelling Study: Tablets were individually weighed and placed in a petri dish containing 50 ml of 0.1 N HCl. The petri dishes were placed in an incubator set to 37±0.5 o C. The tablets were removed from the petri plate at regular 1-hour intervals until 4 hours, reweighed, and the percentage swelling index was calculated using the formula:

$$\text{Water Uptake (WU)} = \frac{W_t - W_o}{W_o} \text{ x } 100$$

Where,

W_t: The weight of the tablet at time t

W_o: Tablet weight before immersion

2. Ex Vivo Mucoadhesion Strength: The modified balance method was employed to assess the proclivity of mucoadhesive material to adhere to the mucosal surface. Sheep stomach mucosa was cleaned and isolated from the slaughterhouse. The membrane was attached to Teflon block A for around 15 mm, with the mucus surface exposed on the upper side. By adding water to the beaker on the right-hand pan, the same amount of weight was increased until the tablet detached from the membrane.

3. Ex Vivo Mucoadhesion Time: Detached fresh sheep stomach mucosa was tied on a glass slide; either every tablet was wetted with 1 drop of 0.1 N HCl and superimposed on the sheep stomach mucosa for 30 seconds using a fingertip. Considering that only the mucoadhesive property was evaluated, the glass slide was placed into the beaker. Tablet adhesion was monitored for 12 hours in 200 ml of 0.1 N HCl at 37°C or 1°C with a slow stirring speed of 50 rpm to simulate the stomach environment. The mucoadhesion time was measured in minutes per second as the tablet detached from the sheep's stomach mucosa.

Evaluation of Super Porous Hydrogels[46]

1. Measurement of Density

The solvent displacement method was employed to determine density. The apparent density of super porous hydrogels was shown by measuring the density of dried super porous hydrogels. To find the item's mass, a piece of super porous hydrogels was removed and weighed. The volume of the polymer was determined by increasing the volume of hexane in a graduated cylinder after a piece of the polymer was submerged there. The density was determined using:

$$\text{Density} = \frac{\text{Mass (Super Porous Hydrogel)}}{\text{Volume (Super Porous Hydrogel)}}$$

2. Measurement of Porosity

The dried Super Porous Hydrogel was immersed in hexane for a whole night before being weighed. Excess hexane was blotted off the surface. The porosity was determined using:

$$\text{Porosity} = \frac{V_p}{T_T}$$

Where, $V_p = V_T - V_{SPHC}$

V_p is the pore volume of Super Porous Hydrogel

V_T is the total volume of Super Porous Hydrogel

Since SPHC is cylindrical in shape, its dimensions can be used to calculate its total volume.

V_T was calculated as $V_T = \pi r^2 h$

3. Determination of Void Fraction

Super porous hydrogels were submerged in HCl solution (pH 1.2) up to equilibrium swelling in order to measure the void fraction within them. Using this information, sample volumes and the dimensions of the swollen hydrogels were calculated. The quantity of buffer absorbed into the hydrogels is determined by the weight difference between the swollen and dry hydrogels, which also reveals the total volume of holes in the hydrogels. The following equation was used to get the void fraction.

$$\text{Void Fraction} = \frac{\text{Dimensional volume of the hydrogel}}{\text{Total volume of pores}}$$

4. Determination of Swelling Ratio

Each experiment started with the dried gel being measured gravimetrically to determine Md, and it was then submerged in extra medium to cause swelling. The hydrogel was taken out of the solution at different times, weighed, and the excess hexane on the surface was wiped to determine the MS. A graph showing the swelling ratio versus time was created (min).

As shown below, the equilibrium-swelling ratio can be computed.

$$\text{Equilibrium Swelling Ratio (Q)} = \frac{(M_s - M_d)}{M_d}$$

Where,

M_s is the mass in the swollen state.

M_d is the mass in the dried state.

APPLICATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Floating drug delivery has several applications for drugs with low bioavailability due to the limited absorption site in the upper gastrointestinal tract. It maintains the dosage form at the site of absorption, boosting bioavailability. These are summarized below:

- **Sustained Drug Delivery:** HBS systems can stay in the stomach for extended periods of time enabling the drug to be released over time. These systems can thus overcome the problem of short gastric residence time encountered with an oral CR formulation. Since these

systems have a bulk density of 1, they can float on the gastric contents. These systems are relatively large, and passage from the pyloric opening is not permitted.

- **Site-specific drug delivery:** These systems are especially beneficial for drugs that are absorbed primarily from the stomach or the proximal part of the small intestine, such as riboflavin and furosemide.

- **Absorption Enhancement:** Drugs with low bioavailability due to site-specific absorption from the upper gastrointestinal tract are potential candidates for formulation as floating drug delivery systems, maximizing absorption.

- **Localized Action:** FDDS also provides an excellent drug delivery system for the eradication of H. pylori, the causative agent of chronic gastritis and peptic ulcers. The treatment necessitates maintaining high drug concentrations at the site of infection, which is within the gastric mucosa. Because of their floating ability, these dosage forms can be retained in the gastric region for an extended period, enabling the drug to be targeted.

GASTRORETENTIVE MARKETED PRODUCTS

Serial No.	**Company Name**	**Brand Name**	**Active Ingredients**
1.	Cadila Pharmaceuticals Limited	Aciloc RD	Omeprazole
2.	Macleods Pharmaceuticals Limited	Rabemac DSR	Rabeprazole
3.	Micro Labs Limited	Esofag D	Esomeprazole
4.	Alkem Laboratories Limited	Pan 40	Pantoprazole
5.	J B Chemicals and Pharmaceuticals	Rantac 150	Ranitidine
6.	Aristo Pharmaceuticals	Fadine	Famotidine
7.	Takeda Pharmaceuticals	Prevacid	Lansoprazole
8.	Cipla Limited	Spasmonil	Dicyclomine
9.	Abbott Healthcare Private Limited	Flagyl 400	Metronidazole
10.	FDC	Drofem	Drotavarine

CONCLUSION

The gastro retention drug delivery system is a suitable starting point for oral drug administration since it offers a number of advantages that might improve bioavailability, absorption, etc. GRDDS strategies improve the drug's bioavailability. The solubility and absorption of oral given dose forms can be managed using GRDDS. The major methods used for gastroretentive drug administration are floating, bioadhesive, swelling, magnetic, and high-density systems. These technologies offer the medication in an absorbable form in absorption-optimal locations while also allowing for regulated drug release. Each of these medication delivery methods has benefits and downsides of its own. This may increase a drug's bioavailability if it has site-specific absorption. The different literature reviews have led us to the conclusion that GRDDS has a particular application in the pharmaceutical industry. The market for GRDDS products would be large with higher patient compliance.

FUTURE POTENTIAL[7]

In the last two decades, controlling medication release patterns has been a top priority for pharmaceutical research and development. This might lead to the introduction of new drugs with novel therapeutic potential and significant patient advantages. Numerous innovative goods utilizing gastroretentive medication delivery techniques are predicted to increase this likelihood. The following ideas may be the focus of more research:

- Utilizing gastroretentive technology, several anti-reflux formulations are being developed.
- Examining the use of several medications to eradicate *Helicobacter pylori.*
- Novel polymers are created and synthesized in accordance with clinical and pharmacological requirements.
- To create bioadhesive medication delivery systems for better gastrointestinal retention, innovative mucoadhesive agents must be designed and synthesized. employing diverse natural mucoadhesive substances to create unique mucoadhesive delivery systems based on clinical and pharmacological needs.
- Design of a variety of gastroretentive drug delivery systems, each with a restricted gastric residence time, for usage in accordance with clinical requirements, such as dose and illness severity.

- The comparative effectiveness of fed and fasted states' gastroretentive medication delivery methods.
- Design and development of drug delivery devices for Parkinson's disease treatments that are gastroretentive.
- A more thorough investigation than earlier research on the effects of different geometric forms.
- The minimum cut-off size, over which dosage forms are kept in the GIT for a long time.
- A useful approach for the treatment of gastric and duodenal malignancies is the design and development of gastroretentive medication delivery devices.

ETHCS APPROVAL AND CONSENT TO PARTICIPATE

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COMPETING INTEREST

Not Applicable

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AUTHORS CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

All the authors confirm that there is no conflict of interest.

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REFERENCES

(1) Mehetre, G.; Thenge, R.; Cheke, R.; Shine, S. *NEW CONCEPTS IN NOVEL DRUG DELIVERY SYSTEMS*. Pee Vee Publications. https://www.amazon.in/CONCEPTS-DELIVERY-SYSTEMS-B-PHARM-SYLLABUS/dp/B08FCQVF4S (accessed 2022-11-11).

(2) Raza, M.; Gokul Jayswal, M.; Ahmed, A.; Majaz, Q.; Khan, G. J. REVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM. *Certified Journal* │ **2015**, *11*. https://doi.org/10.20959/wjpps20229-23130.

(3) Kohri, N.; Naasani, I.; Iseki, K.; Miyazaki, K. Improving the Oral Bioavailability of Sulpiride by a Gastric-retained Form in Rabbits. *Journal of Pharmacy and Pharmacology: An International Journal of Pharmaceutical Science* **1996**, *48* (4), 371. https://doi.org/10.1111/j.2042-7158.1996.tb05935.x.

(4) Streubel, A.; Siepmann, J.; Bodmeier, R. Drug Delivery to the Upper Small Intestine Window Using Gastroretentive Technologies. *Curr Opin Pharmacol* **2006**, *6* (5), 501–508. https://doi.org/10.1016/j.coph.2006.04.007.

(5) Arora S; Ali J; Ahuja A; Khar RK; Baboota S. *Floating drug delivery systems: a review. 2005 Sep; 6(3):E372-90. - Google Search*. pubmed. https://www.google.com/search?q=Arora+S%2C+Ali+J%2C+Ahuja+A%2C+Khar+RK%2C+Baboota+S.+Floating+drug+delivery+systems%3A+a+review.+Aaps+PharmSciTech.+2005+Sep%3B+6(3)%3AE372-90.&rlz=1C1CHBF_enIN1002IN1002&oq=Arora+S%2C+Ali+J%2C+Ahuja+A%2C+Khar+RK%2C+Baboota+S.+Floating+drug+delivery+systems%3A+a+review.+Aaps+PharmSciTech.+2005+Sep%3B+6(3)%3AE372-90.&aqs=chrome..69i57.527j0j7&sourceid=chrome&ie=UTF-8 (accessed 2023-01-20).

(6) Garg, R.; Gupta, G. Progress in Controlled Gastroretentive Delivery Systems. *Tropical Journal of Pharmaceutical Research* **2008**, *7* (3). https://doi.org/10.4314/TJPR.V7I3.14691.

(7) Nayak, A. K.; Malakar, J.; Sen, K. K. *Gastroretentive drug delivery technologies: Current approaches and future potential*. Researchgate. https://www.researchgate.net/publication/208506426_Gastroretentive_drug_delivery_technologies_Current_approaches_and_future_potential (accessed 2022-11-11).

(8) Das, S.; Kaur, S.; Rai, V. K. Gastro-Retentive Drug Delivery Systems: A Recent Update on Clinical Pertinence and Drug Delivery. *Drug Deliv Transl Res* **2021**, *11* (5), 1849–1877. https://doi.org/10.1007/S13346-020-00875-5.

(9) Chaudhry, S. R.; Bordoni, B. *Anatomy, Thorax, Esophagus - StatPearls - NCBI Bookshelf*. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK482513/ (accessed 2022-11-11).

(10) Baviskar, D.; Jain, D. *Novel Drug Delivery Systems Book*. Nirali Publication. https://www.amazon.in/Novel-Delivery-Systems-Dheeraj-Baviskar/dp/B0743DG711 (accessed 2022-11-12).

(11) Landa, S. T.; Dumon, K. R.; Dempsey, D. T. Anatomy and Physiology of the Stomach and Pylorus. *The SAGES Manual of Foregut Surgery* **2019**, 49–64. https://doi.org/10.1007/978-3-319-96122-4_3.

(12) NCERT. *NCERT Biology Textbook*. NCERT. https://ncert.nic.in/textbook.php?kebo1=0-22 (accessed 2022-11-17).

(13) Desai, S.; Bolton, S. A Floating Controlled-Release Drug Delivery System: In Vitro-in Vivo Evaluation. *Pharmaceutical Research: An Official Journal of the American Association of Pharmaceutical Scientists* **1993**, *10* (9), 1321–1325. https://doi.org/10.1023/A:1018921830385.

(14) Mojaverian, P.; Vlasses, P. H.; Kellner, P. E.; Rocci, M. L. Effects of Gender, Posture, and Age on Gastric Residence Time of an Indigestible Solid: Pharmaceutical Considerations. *Pharmaceutical Research: An Official Journal of the American Association of Pharmaceutical Scientists* **1988**, *5* (10), 639–644. https://doi.org/10.1023/A:1015922903843.

(15) AH, E.-K.; MS, S.; SS, A. G.; VF, N. *Preparation and evaluation of ketoprofen floating oraldelivery system. - Google Search*. National Library of Medicine. https://doi.org/https://doi.org/10.1016/s0378-5173(01)00574-9.

(16) Khosla, R.; Feely, L. C.; Davis, S. S. Gastrointestinal Transit of Non-Disintegrating Tablets in Fed Subjects. *Int J Pharm* **1989**, *53* (2), 107–117. https://doi.org/10.1016/0378-5173(89)90234-2.

(17) Jassal, M.; Nautiyal, U.; Kundlas, J.; Singh, D. A Review: Gastroretentive Drug Delivery System (Grdds). *Indian Journal of Pharmaceutical and Biological Research* **2015**, *3* (01). https://doi.org/10.30750/IJPBR.3.1.13.

(18) Maryam Kouchaka; Fatemeh Atyabib. *Ion-exchange, an Approach to Prepare an Oral Floating Drug Delivery System for Diclofenac*. Iranian Journal of Pharmaceutical Research. https://www.google.com/search?q=Maryam+Kouchaka+%2C+Fatemeh+Atyabib%3B+Ion-exchange%2C+an+Approach+to+Prepare+an+Oral+Floating+Drug+Delivery+System+for+Diclofenac%3B+Iranian+Journal+of+Pharmaceutical+Research%2C+2004%3B+2%3A+93-97.&rlz=1C1CHBF_enIN1002IN1002&oq=Maryam++Kouchaka+%2C++Fatemeh++Atyabib%3B+Ion-exchange%2C+an+Approach+to+Prepare+an+Oral+Floating+Drug+Delivery+System++for++Diclofenac%3B++Iranian++Journal++of+Pharmaceutical+Research%2C+2004%3B+2%3A+93-97.&aqs=chrome..69i57.792j0j7&sourceid=chrome&ie=UTF-8 (accessed 2023-01-20).

(19) Mayavanshi AV; Gajjar SS. *Floating Drug Delivery System to Increase Gastric Retention of Drugs*. Research Journal of Pharmacy and Technology. https://www.google.com/search?q=Mayavanshi+AV+and+Gajjar+SS%3B+Floating+Drug+Delivery+System+to+Increase+Gastric+Retention+ofDrugs%3BRJPT%2C+2008%3B1(4)%3A345-348.&rlz=1C1CHBF_enIN1002IN1002&oq=Mayavanshi+AV+and+Gajjar+SS%3B+Floating+Drug+Delivery+System++to++Increase++Gastric++Retention++ofDrugs%3BRJPT%2C+2008%3B1(4)%3A345-348.&aqs=chrome..69i57.1046j0j9&sourceid=chrome&ie=UTF-8 (accessed 2023-01-20).

(20) Krögel, I.; Bodmeier, R. Development of a Multifunctional Matrix Drug Delivery System Surrounded by an Impermeable Cylinder. *Journal of Controlled Release* **1999**, *61* (1–2), 43–50. https://doi.org/10.1016/S0168-3659(99)00096-6.

(21) Streubel, A.; Siepmann, J.; Bodmeier, R. Floating Microparticles Based on Low Density Foam Powder. *Int J Pharm* **2002**, *241* (2), 279–292. https://doi.org/10.1016/S0378-5173(02)00241-7.

(22) P, S.; N, T.; S, P. *Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. - Google Search*. National Library of Medicine. https://doi.org/https://doi.org/10.1016/j.ejps.2004.12.004.

(23) Whitehead L; Fell JT; Collett JH. *Development of a gastroretentive Dosage form*. The University of Manchester. https://www.google.com/search?q=Whitehead+L%2C+Fell+JT+and+Collett+JH%3B+Development+of+a+Gastroretentive+Dosage+form%3B+Eur+J+Pharm+Sci.+1996%3B4%3A182.&rlz=1C1CHBF_enIN1002IN1002&oq=Whitehead+L%2C+Fell+JT+and+Collett+JH%3B+Development+of+a+Gastroretentive++Dosage++form%3B++Eur++J++Pharm++Sci.+1996%3B4%3A182.&aqs=chrome..69i57.942j0j9&sourceid=chrome&ie=UTF-8 (accessed 2023-01-21).

(24) Singh, B. N.; Kim, K. H. Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery via Gastric Retention. *Journal of Controlled Release* **2000**, *63* (3), 235–259. https://doi.org/10.1016/S0168-3659(99)00204-7.

(25) JM, P.; RS, H.; PS, G.; VJ, K. *Trends in floating drug delivery systems*. Journal of Scientific & Industrial Research. https://www.google.co.in/search?q=Patil+JM%2C+Hirlekar+RS%2C+Gide+PS%2C+Kadam+VJ.+Trends+in+floating+drug+delivery+systems.&sxsrf=ALiCzsZ4WzG-pb4_oqDHIbKn1WE-RXO-sQ%3A1668675181117&ei=bfZ1Y53dBpKbseMP69mMkAI&ved=0ahUKEwjdx6m767T7AhWSTWwGHessAyIQ4dUDCA8&ua (accessed 2022-11-17).

(26) Hashim, H.; Li Wan Po, A. Improving the Release Characteristics of Water-Soluble Drugs from Hydrophilic Sustained Release Matrices by in Situ Gas Generation. *Int J Pharm* **1987**, *35* (3), 201–209. https://doi.org/10.1016/0378-5173(87)90131-1.

(27) Ichikawa, M.; Watanabe, S.; Miyake, Y. A New Multiple-unit Oral Floating Dosage System. I: Preparation and in Vitro Evaluation of Floating and Sustained-release Characteristics. *J Pharm Sci* **1991**, *80* (11), 1062–1066. https://doi.org/10.1002/jps.2600801113.

(28) Ingani, H. M.; Timmermans, J.; Moës, A. J. Conception and in Vivo Investigation of Peroral Sustained Release Floating Dosage Forms with Enhanced Gastrointestinal Transit. *Int J Pharm* **1987**, *35* (1–2), 157–164. https://doi.org/10.1016/0378-5173(87)90084-6.

(29) Sheth, P. R.; Tossounian, J. The Hydrodynamically Balanced System: A Novel Drug Delivery System for Oral Use. *Drug Dev Ind Pharm* **1984**, *10* (2), 313–339. https://doi.org/10.3109/03639048409064653.

(30) JK, S.; FJ, A.; A, A.; RK, K. *Formulation and evaluation of a hydrodynamically balanced system of paracetamol - Google Search*. Semantic Scholar. https://www.google.co.in/search?q=Sahni+JK%2C+Ahmad+FJ%2C+Ahuja+A%2C+Khar+RK.+Formulation+and+evaluation+of+a+hydrodynamically+balanced+system+of+paracetamol&sxsrf=ALiCzsaDmSGozRw7T7dKIaWdz64WQk8Whw%3A1668676636462&source=hp&ei=HPx1Y5LhGeiZseMP1eW9yAQ&ifl (accessed 2022-11-17).

(31) LH, R.; RS, M. *Floating dosage system in drug delivery - Google Search*. National Library of Medicine. https://doi.org/https://doi.org/10.1615/critrevtherdrugcarriersyst.v19.i6.20.

(32) Bardonnet, P. L.; Faivre, V.; Pugh, W. J.; Piffaretti, J. C.; Falson, F. Gastroretentive Dosage Forms: Overview and Special Case of Helicobacter Pylori. *Journal of Controlled Release* **2006**, *111* (1–2), 1–18. https://doi.org/10.1016/j.jconrel.2005.10.031.

(33) Kawashima Y; Niwa T; Takenchi H; Hino T; Itoh Y. *Hollow microspheres for use as a floating controlled drug delivery system in the stomach*. pubmed. https://www.google.com/search?q=Kawashima+Y%2C+Niwa+T%2C+Takenchi+H%2C+Hino+T%2C+Itoh+Y.+Hollowmicrospheres+for+use+as+a+floating+controlled+drugdelivery+system+in+the+stomach&rlz=1C1CHBF_enIN1002IN1002&oq=Kawashima+Y%2C+Niwa+T%2C+Takenchi+H%2C+Hino+T%2C+Itoh+Y.+Hollowmicrospheres+for+use+as+a+floating+controlled+drugdelivery+system+in+the+stomach&aqs=chrome..69i57.578j0j9&sourceid=chrome&ie=UTF-8 (accessed 2023-01-22).

(34) Talukder, R.; Fassihi, R. Gastroretentive Delivery Systems: Hollow Beads. *Drug Dev Ind Pharm* **2004**, *30* (4), 405–412. https://doi.org/10.1081/DDC-120030935.

(35) Vyas, S P; Khar, R. K. *Controlled Drug Delivery Delivery*; Vallabh Prakashan, 2012.

(36) GM, C.; JM, N.; MD, S. *Gastrointestinal transit of pellets of differing size and density. - Google Search*. Indian Journal of Pharmaceutics. https://doi.org/https://doi.org/10.1016/0378-5173(93)90078-T.

(37) Klausner, E. A.; Lavy, E.; Friedman, M.; Hoffman, A. Expandable Gastroretentive Dosage Forms. *Journal of Controlled Release* **2003**, *90* (2), 143–162. https://doi.org/10.1016/S0168-3659(03)00203-7.

(38) Klausner, E. A.; Lavy, E.; Barta, M.; Cserepes, E.; Friedman, M.; Hoffman, A. Novel Gastroretentive Dosage Forms: Evaluation of Gastroretentivity and Its Effect on Levodopa Absorption in Humans. *Pharm Res* **2003**, *20* (9), 1466–1473. https://doi.org/10.1023/A:1025770530084.

(39) Caldwell LJ; Gardner CR; Cargill RC. *Drug delivery device which can be retained in the stomach for controlled period of time.* https://www.google.com/search?q=Caldwell+LJ%2C+Gardner+CR%2C+Cargill+RC.+Drug+delivery+devicewhich+can+be+retained+in+the+stomach+for+controlledperiod+of+time.+US+Patent+473+5804.+April+5%2C+1988&rlz=1C1CHBF_enIN1002IN1002&oq=Caldwell+LJ%2C+Gardner+CR%2C+Cargill+RC.+Drug+delivery+devicewhich+can+be+retained+in+the+stomach+for+controlledperiod+of+time.+US+Patent+473+5804.+April+5%2C+1988&aqs=chrome..69i57.626j0j9&sourceid=chrome&ie=UTF-8 (accessed 2023-01-22).

(40) Klausner, E. A.; Lavy, E.; Stepensky, D.; Friedman, M.; Hoffman, A. Novel Gastroretentive Dosage Forms: Evaluation of Gastroretentivity and Its Effect on Riboflavin Absorption in Dogs. *Pharm Res* **2002**, *19* (10), 1516–1523. https://doi.org/10.1023/A:1020412817716.

(41) Moes A. *Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst. - Google Search*. National Library of Medicine. https://www.google.co.in/search?q=Moes+A.+Gastroretentive+dosage+forms.+Crit+Rev+Ther+Drug+Carrier+Syst.&sxsrf=ALiCzsZiGYmUjzv52BNskwdlNM-x_i8v6g%3A1668679901842&ei=3Qh2Y6jlMpOL4-EPspSjoAU&ved=0ahUKEwjox6uG_bT7AhWTxTgGHTLKCFQQ4dUDCA8&uact=5&oq=Moes+A.+Gas (accessed 2022-11-17).

(42) Huang, Y.; Leobandung, W.; Foss, A.; Peppas, N. A. Molecular Aspects of Muco- and Bioadhesion: Tethered Structures and Site-Specific Surfaces. *Journal of Controlled Release* **2000**, *65* (1–2), 63–71. https://doi.org/10.1016/S0168-3659(99)00233-3.

(43) Chen, J.; Blevins, W. E.; Park, H.; Park, K. Gastric Retention Properties of Superporous Hydrogel Composites. *Journal of Controlled Release* **2000**, *64* (1–3), 39–51. https://doi.org/10.1016/S0168-3659(99)00139-X.

(44) Ito, R.; Machida, Y.; Sannan, T.; Nagai, T. Magnetic Granules: A Novel System for Specific Drug Delivery to Esophageal Mucosa in Oral Administration. *Int J Pharm* **1990**, *61* (1–2), 109–117. https://doi.org/10.1016/0378-5173(90)90049-A.
(45) Pallavi, T.; Sharma, G. S.; Rama, B.; Rani, L. J.; Rajkama, B. *Formulation and evaluation of floating bilayer tablet of epleronone*. World Journal of Pharmaceutical Sciences. https://doi.org/https://doi.org/10.54037/WJPS.2022.10040.
(46) Desu, P. K.; Pasam, V.; Kotra, V. Formulation and in Vitro Evaluation of Superporous Hydrogel Based Gastroretentive Drug Delivery System of Vildagliptin. *Journal of Research in Pharmacy* **2019**, *23* (5), 873–885. https://doi.org/10.35333/JRP.2019.35.