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INNOVATIONS IN GASTRO - RETENTIVE DRUG DELIVERY: "A PATHWAY TO ENHANCED MEDICATION EFFICIENCY"

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ABSTRACT

Gastroretentive drug delivery systems (GRDDS) are made to remain in the stomach for prolonged durations, slowly releasing drugs at a controlled rate. GRDDS allow drugs to act best in the upper part of the stomach or intestine, such as ulcers or require frequent dosing, to remain where they get absorbed best. GRDDS enhance therapeutic performance, minimise dosing frequency, and maximise patient compliance. Problems exist, however, in the form of short retention times in the stomach and perturbed stomach evacuation, which might push drugs prematurely out of their position. Units such as float tablets, sinking devices, or adhesive drug formats enable drugs to remain in place. The systems suit medicines that are labile in the lower intestine or rapidly metabolised by the liver. The units do not include acid-sensitive medicine or superior, absorbed-in-the-lower-intestine medicines. Overall, GRDDS strike a balance between advantage and prudent drug choice and clever design.

KEYWORDS: gastro retentive system, drug bioavailability, retention time, controlled release.

INTRODUCTION

Oral controlled-release delivery systems (GRDDS) are being extensively researched for their therapeutic effects, simplicity of dosage, patient compliance, and safety. The systems allow controlled and sustained release of the drug while retaining it within the stomach to maintain constant absorption at the specific site of absorption in the gastrointestinal tract (GIT).[1,2] GRDDS can enhance regulated drug release through continuous discharge of medication at the right rate and desired site of absorption until the complete emptying of the dose form.[3]

However, GRDDS has some challenges in the form of short gastric retention time (GRT) of the stomach and irregular short gastric emptying time (GET), which can decrease the effective number of drugs delivered from the dosage form in the absorption region. To overcome this, GRDDS has introduced strategies like sinking or high-density systems, which can be retained at the lower end of the stomach.[4,5,6]

These are determined by factors like drug solubility, the viscosity grade, the molecular weight of the polymer, the composition of the polymer in the dosage form, and the types of polymers. The physicochemical characteristics of the excipients, including the composition of effervescent agents in effervescent floating systems, as well as the density of the excipients, also play an important role.[7,8]

This review seeks to report details of all GRDDS developed so far, the physiological condition of the stomach, right pharmacological candidates for GRDDS, factors that influence GRDDS, characterisation of GRDDS in vitro and in vivo, and issues and challenges for GRDDS.[9,10]

ANATOMY AND PHYSIOLOGY OF GASTROINTESTINAL TRACT

Three primary areas make up the gastrointestinal tract

1. The stomach
2. The duodenum, jejunum, and ileum of the small intestine
3. The large intestine.

The gastrointestinal tract or GIT is a muscular tube from the mouth to the anus with functions of secretion, motility, digestion, absorption, and excretion. Its four anatomical parts build the stomach, a J-shaped enlargement. The stomach holds food and mixes food with gastric secretions prior to the release of the chyme into the small intestine for absorption and digestion. The volume of the stomach is able to be expanded to 1 litre if full.[11]

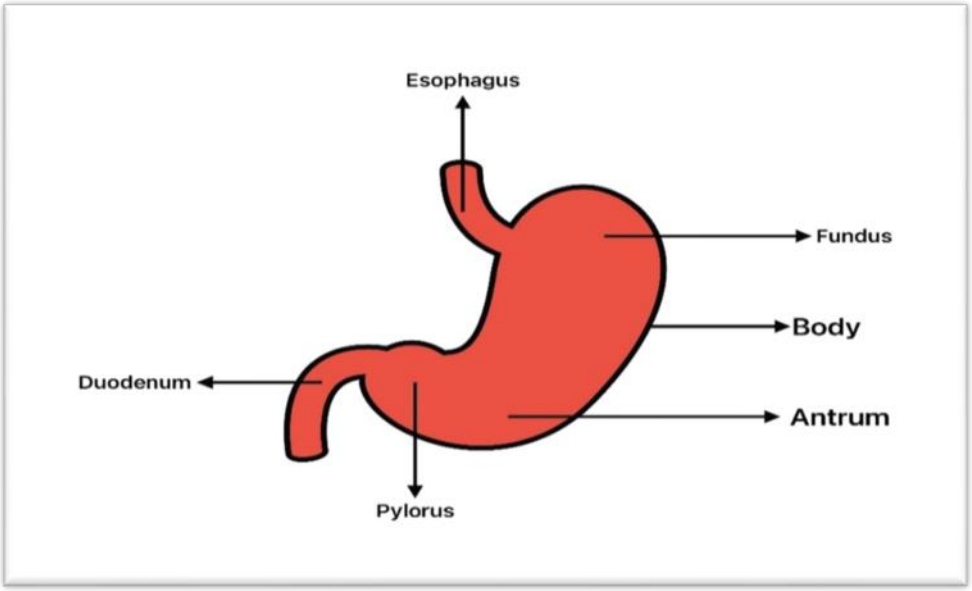


Fig 1: Illustrative view of the anatomy of the stomach.[12]

When fasting, the intestine and stomach have cyclic contractions every 2-3 hours, referred to as the migrating myoelectric cycle (MMC), which consists of four phases. When you are fed, the pattern of contraction shifts to the digestive motility pattern, which consists of four phases as well. The body and fundus are reservoirs for undigested content, whereas the antrum churns and moves food toward digestion. Gastric emptying takes place during fasting and fed states, but motility patterns are different in these states.[13]

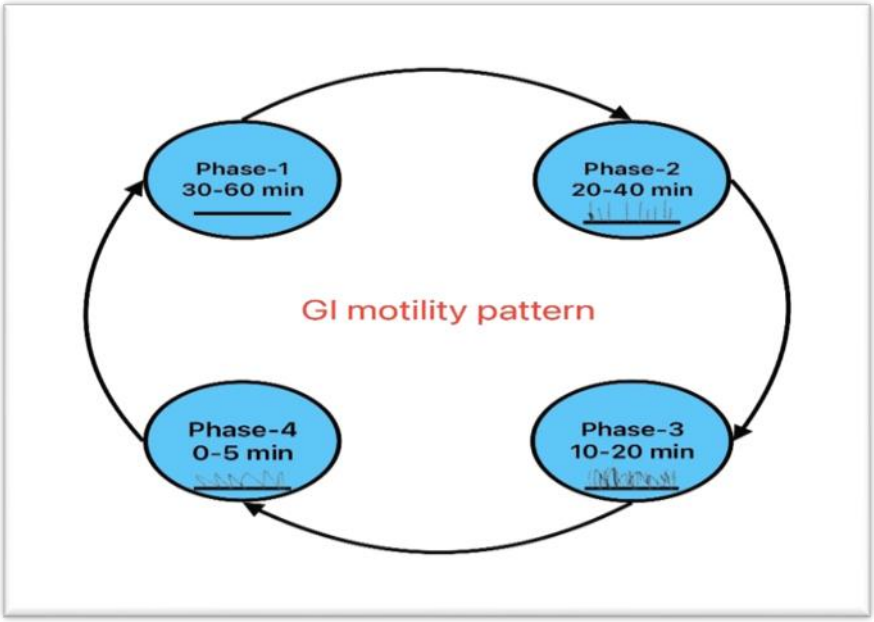


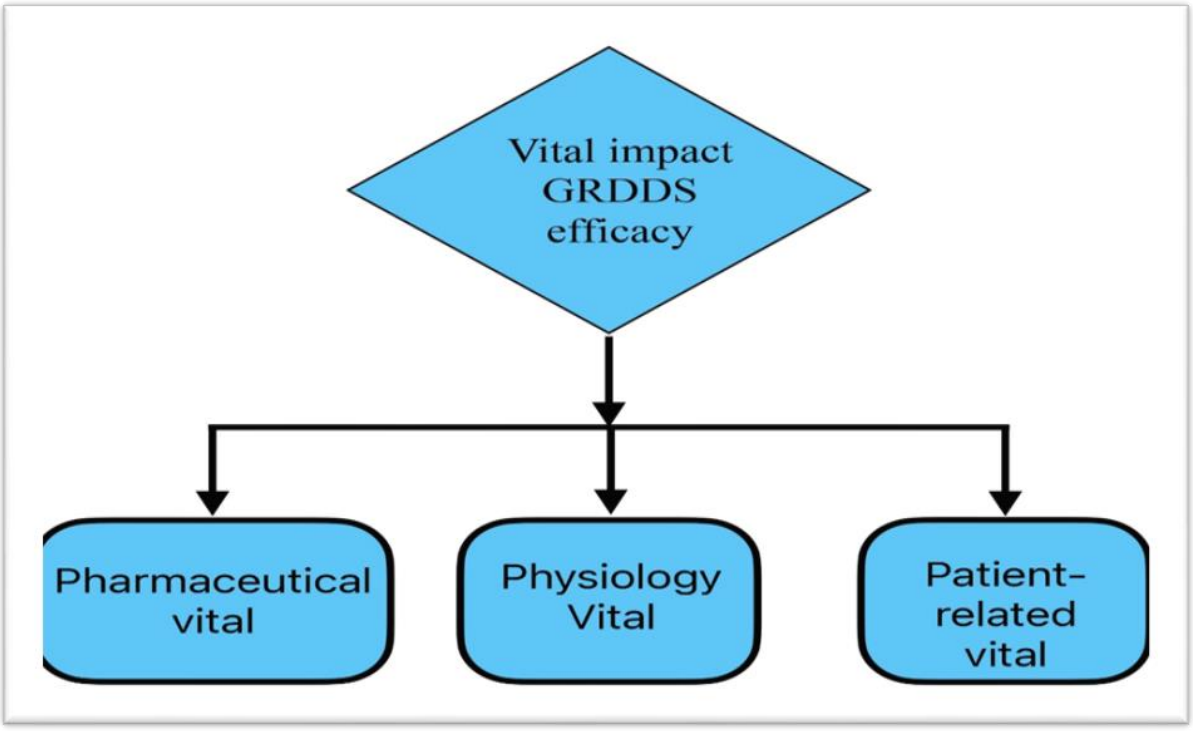
Fig 2: Schematic delineation of inter digestive motility.[14]

Table 1: Four phases in migrating myoelectric complex (MMC).[13,15,16]

Phase 1	**Rest Period**: Lasts 30 to 60 minutes with no stomach contractions—just a time of stillness.
Phase 2	**Gradual Contractions**: Slow and steady contractions start and build up over 20 to 40 minutes. Tiny particles and fluids start moving out of the stomach.
Phase 3	**Intense Cleaning Contractions**: For about 10 to 20 minutes, strong stomach contractions, called "house-keeper waves," happen 4-5 times a minute. These powerful contractions push the stomach contents down into the small intestine.
Phase 4	**Transition Period**: This brief phase, lasting 0 to 5 minutes, marks the end of the intense contractions and leads back into the quiet phase.

VITAL IMPACT GRDDS EFFICACY

Various vital impacts on the performance of gastroretentive dosage forms. These impacts are mainly categorized into pharmaceutical vital, physiological vital, and patient-related vital.



1. Pharmaceutical vital

An understanding of the function of excipients and polymers in various forms of GRDDS is very important for its effective design.[8] The requirement of high mucoadhesion strength polymers such as ascarbopol and hydroxypropyl methylcellulose for mucoadhesive dosage forms,

whereas polymers with a high swelling strength are preferred for expanding systems, can be determined by molecular weight, viscosity, and physiochemical characteristics of the polymers in modifying the dosage formulation.[13] These excipients can comprise super-porous hydrogel formulation using crospovidone, sodium croscarmellose with high swelling capacities as excipients, and carbonating agents of effervescent floating tablets. Shape and unit dosage size also matter. The tetrahedral and ring shapes of the dosage form contain a larger GRT.[17]

Low and high-density systems worry about density. In low-density systems, the density of the dosage form should be lower than gastric fluid to float in the gastric environment.[18] In high-density systems, the density of the dosage form should be greater to sink at the bottom of the stomach and prevent gastric emptying.[19,20]

2. Physiology vital

- **Concentration of the dosage form**

The density of a dose form affects its positioning in the stomach and its gastric emptying rate.[21] High-density systems settle at the bottom, while less dense forms float to the top. The system can be separated from the pylorus, but a density of less than 1.0 gm/cm3 is required.[22]

- **Physical form and dimensions**

The size and shape of indigestible single-unit solid dosage forms are crucial for their stomach residence periods. Larger dose forms have longer gastric retention times (GRT) as they don't allow quick passage of the gastric antrum into the gut.[23] Dosage forms with diameters over 7.5mm have better stomach residence times, while ring and tetrahedron-shaped devices have better gastric residence times.[24]

- **Dietary intake and its nature**

The retention of dose forms in the stomach is influenced by various factors such as meal consumption, food caloric value, viscosity, volume, and frequency of feeding. The gastric retention time (GRT) is determined by the presence or absence of food in the gastrointestinal tract (GIT), with increased acidity and caloric content potentially extending stomach retention of dose forms.[25]

3. **Patient-related vital**

- **Gender and age**

The behaviour of gastroretentive dose forms can be affected by the influence of age and gender on gastrointestinal transit time and physiology.

- **Determinants of disease**

The performance of GRDDS can be affected by some medical diseases that alter stomach emptying and motility, e.g., gastroparesis or gastrointestinal disease.

- **Compliance of the patient**

GRDDS effectiveness is influenced by patient-related factors like drug compliance, dose form acceptability, and dosing instructions. Surveys and studies focus on these factors. Pharmaceutical scientists aim to improve the clinical efficacy, safety, and patient acceptability of GRDDS by considering these parameters during formulation and design.[26]

SUITABLE DRUG CANDIDATES FOR GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS[27]

1. Molecules with low intestinal absorption but superior absorption in the upper portion of the GIT are often the best candidates for GRDDS.
2. Has a local effect on the abdomen.
3. Mainly taken up in the stomach.
4. Medications that require frequent intake and possess a brief half-life.
5. Those that undergo first-pass metabolism.
6. Drugs that are required for local action in the stomach. e.g. Antacids and enzyme preparation.

DRUGS THOSE ARE UNSUITABLE FOR GRDDS[15]

1. Medications that are poorly soluble in acid (such as phenytoin)
2. Medication that is unstable or breaks down in the stomach's acidic environment (such as erythromycin).
3. Medications that are intended to be released specifically into the colon, such as corticosteroids.

Table 2: Potential possibilities for a gastro retentive drug delivery system.[28]

Sr.No	Drug and category	Bioavailability
1	Propranolol (Antihypertensive)	4-26%
2	Verapamil (Antihypertensive)	18-35%

3	Verapamil (Calcium channel blocker)	20-35%
4	Ramipril (ACE inhibitor)	28%
5	Lidocaine (Local anaesthetic)	35%
6	Omeprazole (Proton pump inhibitor)	35-60%
7	Diltiazem (Calcium channel blocker)	40%
8	Atenolol (Antihypertensive)	40-50%
9	Nifedipine (Calcium channel blocker)	45-65%
10	Clarithromycin (Antibiotic)	50%

ADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

1. Improved bioavailability

Because of varied transit and absorption processes in the gastrointestinal tract, riboflavin CR-GRDF exhibits much greater bioavailability compared with non-GRDF CR polymeric formulations.[29]

2. Enhanced biotransformation during the first pass

The steady-state delivery of a drug to metabolic enzymes such as cytochrome P450 and CYP3A4 as opposed to bolus delivery might enhance the pre-systemic metabolism of the test drug considerably, much like the increased efficacy of active transporters.[30]

3. Targeted treatment of upper GIT local conditions

For the local treatment in the stomach and small intestine, extended and sustained delivery of the drug from GRDF to the stomach can be useful. Local drug concentration levels can be achieved therapeutically by this mode of administration, while systemic levels following drug absorption and dispersion are zero.[31]

4. Reduction of medication concentration fluctuations

It allows the pharmacologic effect of drugs that stimulate different receptor types at different doses to be partially selective.

5. Drug delivery to specific sites

A floating dose form is an effective approach, especially for drugs with limited upper small intestine absorption sites.[32]

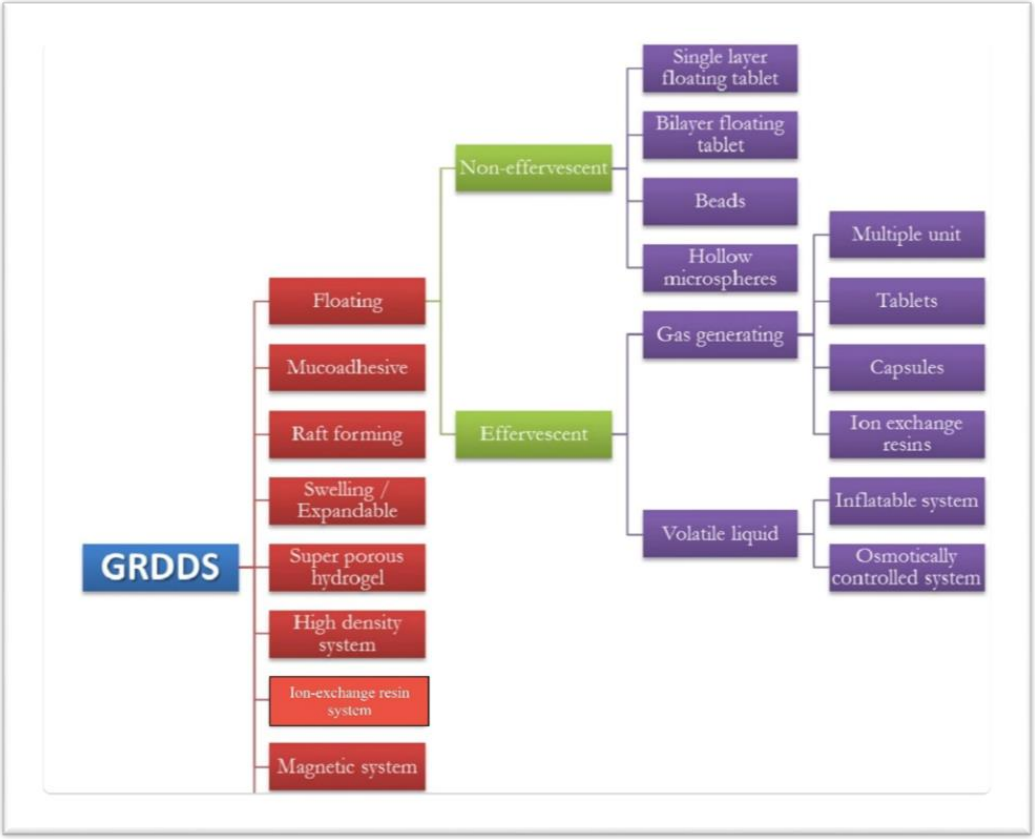
DISADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS[33]

1. It is not appropriate for medications that are unstable in acidic environments.
2. It is not appropriate for medications that are better absorbed in the lower gastrointestinal tract.

3. The challenge of achieving the intended result and the issue of dosage dumping.
4. Poor in vitro and in vivo correlation.
5. Higher cost of formulation.

VARIOUS APPROACHES TO ACCOMPLISH GASTRIC RETENTION OF DOSAGE FORMS

Gastro-retentive drug delivery systems (GRDDSs) are strategies that aim to increase a drug's gastric residence time for enhanced therapeutic effects and oral availability.[34] Three principal systems are floating, bioadhesive, and swelling systems, which provide sustained drug residence time in the stomach, improving absorption profiles for narrow absorption windows. GRDDSs can be single-unit or multi-unit systems, depending on preparation methods and dosage forms.[35] Development involves using special materials like mucoadhesives, resins, low-density materials, super porous hydrogels, magnetic particles, and raft-forming agents to customise performance and meet specific pharmacological and therapeutic needs. Each material plays a vital role in customising GRDDSs' performance.[36,37]



1. Floating Drug Delivery Systems (FDDSs).

FDDSs, or floating sustained release dosage forms, possess lower bulk density than gastric liquids, thus enabling them to float in the stomach for quite some time without influencing gastric emptying rates.[38] Such systems are referred to as hydrodynamically balanced systems (HBS) and demonstrate properties of hydrophilic matrices and are slowly released from the swollen matrix. They float in the gastric content for three to four hours without altering the intrinsic rate of emptying. Research has established that the buoyancy principle holds for prolonged gastric emptying time, enhanced drug bioavailability, and improved clinical outcomes.[39] Cellulose ether polymers, especially hydroxypropylmethylcellulose (HPMC), are frequently utilised for floating form design. FDDSs are used for drugs with best absorption at low ph, useful in GI infection eradication and inflammatory disorders. They may be single or multi-unit, with single-unit systems having high inter-subject variability in gastric emptying time.[40]

- **Non-effervescent system**

Non-effervescent multiple unit systems have been documented in the literature, but there are some scientists who believe that chitosan can be utilized as a polymeric excipient for drug delivery.[41] A needle has been used to extrude an extrusion-produced multiple-unit HBS containing indomethacin, which has been published. Cellulose acetate phthalate, liquid paraffin, and ethyl cellulose have been utilized as release modifiers in other studies.

Floating tablets are manufactured through direct compression and a combination of FDM and HME techniques.[42] Souza et al. developed floating tablets of sildenafil citrate using HPMC K100 CR and HPMC K4M, with low floating lag times and an in vitro floating duration of more than 24 hours. Eberle et al. examined drug release and flotation in a gastro-retentive drug delivery system (GRDDS) from functionalized calcium carbonate, with excellent flotation characteristics and no floating lag time.[43,44,45]

The application of double- and multi-layered floating drug delivery systems (FDDSs) is on the rise and incorporates active pharmaceutical ingredients in one dosage form. Bilayer floating tablets consisting of two distinct layers have demonstrated usefulness for diabetes mellitus treatment.[46] Oral in situ gelling liquid preparations provide extended floating duration and controlled drug discharge rates. Foaming to prepare stable floating systems is a relatively newer method awaiting further studies.[47,48]

- **Effervescent Floating Systems**

Effervescent systems, such as gas-forming and volatile liquid-holding systems, are examined for their capability to generate gas upon drug release.[49] Research revealed that a combination of sodium bicarbonate and hydroxyethylcellulose could form swellable and floatable GRDDSs of losartan, with improved bioavailability and decreased metabolite formation.[50] Increasing the number of effervescent agents may decrease the floating time.

Effervescent systems, such as gas-generating and volatile liquid-containing systems, are investigated for their drug-delivery potential.[51]

2. Expandable Systems

Expandable drug delivery systems (GRDDS) are made to attain higher GRT through volume or shape expansion. They were first created for veterinary purposes and are now applied to humans.[30] The system can be small for oral intake, expand in the stomach to avoid passing through the pyloric sphincter, and return to its original shape once full drug release is attained. Two types of system expansion—swelling and unfolding—allow volume and shape modification.[51] The primary mechanism of swelling is diffusion, employing hydrophilic polymers such as carbopol, polyethylene oxide, and HPMC. In systems of unfolding, the drug and polymer are folded or compressed in a gelatin capsule.[52] The optimal ratio of polymer and gas-forming agent must be employed to obtain the desired GRDDS.[53] However, they possess some limitations, like the storage difficulty of biodegradable polymers, preparation and maintenance difficulty, and susceptibility to intestinal adhesion, gastropathy, and colonic obstruction.[54]

3. Magnetic Systems

Magnetic systems are based on the attraction of an external magnet and a dose form containing a magnetically active chemical, which enables the retention of the dose form for a long time in the stomach. Controlled release profiles of acetaminophen.[55] and acyclovir.[56] from such systems have been demonstrated through studies, but the formulations are limited because they require an external magnet.[35] External magnets were shown to enhance the AUC and mean residence time of tablets. A new dose form comprising sinking magnetic microparticles (SMMP) uniquely formulated for the stomach has also been invented, with high-density amoxicillin.[57] The SMMP possesses good magnetic properties in vitro and in vivo, and can be sustained by the application of an external magnet, leading to higher H. pylori eradication compared to traditional dose forms.[58]

4. Bioadhesive/Mucoadhesive Systems

Mucoadhesive systems, which stick to the stomach lining once ingested, are a potential treatment for localized infections.[35] These systems engage in mucoadhesion with mucin via electrostatic forces, hydrogen bonds, hydrophobic bonding, and disulfide bonding.[37] Sodium alginate, pectin, gelatin, and guar gum are natural polymers employed in their formulation, whereas semi-synthetic polymers such as gliadin, lectins, polycarbophil, carboxymethylcellulose, chitosan, and carbopol are employed.[36] The physical properties of the polymer, including flexibility, shape, cross-link density, H-bond-forming ability, hydration properties, and charge, control mucoadhesive properties and contact strength. Yet, they may lead to possible drug-induced damage owing to their ulcerogenic nature.

Multi-unit dosage forms, also known as bioadhesive microspheres, combine the strengths of mucoadhesive systems with those of traditional microspheres. Such systems can be printed onto tablets using 3D printing.[35] A new bioadhesive system, fabricated using nanomaterials, is being investigated in the field of pharmaceuticals and contemporary medicine.[59] In vivo investigations revealed that the mucoadhesion capacity of gliadin nanoparticle-loaded amoxicillin (AGNP) exhibited activity in eradicating H. pylori.[60]

Table 3: Different theories of the Mucoadhesive system.[35,60,61]

Sr.no	Theories	Mechanism
1.	Diffusion	The degree of bonding is determined by the interpenetration of the polymer and mucin chain. The mucoadhesive rises in direct proportion to the interpretation of the polymer.
2.	Adsorption	A number of main and secondary factors, including covalent, ionic, and hydrogen bonds, contribute to mucoadhesion.
3.	Wet ability	The angle of contact between the mucoadhesive and the surface decreases adherence. For best results, the contact angle must be as small as possible.
4.	Electronic	predicated on the notion that the mucoadhesive layer and the biological layer are attracted to one another due to their opposing charges, which causes mucoadhesion.
5.	Fracture	The basis of this idea is the amount of mechanical force needed to separate the glued surface.

5. Raft-Forming Systems

Raft-forming drug products are prepared to form a gel floating cover over the stomach contents, commonly composed of sodium alginate and effervescent aids such as carbonates or bicarbonates.[35] Such systems are useful in eradicating H. pylori and gastroesophageal reflux treatment. Manna et al. reported that an HPMC-alginate-PVP combination could be

employed to prepare anti-acidic raft-forming systems with improved bioavailability.[63] Hampson et al. reported that systems with high acid-neutralizing strength and no sources of calcium ions produced rafts that were similar to suspended precipitates.[64] Wannasarit et al. created a liquid raft-forming system with Eudragit® EP (GR-SD) and Centella asiatica extract, releasing more than 80% of the active glycosides within 8 hours. Such raft-forming systems have been demonstrated to be potential treatments for gastric ulcers and are effective in in vivo testing.[65,66]

6. High-Density Systems

High-density systems use their high weight density to retain substances, extending their mean stomach retention time from 5.8 to 25 hours.[67.68] They quickly descend through gastric contents to the stomach floor, allowing APIs to diffuse and remain intact slowly. To increase dose density, barium sulfate, iron powder, titanium oxide, and zinc oxide are used. More studies are needed to prove their efficacy.[69]

7. Ion-Exchange Resin Systems

Ion-exchange systems consist of an API and a water-insoluble cross-linked polymer, known as resin, which is either cationic or anionic. When a drug comes into contact with an anionic polymer, ions enter the resin matrix, and protons take the place of the cationic APIs. The release rate of the resins is influenced by parameters such as ionogenic group type, cross-linking density, particle size, test solution, ionic environment, and drug type.[70] Polystyrene and polymethacrylate polymers are the most used. Daihom et al. sought to create a domperidon-loaded resinate complex with controlled release of the drug to explore the possibility of using ion-exchange systems in gastroretentive formulations.[70]

CAPABILITY NATURAL POLYMERS FOR GRDDS

Natural polymers are non-toxic, non-irritating, and biocompatible as a result of their high carbohydrate content. Natural polymers are obtained from natural sources and may be harvested inexpensively. Manufacture in developing countries is favoured because of their extensive application.[71] Table 4 shows various commonly used natural polymers in GRDDS.

Table 4: Natural polymers in GRDDS.

Sr. No.	Natural polymers	Applications in GRDDS
1.	*Colocasia esculenta gum*	Swelling agent, Mucoadhesive, Sustained effect
2.	Psyllium husk	Swelling agent, Sustained effect
3.	Gum karaya	Swelling agent, Mucoadhesive, Sustained effect

4.	Guar gum	Swelling agent, Mucoadhesive, Sustained effect
5.	Okra gum	Swelling agent, Mucoadhesive, Sustained effect
6.	Tamarind gum	Swelling agent, Mucoadhesive, Sustained effect
7.	Tara gum	Swelling agent, Mucoadhesive, Sustained effect
8.	Carrageenan	Swelling agent, Sustained effect
9.	Chitosan	Swelling agent, Sustained effect
10.	Pectin	Swelling agent, Sustained effect

COMMON DRUGS AND MARKET TRENDS IN GASTRORETENTIVE DOSAGE FORM

Table 5: Common drugs for gastroretentive formulations.[22,72]

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

Table 6: Gastroretentive products available in the market.[72,73]

Brand Name	Active Ingredient(s)
Cifran OD ®	Ciprofloxacin
Cytotec®	Misoprostal
Madopar ®	L-DOPA and Benserazide
Conviron	Ferrous sulfate
Valrelease ®	Diazepam
Liquid Gavison ®	Aluminium hydroxide,
Topalkan ®	Aluminium -magnesium antacid
Almagate FlatCoat ®	Aluminium -magnesium antacid

CONCLUSION

Particularly for drugs that work best in the upper gastrointestinal tract or require longer retention, gastroretentive drug delivery systems (GRDDS) offer a valuable method of increasing therapeutic efficacy. GRDDS enhances patient compliance and treatment efficacy by reducing dosage frequency and increasing bioavailability. New formulations like floating, sinking, or adhesive types are required to counter problems with low stomach retention and

inconsistent gastric emptying. When well selected and engineered, GRDDS exhibit unprecedented benefits, with justification in drug delivery approach with targeting, albeit not suitable for lower-intestinal or acid-sensitive drugs.

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