

Review Article

Recent Innovations in Gastroretentive Drug Delivery System and It's Prospect In The Future

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ABSTRACT

The use of conventional oral drug delivery systems is convoluted by limited gastric residence time for the drugs having a narrow absorption window. Rapid GI transit can prevent the complete release of the drug in the absorption zone and it reduces the efficacy of the provided dose. Since the majority of the drugs are absorbed in the stomach or in the upper part of the small intestine. To conquer these limitations various advanced drug delivery systems have been developed to increase the gastric residence of the drugs in the upper part of GIT and to maximize the oral absorption of drugs. One such novel approach is the gastro-retentive drug delivery system. In general, this study could help researchers to explore new approaches for creating safe and effective gastroretentive systems in order to make them more widely used in clinical practices and the treatment of diseases. This review paper highlights several factors, including modern innovative technology, that are helpful in the development of gastroretentive drug delivery systems.

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INTRODUCTION

The oral route is the most suitable and extensively used route for drug administration. This route has high patient acceptability, due to ease of administration. But at the same time, a few challenges exist in oral drug delivery systems which lead to the development of controlled and novel drug delivery systems. This helps in achieving predictable drug concentration essential for therapeutic action, it also reduces dosing frequency. One such essential requirement for good performance of oral CRDDS is that the drug should have better absorption through GIT. This ensures the better bioavailability of the drug as the drug is continuously absorbed through GIT^[1]. Therefore, different approaches have been developed to retain drugs in the stomach, one such novel approach is the gastro-retentive drug delivery system^[2].

Gastro-retentive drug delivery system allows the drug to remain in the gastric region for several hours in order to extend its gastric residence time. ^[3]

GRDDS is useful for those drugs, which are: ^[2]

- Absorbed from the stomach or from the upper part of the GIT.
Eg. Albuterol.
- Drugs those are less soluble or labile at basic pH.
Eg. Metformin, Furosemide.
- For drugs having a narrow absorption window.
Eg. Riboflavin, Levodopa
- Drugs that affect or destroy the normal intestinal microflora.
Eg. Antibiotic against Helicobacter pylori.
- Drugs those are not stable in the intestinal environment.
Eg. Ranitidine.

Anatomy of the Gastrointestinal Tract:

The stomach plays an important role in the GRDDS; thus, a thorough understanding of the anatomy and physiology of the stomach is required for the successful development of the gastro-retentive dosage form.

The gastrointestinal tract is divided into three main regions, which are as follows:

Stomach

- a) Cardia
- b) Fundus

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- c) Body of the stomach
- d) Pyloric part-
 - i. Antrum
 - ii. Anal

Small Intestine

- a) Duodenum
- b) Jejunum
- c) Ileum

Large Intestine

- a) Colon
- b) Rectum
- c) Anus

The complicated anatomy and physiology of the GI system, variations in stomach acidity, bile salts, enzyme concentration, and mucosal absorptive surface from mouth to rectum have significant impacts on drug release, solubility, and absorption of orally administered dosage forms. The luminal surface of the gastrointestinal tract is not smooth but rather rough, which increases the surface area for absorption [Fig. 1] [2-4].

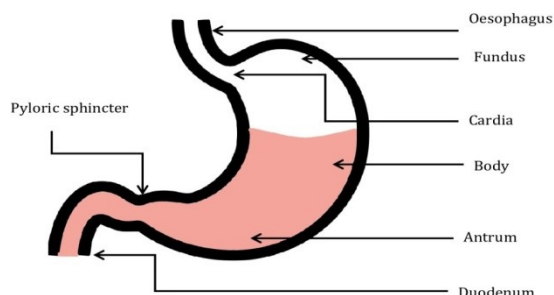


Figure 1: Schematic diagram of stomach

The stomach is located in between the oesophagus and the small intestine, which is the most dilated section of the GI tract.

The Major Functions of the Stomach are as follows:

It acts as a temporary storage area for ingested food, allowing it to be delivered to the duodenum in a controlled manner.

By the action of acid and enzymatic digestion, ingested solid is reduced into chyme. This improves contact between the ingested material and the mucous membrane of the intestines, facilitating absorption.

The fundus and body primarily serve as a reservoir for undigested food, whereas the

antrum functions as a pump for gastric emptying via propelling action.

Gastric Fluid:

The stomach has a capacity of about 1.5 litres, however, during fasting; it generally contains about 50 mL of fluid, most of which is gastric secretions. This consists of:

- Acid produced by the parietal cells, which keeps the stomach's pH between 1 and 3.5 in a fasting condition.
- Gastrin is a hormone that stimulates the production of stomach acid. Peptides, amino acids, and stomach distention all trigger the release of gastrin.
- Pepsins are digestive enzymes that are released by peptic cells in the form of pepsinogen. At low pH, pepsins are peptidases that break down proteins into peptides. Pepsin is denatured above pH 5.
- Mucus lines the gastric mucosa and is secreted by surface mucosal cells. The mucus protects the gastric mucosa from auto-digestion by the pepsin-acid combination in the stomach.

Due to its limited surface area compared to the small intestine, the stomach absorbs a less amount of drugs. The rate of gastric emptying can influence the onset of drug absorption from the small intestine, which is the primary absorption site.

Gastric Emptying

The time taken by a dosage form to travel the stomach is known as the Gastric residence time or gastric emptying time or gastric emptying rate.

The gastric emptying of pharmaceuticals varies greatly depending on the dosage form and the fed/fasted state of the stomach. The normal Gastric residence time typically varies between 5 minutes to 2 hours. Particularly for large single unit longer, GRT has been recorded (over 12 hours).

The interdigestive myoelectric cycle, also known as the migrating myoelectric complex, regulates the stomach's electrical activity in the fasted state, which in turn affects how quickly dosage forms pass through the stomach. MMC is characterized by a repeating cycle of four phases (Table 1).

Table 1: Phases in migrating myoelectric cycle [5]

PHASE	NAME	PERIOD	DISCRIPTION
Phase I	Basal phase	30-60 min.	There are no contractions during this quiescent period.
Phase II	Preburst phase	20-40 min.	It consists of irregular contractions and its intensity increases as the phase progresses. Later on in this phase, gastric discharge of the fluid and extremely small particles starts.
Phase III	Burst phase	10-20 min.	This phase is of a short period with intense distal and proximal gastric contractions. These contractions are also called "house keeper waves". Gastric contents are swept down the small intestine by these contractions.
Phase IV		0-5 min	It is a short period of transition between phase III and I.

Factors Affecting Gastric Retention of Dosage Form

Particle Size and Density:

Particles should be in the range of 1-2 mm in size in order to pass through the pyloric valves into the small intestine^[6].

The density of the dosage form should be between 1g/cm³ to 2.5g/cm³.

Food Intake and its Nature:

In the fed State, GRT is longer. A meal high in protein and fat content increases GRT.

Gender: Compared to men, women have shorter GRT^[7].

Age: GRT increases with age above 70^[7].

Nature of Drug: GRT is increased by drugs that affect gastrointestinal transit time^[8].

Ex. Codeine and pharmacokinetic agents like Metoclopramide, Cisapride.

Other Factors

Disease state (diabetes mellitus, chronic diseases, etc.)

Gastric retention time is increased in cases like gastric ulcer, diabetes, and hypothyroidism whereas gastric retention time is decreased in cases like hyperthyroidism and duodenal ulcers. Drug lipophilicity depends on its ionization state^[9].

Advantages of Gastro Retentive Drug Delivery Systems

1. It ensures the improved bioavailability of the drug.
2. GRRDS shows the controlled and sustained release of drugs which reduces dosing frequency.

3. GRDDS is useful in targeted therapy for local ailments in the upper GIT.
4. Fluctuations in drug concentration are minimized.
5. Undesirable effects of the drug in the colon may be prevented or minimized.
6. Site-specific delivery of a drug^[2].

Disadvantages of Gastro Retentive Drug Delivery Systems

1. GRDDS is not appropriate for drugs with low acid solubility.
Ex. Phenytoin.
2. GRRDS is not suitable for drugs that are unstable in acidic conditions.
Ex. Erythromycin.
3. 3. Drugs that specifically absorb in the colon are unsustainable for GRDDS.
Ex. Corticosteroid.
4. 4. Not useful for the drugs that irritate and cause gastric lesions on slow release.
Ex. Aspirin and NSAIDs^[10].

Strategies for Delaying Gastric Emptying

1. Pharmacological Approach:

In this approach co-administration or inclusion of a drug into the pharmaceutical product is done. This drug prolongs gastric emptying.
Ex. Antimuscarinics e.g. propantheline^[10].

2. Physiological Approach:

It refers to the use of natural materials or fat derivatives, such as triethanolaminemyristate, to activate the duodenal or jejunal receptors and so delay stomach emptying^[11].

3. Pharmaceutical Approach:

The first two approaches are not employed because of their toxicity issues. The different pharmaceutical approaches are as Fig. 2.

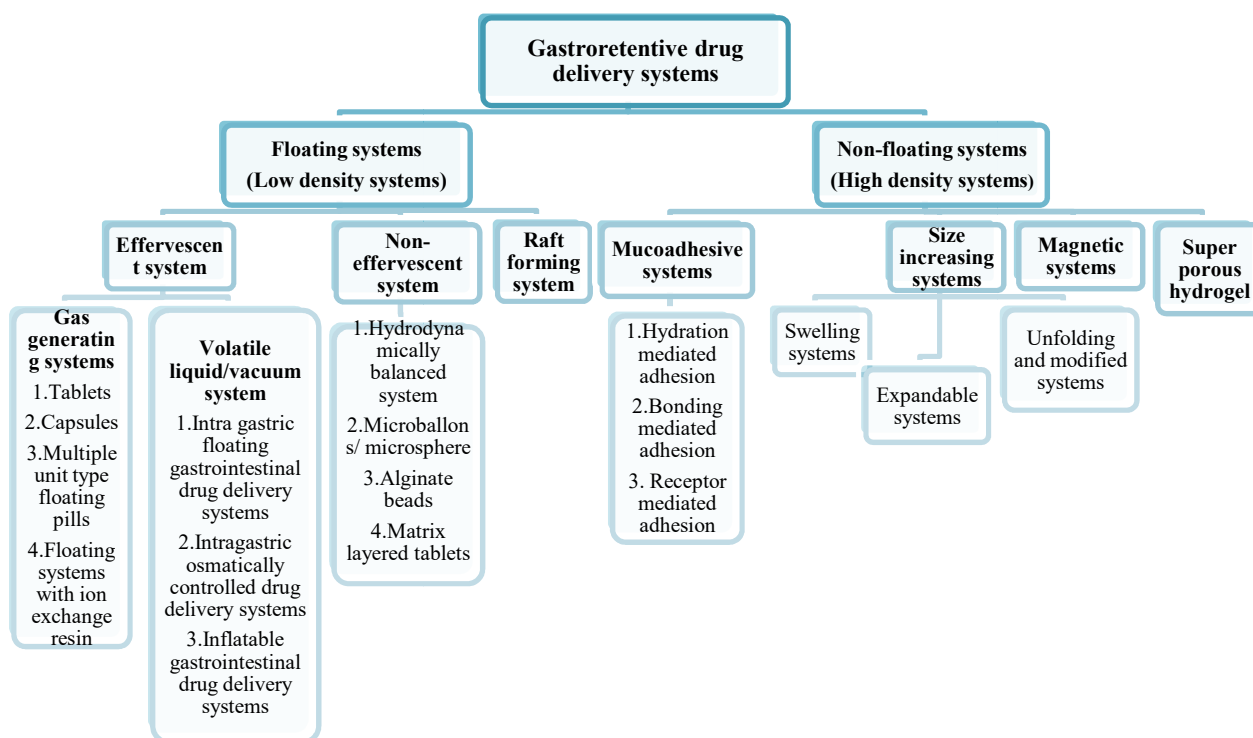


Figure 2: Types of gastro-retentive drug delivery system

Floating or Low-Density Systems

The most convenient and well-researched gastro retentive dosage form is low-density or floating systems [3, 12-14]. In 1968, Davis introduced the floating system. In this approach, the dosage form's bulk density is less than that of gastric fluid ($1.004/\text{cm}^3$). This characteristic enables the system to float in the stomach for an extended period of time whereas the drug is released from the system at the desired rate. Depending on the buoyancy mechanism, these systems are divided into two categories as follows [3, 12,14]:

- A. Effervescent systems
- B. Non-effervescent systems

A. Effervescent System:

These systems are of the matrix type, prepared with the use of several effervescent compounds and swellable polymers, including methylcellulose and chitosan.

Ex. Sodium bicarbonate, tartaric acid, citric acid.

These are designed in such a way that when they come in contact with gastric contents, CO_2 is released and entrapped in swelling hydrocolloid which provides Buoyancy to the dosage form. This system is again divided into the following categories [15].

Gas Generating System:

Gas bubble production is one way to attain floatability. These buoyant systems employ matrices made with swellable polymers, such as polysaccharides (chitosan) and effervescent compounds (tartaric acid, citric acid, sodium bicarbonate) [16]. The optimal stoichiometric ratio of citric acid and sodium bicarbonate is 0.76:1 for best results [17]. Achieving a proper balance between the polymers' elasticity, plasticity, and permeability is the main challenge of these formulations. Various gas-generating floating systems are as follows:

a) Capsules:

Drugs are encapsulated in hydrophilic polymers like ethyl cellulose and eudragit RS-100 along with effervescent substances like sodium bicarbonate, calcium carbonate, etc. A hydrodynamically balanced capsule prepared by Moursy and Afifi has a combination of hydrocolloids and nifedipine hydrochloride. The capsule shell dissolves and swells when it comes in contact with gastric fluid, creating a gelatinous barrier that floats in gastric fluid for a long time.

b) Pills:

It is basically a multiple-unit type of dosage form. It consists of two layers. The outer layer is

composed of a swellable polymeric membrane, and the inner layer is composed of effervescent substances. The hydrophilic polymer's outer layer starts to swell as it comes in contact with the gastric fluid and eventually sinks [18]. However, once the effervescent agent comes in contact with the gastric content, it produces Oxygen, which causes the system to float [19, 20].

c) System with Ion Exchange Resins

This system consists of drug resin complex beads that have been loaded with bicarbonate ions and coated with a hydrophobic polymer. The system is designed in such a manner that chloride ions are exchanged with bicarbonate and drug ions when the beads reach the stomach. As a result of the generated CO₂ being trapped in the polymeric-coated resins, the beads float [21].

Liquid/ Vacuum System

These systems have an inflatable chamber with a liquid inside, such as ether or cyclopentane, which gasifies at body temperature to inflate the chamber in the stomach. These systems are osmotically controlled floating systems with a hollow deformable unit. The system has two chambers: one holds the drug, and the other holds the volatile system. The system is classified as follows:

Intra-gastric Floating Gastrointestinal Drug Delivery System:

This system includes a floatation chamber filled with a vacuum or an inert, harmless gas, as well as a microporous compartment containing a drug reservoir.

Intra-gastric- Osmotically Controlled System:

A biodegradable capsule containing inflatable floating support can be used to achieve osmotic control [22]. To prepare an oral push-pull osmotic pump Zaho and Hao used fenofibrate-loaded mesoporous silica nanoparticles (MSNs) [23].

Inflatable System:

These systems use an inflatable chamber filled with liquid ether that gasifies at body temperature to inflate the stomach. The inflatable chamber contains bio erodible polymer filaments, such as a copolymer of polyvinyl alcohol and polyethylene, which steadily dissolve in gastric fluid, causing the inflatable chamber to release gas and collapse.

B. Non effervescent Systems:

When a drug comes in contact with gastric fluid, it swells. It maintains its shape and maintains a density below one, which allows it to float in gastric juice [24]. These floating systems employ matrix-forming polymers or swellable hydrocolloids. Further classification of the non-effervescent system is as follows:

Hydrodynamically Balanced System (HBS):

This system is primarily composed of a drug-and-hydrocolloid mixture. When it comes in contact with gastric fluid, forms a gelatinous barrier due to swelling of the combination. Since its bulk density in the gastric fluid is less than 1, it floats in the stomach for a long time. Using hydroxypropyl methylcellulose, polyethylene oxide, polyvinyl pyrrolidone, ethyl cellulose, liquid paraffin, and lactose, Nayak and Malakar formed gastroretentive theophylline HBS capsules to regulate the delivery of theophylline for a longer period in the stomach with a minimum floating time of 6 hours [25].

Micro Balloons or Microspheres:

Solvent evaporation, solvent diffusion, or evaporation methods were used to develop Microballoons or hollow microspheres loaded with drugs in the polymer [26]. The amount of polymers used, the plasticizer polymer ratio, and the solvent used in formulation all influence buoyancy and drug release from dosage forms [27]. Gupta and Kumar used an emulsion solvent diffusion method with a non-effervescent approach to prepare pantoprazole sodium-loaded microspheres using eudragit L100 (Fig. 3) [28].

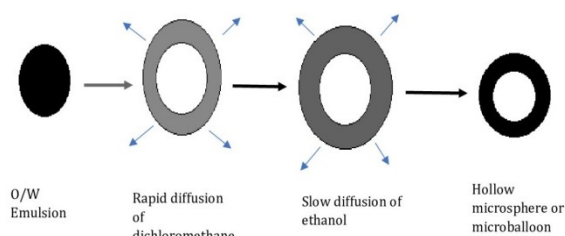


Figure 3: Formulation of floating hollow microsphere or micro balloons

Alginate Beads:

Recent advancements by Talukdar and Fassihi include a multiple-unit floating system based on cross-linked beads. Ca²⁺ and low methoxylated pectin (anionic polysaccharide) or Ca²⁺ low

methoxylated pectin and sodium alginate were used to synthesize alginate beads [5]. In this method, calcium alginate is typically precipitated by dropping sodium alginate solution into an aqueous calcium chloride solution. These beads are separated and dried using air convection and freeze drying, forming a porous structure that can sustain a floating force for more than 12 hours. It improves GRT by more than 5.5 hours [29, 30].

Microporous Compartment System:

This method is based on the encapsulation of a drug reservoir inside a microporous compartment having pores along its top and bottom walls [16]. The device's outer layer is hermetically sealed to prevent any direct contact of the gastric surface with the undissolved drug. The floatation chamber containing entrapped air causes the system to float in the gastric fluid in the stomach [34]. Gastric fluid enters the aperture, dissolves the drug, and causes the dissolved drug to be transported continuously across the intestine for drug absorption.

Raft Forming Systems:

In this approach, carbonates or bicarbonates react with gastric fluid to form a thick gel containing trapped carbon dioxide bubbles [32, 33]. Antacids like calcium carbonates or aluminum hydroxide are usually included in formulations to reduce acidity. It provides a layer on top of the gastric fluid, which is frequently used to treat gastro-oesophageal reflux [18, 34].

High-Density System:

Due to their higher density than gastric fluid, these systems settle to the bottom and persist in the stomach. These are prepared by coating a drug with a dense, inert substance, such as zinc oxide, titanium dioxide, iron powder, etc. various high-density systems are as follows:

Mucoadhesive Systems:

A mucoadhesive polymer is present in mucoadhesive drug delivery systems, which adheres to the mucosal surface of the stomach and increases gastric retention in the gastrointestinal tract. Mucoadhesive polymers are excellent excipients in GRDDS due to their ability to adhere to the mucosal layer. Natural polymers include sodium alginate, gelatin, guar gum, and others. Semi-synthetic polymers like sodium carboxymethyl cellulose, carbopol and HPMC [5].

Polymer adhesion to mucous membranes can be facilitated by hydration, bonding, or receptor-mediated mechanism. When a hydrophilic polymer is hydrated, it develops into a sticky, mucoadhesive substance in the hydration-mediated mechanism. Mechanical and chemical bonding is involved in bonding-mediated mechanisms. Chemical bonds are formed by ionic or covalent bonds or Vander Waal forces between polymer molecules and the mucous membrane. Receptor-mediated adhesion occurs between certain polymers and specific receptors present on gastric cells [35, 36].

Swelling, Unfoldable and Swellable Systems:

It is a form of non-floating GRDDS that, when reaches the stomach, expands (due to the presence of swellable polymers) to such an extent that it cannot pass through the pyloric sphincter, causing its retention in the stomach [18]. The degree of cross-linking of the biodegradable hydrophilic polymer network predominantly determines its ability to swell (Fig. 4) [37, 38].

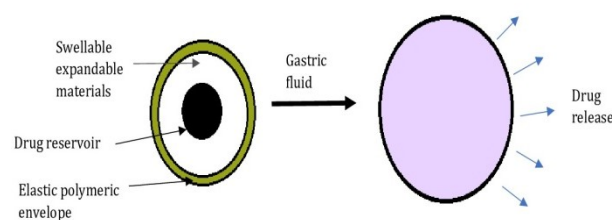


Figure 4: Drug release from the swellable systems

Magnetic System:

It comprises of the drug blended with a tiny internal magnet. An extracorporeal magnet controls the tiny magnet's position which is inside the stomach [39, 40]. The peroral acyclovir depot tablets with internal magnet were formulated by Groning and Berntgen [41].

Superporous Hydrogels:

A three-dimensional network of hydrophilic polymers called superporous hydrogels contains a large number of super-size pores. Superporous hydrogels swell as a result of capillary wetting that takes place through open, interconnected pores. In order to develop Superporous hydrogels, certain components, such as initiators and cross-linkers, are used [42]. Foam stabilizers, foaming agents, and foaming aids are additional components. Using N',N'-methylene bisacrylamide (BIS) as the

crosslinking agent, polyvinyl alcohol as a polymer, ammonium persulfate and N,N-tetra methylene diamine as an initiator pair, and span 80 as the surfactant, Desu and Paasam

formulated a Superporous hydrogels system. They are utilized as a froth stabilizer to create a permeable structure by using the gas-forming method [43].

Table 2: Polymers used in different GRDDS

Sr. no.	GRDDS	Polymers used
1.	Tablets	Hydroxypropyl Methylcellulose (HPMC K4M, HPMC K100M) HPMC E15LV, HPMC E50LV, HPMC K100LV, Polyvinyl Pyrrolidone (PVP K30) HPMC K15M, Xanthan Gum, Karaya Gum, Guar Gum, Carrageenan, Carbopol, Sodium Carboxymethyl Cellulose, PVP K30 Psyllium Husk, Crospovidone.
2.	Mucoadhesive System	HPMC, Carbopol, chitosan, carboxymethyl cellulose, polyacrylic acid.
3.	Microspheres	Eudragit RL100, cellulose acetate, ethyl cellulose.
4.	Matrix tablet	Ethyl cellulose, HPMC K4M, HPMC K15M, HPMC K100K.
5.	Micro balloons	Ethyl cellulose, HPMC K4M.
6.	Hydrodynamically Balanced system	HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, alginic acid, Polycarbophil, polyacrylate, Polystyrene.
7.	Super porous hydrogel	Chitosan, ethyl cellulose, sodium carboxymethyl cellulose, HPMC, Carbopol 934P

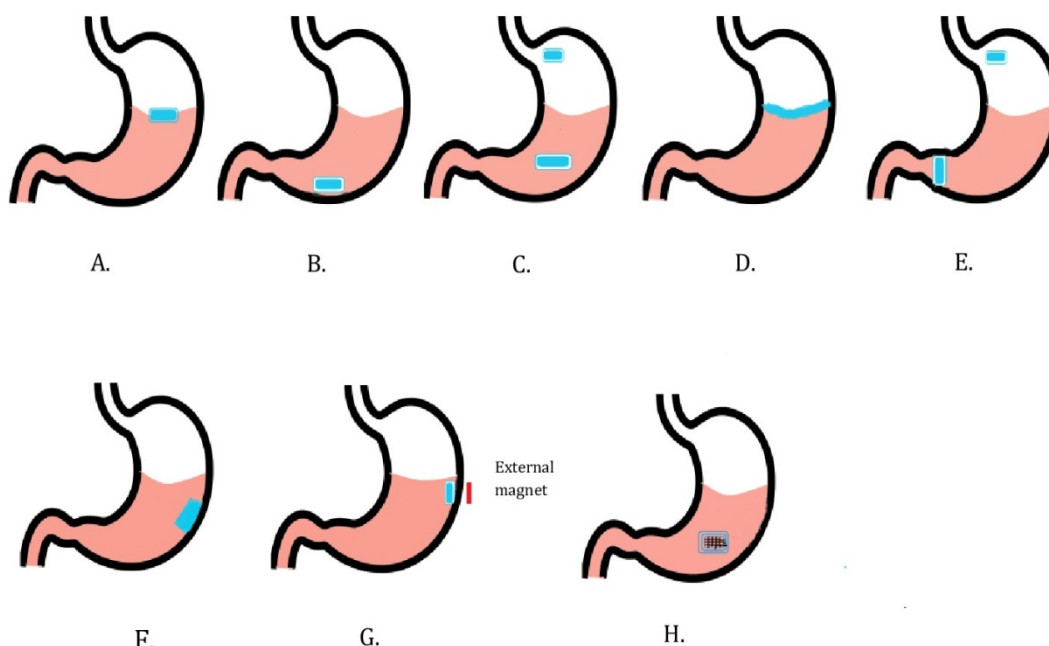


Figure 5: Types of gastro-retentive drug delivery system. A. floating or low-density system, B. High density system, C. Expandable system, D. Raft forming system, E. Inflatable system, F. Mucoadhesive system, G. Magnetic system, H. Ion-exchange resin system.

Novel Technologies: Accordion Pill™:

It is a unique polymer-based gastro-retentive formulation. It is compressed into a uniformly sized capsule. As soon as the capsule enters the stomach, it melts. Under frequent calorie diets, the accordion pill unfolds and remains in the stomach for up to 12 hours. The Accordion Pill™ delivers the drug in a regulated manner to the

upper region of the gastrointestinal tract. The Accordion Pill™ is transferred from the stomach and completely broken down in the intestine. It is utilized for the drugs having a narrow absorption window from the III and IV classes.

Acuform® Systems:

This system is designed specifically for targeted and controlled drug release. Because of

technological advancements, the tablet can remain in the stomach for eight to ten hours. During this phase, the tablet's active ingredient is continuously administered at the optimal rate and duration to the upper GI tract. With the ease of one or two daily doses, it offers the potential for greater therapeutic effectiveness and improved medication tolerability. This new development may be a suitable delivery method for drugs that are consumed in the upper gastrointestinal tract, irritating to the stomach mucosa, and for drugs that are not dissolved in water.

Gastro Retentive Innovative Device (GRID):

Only the stomach or small intestine can receive drugs from this system. GRID was developed in order to retain the drug in the stomach for longer than eight hours. The tablet offers a combination of immediate and sustained drug release profiles and also it improves patient compliance. Expected drug release can be achieved by using this inventive technique which is designed to achieve a combination of slow and immediate release of the drug.

Multiple Polymer Hydrophilic Matrix Technology:

It is useful for the prolonged release of metformin hydrochloride as a gastro-retardant delivery method. In this technique polymer is a mixture of ionic and non-ionic hydrophilic polymers blended with metformin hydrochloride to form a tablet. It allows the tablets to release drugs irrespective of pH. A swelling gelatinous matrix is created when metformin absorbs water hydrates. As the tablet expands, they remain in the stomach and exhibit a longer period of release.

Oleotec™ and Soctec™:

Oleotec™ is primarily designed for medications that require high pharmacological doses and are incompatible with traditional dosage forms. Basically, Oleotec™ is a stick-loaded gel that forms a continuous pattern of gel on the surface of the Gastric fluid. Soctec™ has been developed to allow medications to stay in the stomach for extended periods of time and it is used for drugs having narrow absorption windows. Typically, peristaltic contractions disintegrate the stomach's contents, which are then quickly ejected into the duodenum via the pylorus. Soctec™ is easy to ingest. During this procedure, Soctec™ releases the drug load at a fixed rate,

allowing for ingestion in the upper portions of the small intestine.

Gastrointestinal Permeation Enhancement Technology and Micropump:

A novel strategy enables the conversion of commonly injected medications into oral formulations while improving the absorption of existing oral medications. It improves the bioavailability of the drug. Between 5,000 and 10,000 microparticles are contained in each capsule or tablet of a micro pump. The particle with a size ranging from 200-500 microns exhibits prolonged release rates in the GI tract for up to 24 hours. It reduces toxicity and improves the efficacy of the medication.

EUDRATEC ® GRS:

It is a nutritional supplement product from Evonik that increases gastro retention. By enabling the EUDRATEC ® GRS technology, ingredients are released into the stomach gradually. The EUDRATEC ® GRS system is formed by incorporating active constituents with gas-forming agents. EUDRAGUARD ® control and other excipients are coated on the capsule. When the outer layer is exposed to gastric acid, it becomes porous, enabling carbon dioxide gas to escape. By coating the capsule with EUDRAGIT ® NM 30 D, release control is obtained [32].

Excipients Used In a Different Floating System:

Hydrocolloids:

The substance that has the ability to swell and form a gel when it comes in contact with the gastric fluid is called a hydrocolloid.

Eg. Carbopol, Agar, HPMC, sodium alginates, ethyl cellulose, pectin.

Release Rate Accelerants:

Agents which are used to increase the release rate of the dosage form are known as release rate accelerants.

Eg. Lactose, mannitol

Release Rate Retardant:

These are the chemical agent that delays the drug's release action by reducing the solubility.

Eg. Talc, calcium phosphate, magnesium stearate

Buoyancy Enhancing Agent:

It enhances buoyancy by using materials with low density.

Eg. Ethyl cellulose

Gas Generating Agents:

These are the agents that generate carbon dioxide when it comes in contact with an acidic medium [39].

Eg. Tartaric acid, citric acid, sodium bicarbonate [32]

Evaluation of Gastro-Retentive Drug Delivery Systems:***In Vivo* Evaluation Parameters:**

Well-designated *in-vivo* study in an animal model or humans is required to demonstrate the *in-vivo* efficacy of GRDDS. The information related to GRT and the drug's bioavailability is obtained by *in-vivo* studies. The first requirement for a

successful *in vivo* study is the selection of an appropriate animal model [39, 44, 45]. For *in vivo* assessments of GRDDS, a variety of diagnostic imaging methods can be used, including gamma scintigraphy, gastroscopy, ultrasonography, magnetic resonance imaging (MRI), and radiology.

Gamma Scintigraphy:

It is used to assess the gastroretentive dosage forms *in vivo* floating behavior. Instead of using an X-ray to engulf the formulation, scintigraphy uses ^{99m}Tc pertechnetate as an emitting material to record the image [31, 46].

Table 3: *In-vitro* evaluation parameters

GRDDS	Evaluation	Description
Expandable System [53]	<i>In-vitro</i> unfolding study	The test is conducted by placing the folded dosage form into the dissolution medium and monitoring its unfolding behavior over time
Ion Exchange Resin System [54-56]	Particle size	Particle size is measured using optical microscopy, sieve shaker, laser diffraction, Coulter counter analyzer
	Ion-exchange capacity	The functional group that is available for crosslinking determines the ion exchange capacity.
	Moisture content	Karl Fischer titration can be used to measure moisture content.
Low Density System, Raft Forming System [3, 57-61]	Floating lag time (FLT) and total floating time (TFL)	The test is conducted at 37°C in simulated gastric fluid (SGF). Time taken by medicament to emerge on the surface of the SGF is measured as FLT and the time the tablet constantly floats on the surface of the SGF is measured as TFL.
	Floating strength	A specially constructed basket holder coupled with an analytical balance is used to measure the floating strength. The floating strength is determined over time by the weight loss on the analytical balance.
Microballoons [18]	Particle size, bulk density, tapped density, Carr's index, Flow properties	It is characterized by micromeritic study.
	Morphology	Using a sputter coater and vacuum, dried micro balloons were covered with gold film. Using scanning electron microscopy, the surface of micro balloons can be examined.
	Floating behaviour	The weight ratio of floating particles to the total of floating and sinking particles determines buoyancy.
	Stability study	Perform assay for determination of drug content.
Mucoadhesive and Raft Forming System [62]	Viscosity and rheology	When a polymer comes into contact with gastric fluid, it changes the consistency of the dosage form. The texture analyzer and Brookfield or Ostwald's viscometer are frequently used.
Superporous Hydrogel and Expandable System [63, 64]	Swelling studies	The dosage form is weighed and then placed into the swelling medium (0.01 N HCl), after which the samples' weight, diameter, and length are measured at a predetermined time point.
Applicable for all GRDDS	<i>In-vitro</i> drug release	The test is performed in SGF using USP type-II dissolution apparatus at 50 rpm and maintained at 37°C at a predetermined time interval (typically 0 to 12 h) [65-68].
	Gel strength	For greater mechanical integrity, high gel strength is desirable [65, 69].
	Drug-excipient interaction study	FT-IR spectroscopy, high-performance liquid chromatography, and differential scanning calorimetry can be used to study drug-excipient interactions [3, 70].

Gastroscopy:

For the visual inspection of gastroretentive dosage forms, gastroscopy is frequently used. In this method, an endoscope is used to see inside the stomach, oesophagus, and small intestine in detail. It is an illuminating optical, tubular, and thin instrument [47, 48].

Ultrasonography:

It is a method of diagnostic imaging in which internal body structures are imaged using ultrasound. Non-detectability in entrails (intestinal part) is the main drawback of this test [49].

Magnetic Marker Monitoring:

Since this method does not use radiation, it is safer than radiology and scintigraphy. It involves monitoring the dosage form's progress throughout the gastrointestinal system in real time. This method is primarily employed to assess the behavior of pharmaceutical's gastrointestinal motility and dissolution. In this method, a trace of ferromagnetic particles is added to the dosage form to label it as a magnetic dipole. A device sensitive to bio-magnetic measurement then records the magnetic dipole field [50].

Radiology:

This method is primarily used to locate the gastroretentive dosage form filled with radio opaque marker barium sulphate inside the body concerning time using X-rays. At various intervals, X-ray images are taken to capture the exact location of the dosage form [51,52].

¹³C Octanoic Acid Breath Test:

To evaluate the degree of drug absorption from GRDDS, radioactive ¹³C Octanoic acid is used. This radiolabeled substance is absorbed from the duodenum the amount of Octanoic acid absorbed can be determined by comparing the amount of CO₂ exhaled during metabolism. Isotope ratio mass spectroscopy is used to measure radiolabeled CO₂ [47, 48].

In-Vitro Evaluation Parameters:

GRDDS *in vitro* evaluation can be used to estimate *in vivo* performance (Table 3).

CONCLUSION

For drugs with limited absorption windows, high solubility at acidic pH and instability at alkaline pH, GRDDS have emerged as new techniques for enhancing therapeutic efficacy, controlled

delivery, and bioavailability of drugs. For the successful design of GRDDS, it is essential to take into account the physiological event in the GIT, the choice of appropriate drug and excipient combinations, and the design of optimal formulation strategies. Additionally, a QbD approach can be employed for a better understanding of how formulation and process variables affect the performance of the final product. To develop the optimal GRDDS formulation, *in-vivo* studies are necessary due to the complexity of the pharmacokinetics and pharmacodynamics characteristics of specific drug. In the future, experts predict that the importance of gastroretentive dosage forms will rise, ultimately resulting in increased efficacy of various pharmacotherapies.

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