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Gastroretentive Drug Delivery System: A Comprehensive Review of Approaches, Mechanisms, and Applications

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Abstract: Gastroretentive drug delivery systems (GRDDS) represent an innovative strategy developed to overcome the drawbacks associated with conventional oral dosage forms, such as rapid gastric emptying and poor bioavailability. These systems are specifically designed to increase the residence time of drugs in the stomach, thereby improving drug absorption, particularly for drugs having a narrow absorption window, low solubility at intestinal pH, or those intended for local gastric action, GRDDS employ different mechanisms, including floating, mucoadhesion, swelling, high-density, and raft-forming approaches to achieve prolonged gastric retention. Their performance is influenced by various physiological factors, such as gastric pH, motility, and feeding conditions, along with formulation-related factors like size, density, and polymer characteristics. Polymers and excipients play a significant role in controlling drug release and maintaining formulation stability. These systems offer advantages such as enhanced bioavailability, reduced dosing frequency, and improved therapeutic outcomes. However, certain limitations, like variability in gastric retention and formulation complexity, still exist. With continuous advancements in polymer science, nanotechnology, and formulation techniques, GRDDS are expected to play a crucial role in future controlled and targeted drug delivery systems.

Keywords: *Gastro-Retentive Drug Delivery System, Gastric Residence Time, Controlled Drug Delivery, Floating Drug Delivery System, Gastrointestinal Physiology.*

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I. INTRODUCTION

The oral route remains the most commonly used method for drug administration due to its convenience, safety, and high patient adherence. Recent advancements in oral drug delivery systems have enabled the development of controlled-release platforms that act as reservoirs for active pharmaceutical ingredients, facilitating sustained and regulated drug release.[1] Conventional oral formulations, however, face physiological limitations such as variable gastric emptying, short gastrointestinal transit times (typically 8–12 hours), and restricted absorption windows for certain drugs in the upper small intestine.[2] Gastric emptying is highly dependent on meal type and composition; liquids typically empty within 1–2 hours, whereas solids may take 3–6 hours, and mixed meals generally have half-emptying times ranging from 50 to 110 minutes.[2] This variability can adversely affect drug absorption and overall bioavailability. To address these challenges, gastroretentive drug delivery systems (GRDDS) have been developed to prolong gastric residence, enabling predictable drug release, sustained plasma drug concentrations, and reduced dosing frequency.[2,3] Nevertheless, rapid or inconsistent gastric emptying in some individuals may still compromise release efficiency, making site-specific retention particularly advantageous for drugs with narrow absorption windows or stability concerns.[3]

➢ *Anatomy of Stomach*

The gastrointestinal tract is a long muscular tube extending from the mouth to the anus, measuring approximately 9 meters in length and consisting of the stomach, small intestine, and large intestine.[4] The stomach is a curved organ located in the upper left abdominal region and is divided into the fundus, body, and pylorus. Its wall is made up of three smooth muscle layers—oblique, circular, and longitudinal—which help in mixing and movement of gastric contents. The gastric mucosa contains specialized cells such as mucous cells (protective mucus), parietal cells (hydrochloric acid), chief cells (pepsin for protein digestion), and G-cells (gastrin secretion for regulation of gastric activity). [5]

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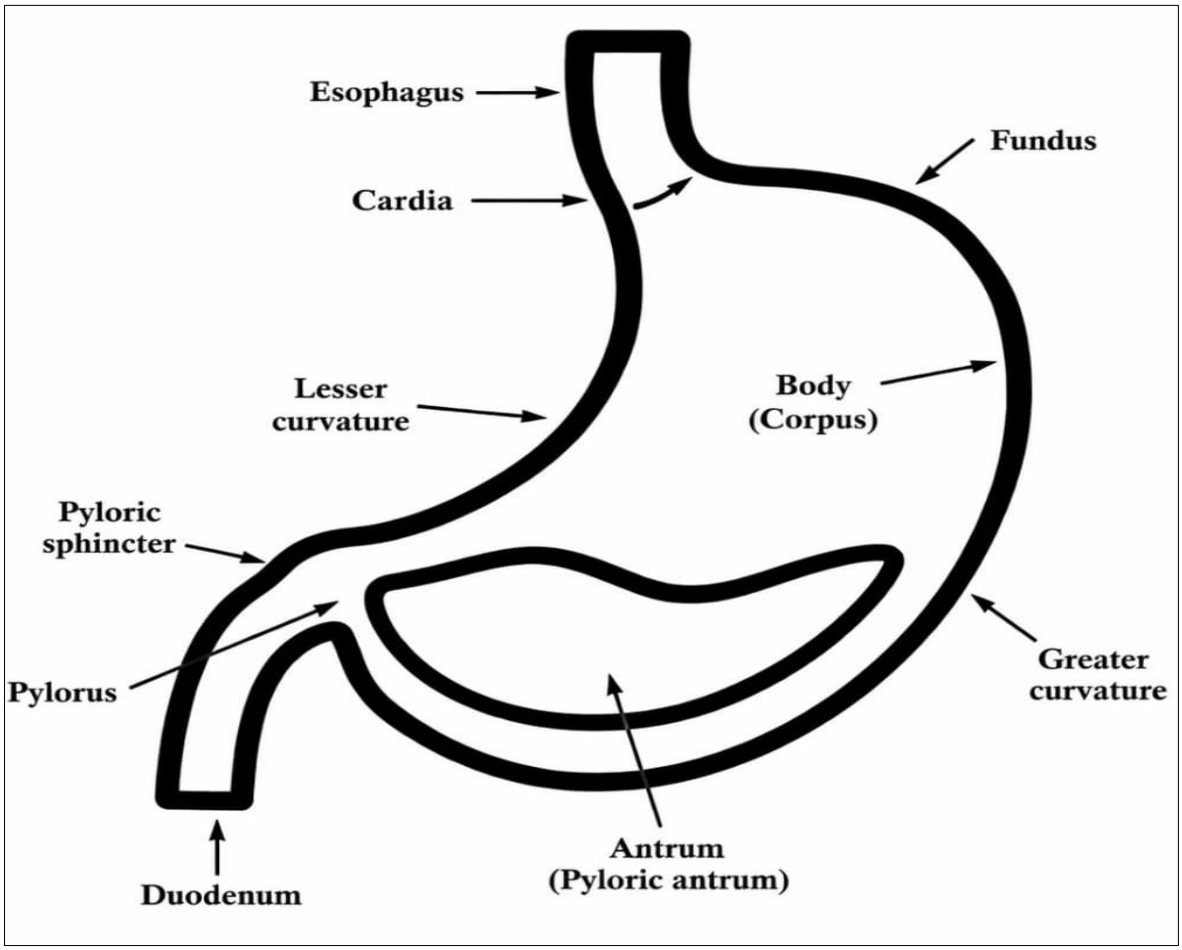

Fig 1 Schematic Illustration of the Anatomical Regions of the Stomach

➢ *Physiology of Stomach*

The gastrointestinal system plays an important role in drug release and absorption, which are influenced by factors such as gastric pH, enzymes, and mucosal characteristics. Gastric activity occurs in two states: fasted and fed. In the fasted state, motility follows the migrating motor complex (MMC), consisting of four phases: resting phase, intermittent contractions, strong contractions (housekeeper wave), and a short transition phase. These cycles repeat every 2–3 hours and help clear stomach contents. After food intake, this pattern is replaced by continuous contractions known as postprandial motility, which increases gastric residence time and affects the performance of gastroretentive drug delivery systems.[6]

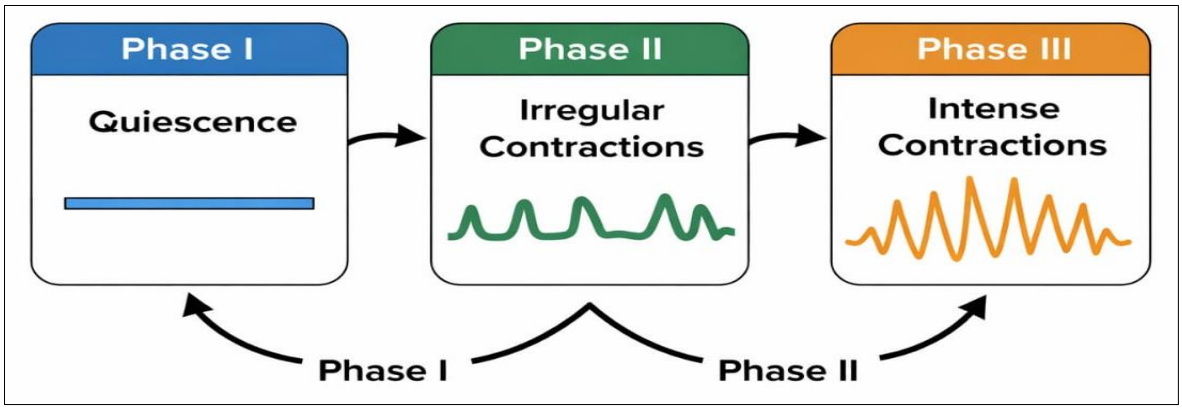

Fig 2 Phases of Gastric Motility and Gastric Emptying Rate

➢ *Rationale of GRDDS*

- Conventional oral drug delivery systems are widely used but often fail to provide targeted drug release at a specific site in the gastrointestinal tract.
- Certain drugs exhibit site-specific absorption, meaning they are absorbed efficiently only in particular regions of the GIT, which requires controlled drug release at that location.

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- To overcome these limitations, modern pharmaceutical research is focused on designing advanced delivery systems capable of site-directed drug release.
- Gastroretentive drug delivery systems (GRDDS) are developed to retain the dosage form in the stomach for an extended period and enable controlled drug release in target regions such as the stomach, duodenum, or upper intestine.
- Variations in gastric emptying time can result in inconsistent drug release and unpredictable absorption from conventional dosage forms.[7]

➢ *Objective of GRDDS*

- Prolongation of gastric residence time: To design systems that remain in the stomach for an extended duration, thereby enhancing therapeutic efficiency.
- Sustained and controlled drug release: To achieve predictable and prolonged drug release, which helps in reducing dosing frequency and improving patient compliance.
- Exploration of formulation strategies: To evaluate different gastroretentive approaches such as floating, mucoadhesive, swelling, and high-density systems for improved retention.
- Identification of formulation challenges: To recognize potential issues like gastric irritation or weak adhesion and develop strategies to enhance safety and performance.
- Minimization of adverse effects: To maintain stable plasma drug levels and reduce fluctuations that may lead to side effects.
- Evaluation of cost-effectiveness: To compare GRDDS with conventional systems in terms of manufacturing feasibility and therapeutic benefits.[8]

➢ *Factors Affecting Gastro-Retention Time (GRT)*

- Density of dosage form: The density should be lower than gastric fluid (~1.004 g/mL) to ensure floating and prolonged retention.
- Size of dosage form: Larger dosage forms (generally >7.5 mm) tend to remain in the stomach for a longer duration.
- Shape of dosage form: The geometry of the system influences retention; specific shapes like tetrahedral structures may enhance gastric residence.
- Single-unit vs. multiple-unit systems: Multiple-unit systems provide more uniform drug release and reduce the chances of dose dumping compared to single-unit forms.
- Fed and fasting state: During fasting, the MMC clears gastric contents every 1.5–2 hours, reducing retention, whereas food intake increases gastric residence time.
- Type of meal: Fat-rich meals delay gastric emptying and help in prolonging retention time.
- Caloric value of food: High-fat and high-protein meals can significantly increase GRT, sometimes by 4–10 hours.
- Feeding frequency: Repeated intake of food can extend gastric residence time beyond 400 minutes.
- Gender differences: Gastric residence time is generally shorter in males (~3.4 hours) compared to females (~4.6 hours).
- Age factor: Older individuals (above 70 years) usually exhibit prolonged gastric retention.[10-14]

➢ *Potential Drug Candidates for GRDDS*

- Drugs that are primarily absorbed in the stomach are considered ideal candidates for GRDDS, as prolonged gastric retention enhances their overall absorption (e.g., Ampicillin).
- Drugs that exhibit poor solubility at alkaline pH benefit from extended exposure to the acidic environment of the stomach (e.g., Furosemide, Diazepam).
- Drugs with a narrow absorption window in the upper gastrointestinal tract require prolonged gastric residence time to achieve improved bioavailability (e.g., Levodopa, Methotrexate).
- Drugs that are unstable or undergo degradation in the colon are more suitable for gastroretentive drug delivery systems (e.g., Ranitidine, Metformin HCl).
- Drugs that are rapidly absorbed from the gastrointestinal tract or intended for local action in the stomach can also benefit significantly from GRDDS.[8]

Table 1 Good Candidates for Gastroretentive Drug Delivery System[8]

S. No	Drug	Category	Bioavailability
1.	Verapamil	Calcium channel blocker	20-35%
2.	Nifedipine	Calcium channel blocker	45-65%
3.	Omeprazole	Proton pump inhibitor	35-60%
4.	Atenolol	Antihypertensive	4-26%
5.	Diltiazem	Calcium channel blocker	~40%
6.	Lidocaine	Local anaesthetic	~35%
7.	Clarithromycin	Antibiotic	~50%
8.	Ramipril	ACE inhibitor	~28%
9.	Propranolol	Antihypertensive	4-26%

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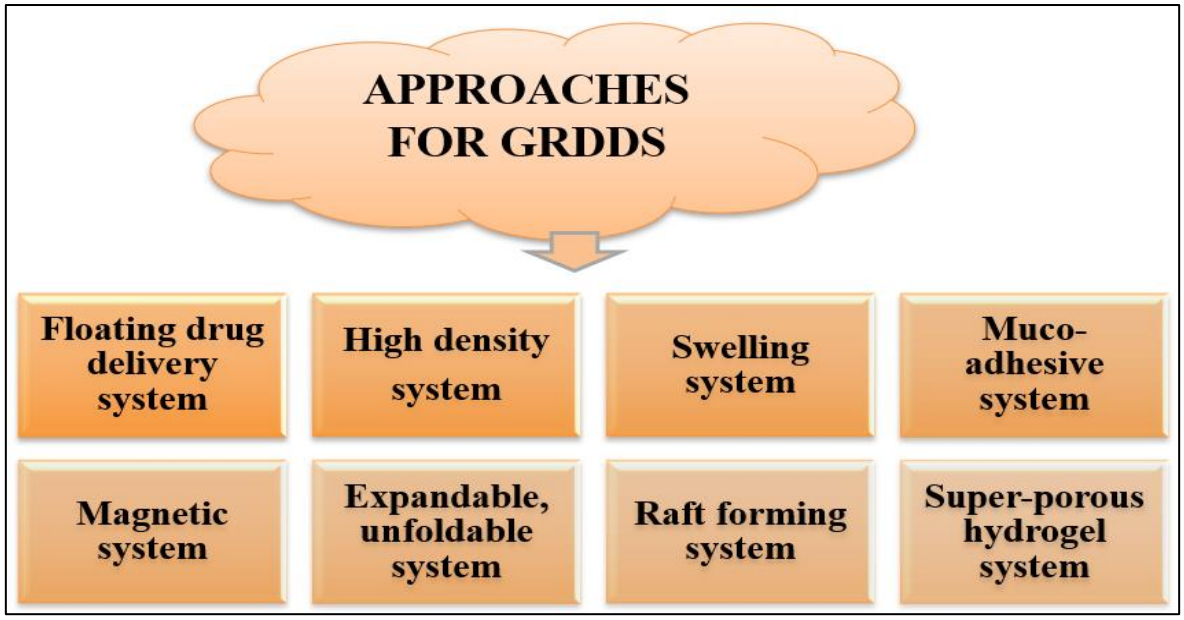
➢ *Approaches for GRDDS*



- *Floating Drug Delivery System:*

Floating drug delivery systems (FDDS) are low-density formulations that remain buoyant on gastric fluid, allowing prolonged gastric residence time (GRT). These systems release the drug in a controlled manner, helping to maintain stable plasma drug levels. FDDS are widely used as they do not significantly affect normal gastric motility. They are classified into effervescent and non-effervescent systems.[15]

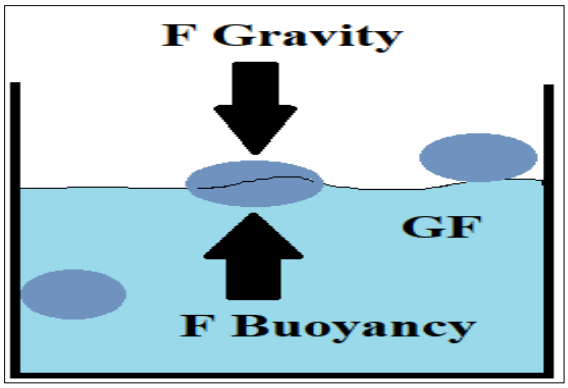


Fig 3 Mechanism of Floating System

➢ *Effervescent Floating System:*

These systems achieve buoyancy through gas generation, which lowers the density of the dosage form. Gas is produced either by: volatile liquids (e.g., ether, cyclopentane) and reaction of acids with carbonate/bicarbonate salts (CO_2 generation).

- *Volatile Liquid Systems*

✓ Contain two compartments (drug + volatile liquid)
✓ Liquid vaporizes at body temperature, causing flotation
✓ May include a bioerodible plug for controlled gas release
✓ Drug is released during the floating phase[12]

- *Gas-Generating Systems*

✓ CO_2 is generated by reaction of acids with carbonate salts
✓ Reduces density and enables floating
✓ Available as single or multiple-unit systems

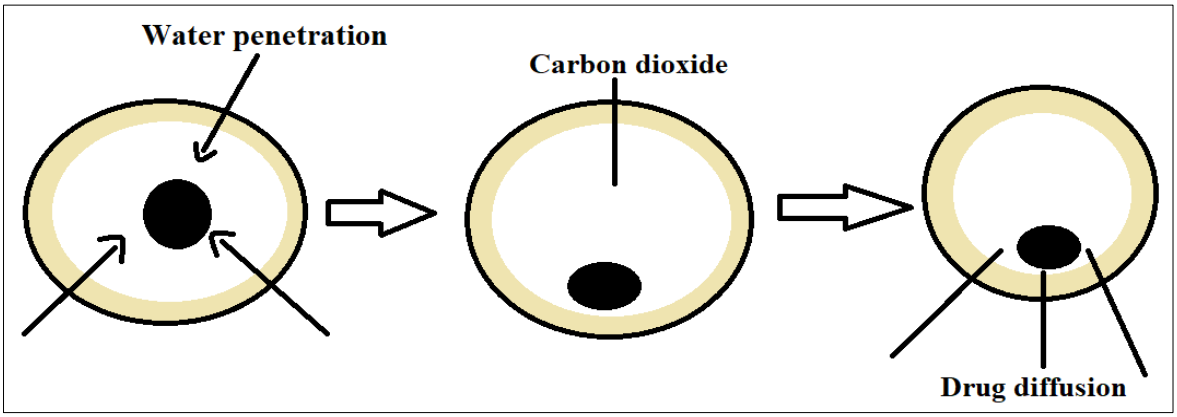


Fig 4 Gas Generating System

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➢ *Non-Effervescent Floating System:*

These systems rely on swelling and gel formation instead of gas generation. Use polymers like HPMC, sodium CMC, and polyacrylates. Form a gel barrier on hydration, trapping air and enabling flotation[18]

- *Hydrodynamically Balanced Systems (HBS)*

✓ Contain gel-forming polymers
✓ Float by forming a hydrated gel layer
✓ Drug release via diffusion and erosion

- *Microporous Systems*

✓ Drug reservoir enclosed in a microporous membrane
✓ Air chamber provides buoyancy
✓ Enables controlled drug release

- *Alginate Beads*

✓ Prepared using calcium alginate
✓ Porous structure provides floating ability[17]

- *Microballoons/Hollow Microspheres*

✓ Prepared by solvent evaporation/diffusion
✓ Remain buoyant for long duration
✓ Provide uniform drug release[18]

➢ *Disease-wise Representation of Drugs Formulated in Floating Drug Delivery System*

Table 2 Disease Wise Representation of Drugs Formulated in Floating Drug Delivery System

Disease	Drug+ Category	Method of Preparation	Therapeutic uses	References
Hypertension	Propranolol HCL (Beta-blocker) Losartan potassium (ARB) Amlodipine Besylate (Calcium channel blocker)	3D-Printed floating system Effervescent floating tablets Direct compression floating tablets	Hypertension cardiovascular disorder BP control Hypertension, Angina	79 80 81
Diabetes mellitus (Type 2)	Metformin HCL Metformin HCL	3D-Printed floating system Direct compression floating tablets	Glycemic control Blood glucose regulation	82 83
Peptic Ulcer/GERD	Famotidine Esomeprazole +Clarithromycin Amoxicillin	Semi-solid 3D printing Effervescent bilayer tablets Floating alginate beads	Ulcer treatment GERD+ infection H. Pylori treatment	84 85 86
Bacterial Infections	Ciprofloxacin HCL (Fluoroquinolone) Ofloxacin (Fluoroquinolone) Cefuroxime (Cephalosporin)	Direct Compression SFGRDDS Floating capsules (HBS) Hot melt extrusion	Broad-spectrum antibacterial Infection treatment Bacterial infections	87 88 89
Neurological disorder	Brivaracetam (Antiepileptic) Gabapentin (Anticonvulsant) Pregabalin (Anticonvulsant)	Direct compression tablets 3D-printing system Direct compression tablets	Epilepsy Neuropathy Epilepsy, Anxiety	90 91 92
Liver disorder	Silymarin (Hepatoprotective)	Direct compression tablets	Liver diseases	93

➢ *Bio/Mucoadhesive Systems:*

Bio/mucoadhesive drug delivery systems (BDDS) are designed to enhance drug retention in the stomach by adhering to the gastric mucosa. These systems use bioadhesive polymers that attach to the mucus layer or epithelial surface, thereby increasing gastric residence time (GRT) and improving drug absorption and bioavailability. However, their effectiveness may be reduced due to gastric motility, continuous mucus secretion, and mucus turnover. Commonly used bioadhesive polymers include polycarbophil, Carbopol, chitosan, gliadin, and lectins.

- *Mechanisms of Bio/Mucoadhesion:*

✓ Wetting theory: Polymer spreads over the mucus surface, ensuring close contact.
✓ Diffusion theory: Interpenetration of polymer chains with mucin leads to adhesion.
✓ Adsorption theory: Adhesion occurs due to secondary forces like hydrogen bonding and van der Waals interactions.
✓ Electron theory: Electrostatic attraction between oppositely charged polymer and mucosal surface contributes to adhesion.

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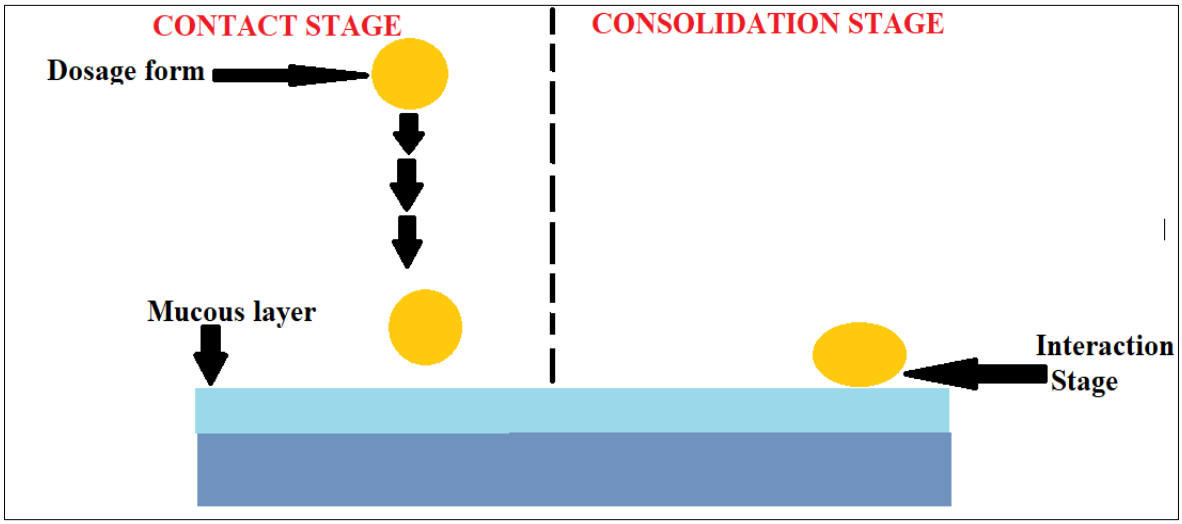

Fig 5 Bio/Mucoadhesive System

➢ *Types of Polymer–Mucus Interaction:*

- *Hydration-Mediated Adhesion*

✓ Hydrophilic polymers absorb water and become sticky
✓ Hydration level influences adhesive strength and retention[19]

- *Bonding-Mediated Adhesion*

✓ Adhesion occurs via mechanical and chemical interactions
✓ Includes ionic bonds, hydrogen bonding, and van der Waals forces[21]

- *Receptor-Mediated Adhesion*

✓ Specific binding occurs between polymers and epithelial receptors
✓ Example: Lectins interact with sugar residues in mucus/glycocalyx [22]

➢ *Representation of Drugs Formulated in Bio/Mucoadhesive Drug Delivery System*

Table 3 Representation of Drugs Formulated in Bio/Mucoadhesive Drug Delivery System

Drug	Category	Method of Preparation	Therapeutic Uses	References
Metronidazole	Antibiotic	Ion-sensitive in-situ gelation	Gastrointestinal infections Anaerobic bacterial infections Protozoal diseases include; Helicobacter pylori	93
Amoxicillin	Penicillin antibiotic	Ionic gelation method	Respiratory tract infections Urinary tract infection Skin infection	94
Piperine	Alkaloid (bioenhancer)	Ionic gelation method	Improve bioavailability of drugs Improve digestion Anti-inflammatory agent	94

- *Expandable, Unfoldable and Swellable Systems:*

Expandable gastroretentive systems are designed to increase in size after reaching the stomach, preventing their passage through the pyloric sphincter and thereby prolonging gastric residence time. At the same time, the system must be easy to swallow and safe for elimination without causing obstruction.

- *An Ideal System Generally Follows Three Stages:*

✓ Compact form for easy oral administration
✓ Expansion/unfolding in the stomach for retention
✓ Size reduction after drug release for safe removal

➢ *Types:*

- *Unfoldable Systems*

✓ Prepared using biodegradable polymers
✓ Compressed into capsules and unfold into shapes (e.g., ring, tetrahedral) after ingestion
✓ Larger size helps in prolonged retention

- *Swellable Systems*

✓ Absorb gastric fluid and increase in volume
✓ Swelling helps in retaining the dosage form in the stomach

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➢ *Limitations*

- Complex formulation design and higher production cost
- Stability issues of polymers during storage
- Risk of gastric irritation if retained for prolonged duration[20-25]

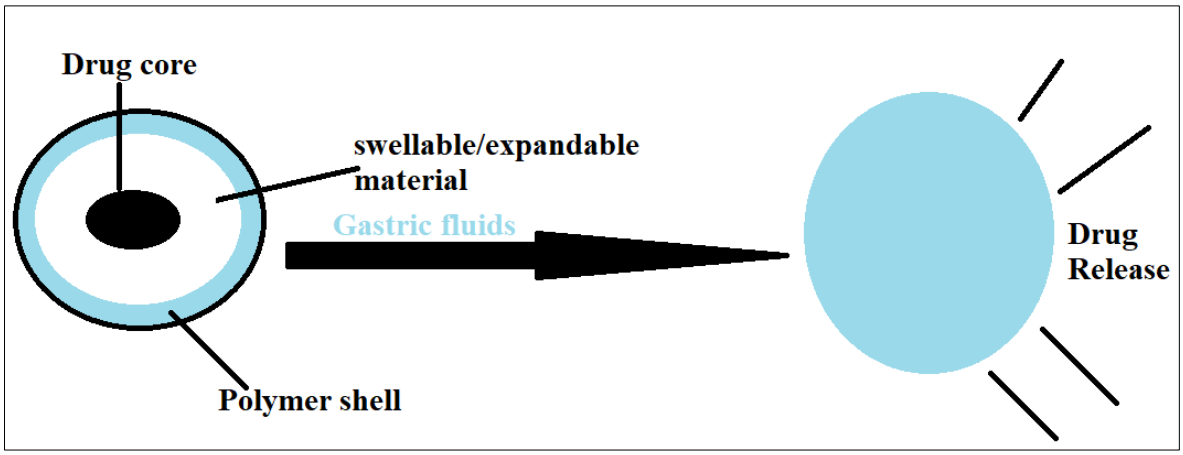

Fig 6 Unfoldable and Swellable System

➢ *Representation of Drugs Formulated in Unfoldable and Swellable Drug Delivery System*

Table 4 Representation of Drugs Formulated in Unfoldable and Swellable System

Drug	Category	Method of Preparation	Therapeutic Uses	References
Ciprofloxacin HCL Tablet	Fluoroquinolone antibiotic	Wet granulation method	Urinary tract infection Respiratory tract infection Gastrointestinal infections	95,96
Ofloxacin	Fluoroquinolone antibiotic	Wet granulation method	Urinary tract infection Respiratory tract infection Gastrointestinal infections	95
Metformin HCL	Biguanide anti-diabetic drug	Wet granulation method	Used to treat type 2 diabetes Improve insulin sensitivity	97
Metoprolol	Selective Beta-1 adrenergic blocker	Solvent casting method	Hypertension Angina Heart failure	98

- *High-Density Systems:*

High-density gastroretentive systems are designed with a density of around 3 g/cm³, which enables them to sink to the lower part of the stomach and resist gastric motility, thereby prolonging gastric residence time. Dosage forms with a density above 2.4–2.8 g/cm³ can become entrapped in the gastric folds (rugae), which further supports retention. However, maintaining such high density while ensuring sufficient drug loading remains a major challenge. High density helps the system remain in the stomach for a longer duration, retention occurs by settling in the lower gastric region and useful for drugs requiring prolonged gastric exposure.

- *Common Density-Enhancing Agents Include:*

✓ Barium sulfate
✓ Zinc oxide
✓ Titanium dioxide
✓ Iron powder

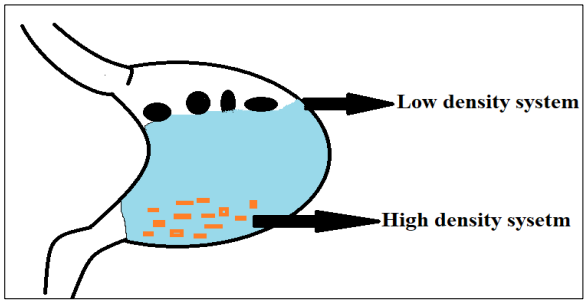

Fig 7 High Density System

➢ *Magnetic Systems:*

Magnetic gastroretentive systems incorporate a small internal magnet within the dosage form, which is controlled using an external magnet placed over the stomach. This magnetic interaction helps in retaining the dosage form at a specific gastric location.

- Enables site-specific retention in the stomach
- Requires proper alignment of the external magnet
- Limited clinical use due to reduced patient convenience and compliance [2]

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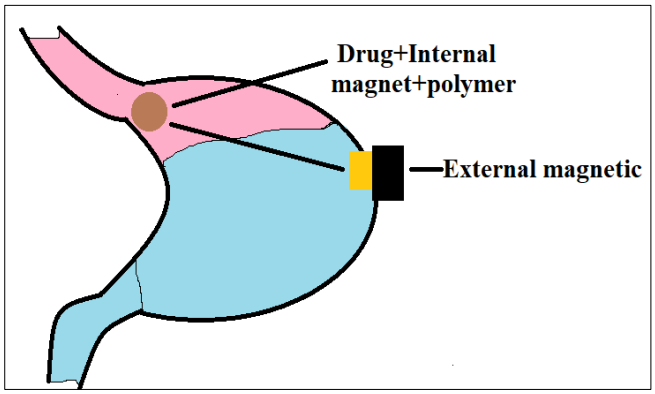

Fig 8 Magnetic System

➢ *Raft-Forming Systems:*

Raft-forming systems are liquid or semi-solid formulations that form a floating viscous gel (raft) upon contact with gastric fluid.

- Contain alginate polymers and gas-generating agents (bicarbonates)
- CO_2 gets trapped in the gel, enabling buoyancy
- Forms a barrier to prevent acid reflux
- Useful in GERD and other gastric disorders[26]

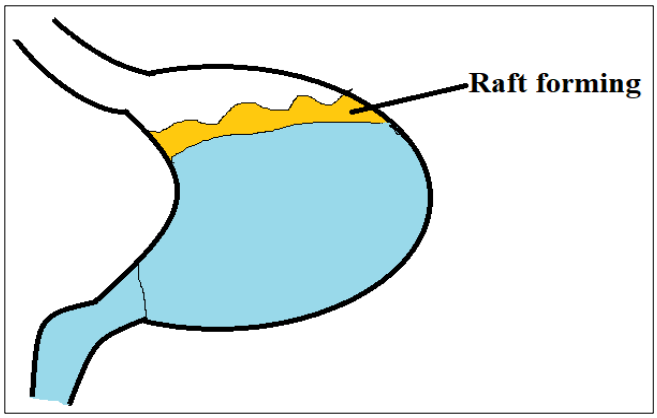

Fig 9 Raft forming System

➢ *Representation of Drugs Formulated in Raft-forming Drug Delivery system*

Table 5 Representation of Drugs Formulated in Raft Forming Drug Delivery System

Drug	Category	Method of Preparation	Therapeutic uses	References
Bupropion	Antidepressant and NDRI	Solvent-gel raft system based on controlled floating raft system	Depression Smoking cessation	99
Nizatidine	H_2 receptor antagonist	Tablet/compression based on immediate floating raft system	Peptic ulcer GERD	100
Metronidazole	Nitroimidazole antibiotic	Ion-sensitive in-situ gelation based on floating ionic raft system	Used to treat anaerobic bacterial infections Used to treat protozoal infections like amoebiasis, Giardiasis	101
Curcumin	Herbal anti-inflammatory	Solvent evaporation based on gas-forming floating raft system	Anti-inflammatory Antioxidant	102

➢ *Super Porous Hydrogels:*

Super porous hydrogels are highly porous swellable systems with interconnected pores (>100 µm).

- Absorb water rapidly through capillary action
- Reach equilibrium size within minutes
- Rapid swelling prevents premature gastric emptying
- Suitable for gastroretentive applications[25]

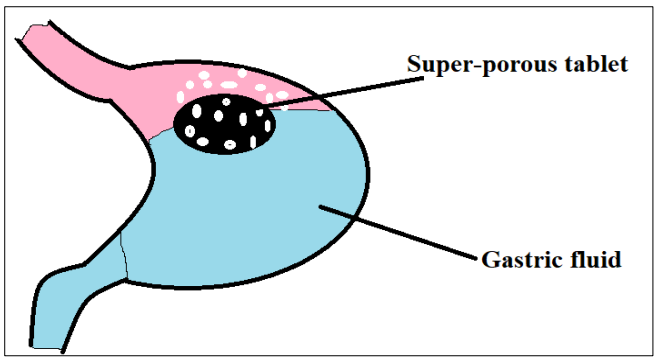

Fig 10 Super Porous System

➢ *Swelling Systems:*

Swelling systems are polymeric dosage forms that expand after absorbing gastric fluid, increasing their size beyond the pyloric opening to enhance gastric retention.

- *Swelling Occurs Due to Hydration of Polymer Networks*

Crosslinking influences behavior:

✓ High → strong structure, limited swelling
✓ Low → greater swelling, faster erosion[30]

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➢ *Comparison of Various GRDDS Approaches:*

Table 6 Comparison of Various GRDDS Approaches

Approaches	Mechanism	Advantages	Limitation
Floating drug delivery system	The dosage form remains buoyant in gastric fluid because its density is lower than that of stomach contents.[54,55,56,57]	Prolongs gastric residence time; improves bioavailability; enhances therapeutic efficacy of drugs with short half-life.	Requires sufficient gastric fluid for buoyancy; not suitable during sleep (supine position); depends on gastric conditions.
High-density systems	The dosage form settles at the bottom of the stomach due to higher density than gastric fluid.[54]	Provides prolonged gastric retention; suitable for targeted drug delivery.[34]	May cause gastric irritation; complex formulation; limited practical use.
Expandable/ Swelling systems	The dosage form enlarges or unfolds after contact with gastric fluids, preventing passage through the pylorus.[58,59,60]	Improves gastric retention; enables controlled drug release; useful for drugs with the narrow absorption window.	Risk of gastric obstruction if improperly designed; must resist gastric motility; requires rapid and controlled expansion.
Bioadhesive/ Mucoadhesive system	Adhesion occurs between the dosage form and gastric mucosa through mechanisms such as diffusion, wetting, and electrostatic interactions.[59,61]	Allows site- specific drug delivery; enhances absorption; reduces dosing frequency.	Limited adhesion due to mucus turnover; risk of unwanted adhesion; variability in performance.
Raft-forming system	Forms a floating viscous gel layer due to polymer swelling and CO_2 generation.[62,63]	Effective for local action; protects gastric lining; beneficial in GERD management.	Depends on gastric pH and fluid volume; may show shorter retention in some cases.
Super porous hydrogel system	Rapid swelling occurs due to capillary uptake of gastric fluid through a porous network.[59,64]	Very fast expansion; strong gastric retention; improved control over drug release.	Limited mechanical strength; complex formulation process.
Magnetic systems	Contains an internal magnet that is controlled externally to retain the dosage form in the stomach.[65]	Enables targeted and prolonged retention.	Requires external devices; not practical for routine use.
Ion- exchange resin systems	Drug bound to resin- exchange resin and released through exchange with ions present in gastric fluids.[65]	Provides controlled drug release; can be combined with other delivery systems.[4]	Complex formulation; drug release may vary with ionic conditions.[2]

II. FORMULATION STRATEGIES FOR GRDDS

➢ *Polymers Used in GRDDS*

- Polymers form the structural basis of GRDDS and are responsible for prolonged gastric retention and controlled drug release.
- Their selection depends on the retention mechanism (floating, swelling, bioadhesion) and drug properties.
- Hydroxypropyl methylcellulose (HPMC): Forms a gel barrier in gastric fluid, enabling sustained drug release.
- Sodium alginate: Natural polymer that swells in acidic medium, improving gastric retention.
- Ethyl cellulose: Hydrophobic polymer that enhances buoyancy in floating systems.
- Chitosan: Provides bioadhesive characteristics and promotes interaction with gastric mucosa.
- Carbopol: Increases viscosity upon hydration and supports controlled drug release.
- Polylactic acid (PLA) and Polyglycolic acid (PGA): Biodegradable polymers used in erodible systems.
- Polyvinyl alcohol (PVA): Used for film formation and regulation of drug release.[28]

➢ *Excipients Used in GRDDS*

- Excipients are included to improve stability, floating ability, adhesion, and release profile.
- Gas-generating agents (e.g., sodium bicarbonate, calcium carbonate): Produce CO_2 in gastric fluid, enabling flotation.
- Bioadhesive agents (e.g., chitosan, polyacrylic acid): Enhance adhesion to gastric mucosa.
- Release modifiers (e.g., lactose, mannitol): Help regulate drug release rate.
- Plasticizers (e.g., glycerin, propylene glycol): Improve flexibility of polymer matrices.
- Surfactants (e.g., polysorbate 80): Enhance solubility of poorly soluble drugs.

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- Stabilizers (e.g., ascorbic acid, tocopherols): Protect drugs from degradation.[29]

➢ *Preparation Methods for GRDDS*

- Various techniques are used to achieve uniformity, controlled release, and prolonged gastric retention.
- Wet granulation: Ensures uniform mixing and distribution of drug in tablets.
- Extrusion–spherization: Produces spherical pellets suitable for sustained release.
- Spray drying: Generates particles with controlled size and morphology.
- Microencapsulation (e.g., solvent evaporation): Protects drug and prolongs release.
- Hot-melt extrusion: Improves drug solubility and release characteristics.
- 3D printing: Emerging technique offering precise control over dosage form design.[30]

➢ *Nano-Based Formulation Strategies*

- Nanoparticles (<100 nm) offer enhanced bioavailability, improved interaction, and controlled drug delivery.[47,48]
- These systems improve gastric retention but may raise toxicity concerns.[49]

- *Zero-Valent Iron Nanoparticles (ZVINPs)*

✓ High-density systems capable of rapid settling in the stomach.
✓ Often formulated using agents like barium sulfate.
✓ Provide prolonged gastric retention and sustained drug release (~19 h).[50]

- *Gliadin Nanoparticles*

✓ Exhibit strong mucoadhesive properties, enhancing gastric residence time.
✓ Effective for targeted delivery, especially against H. pylori.
✓ Require lower doses compared to conventional formulations.[51]

- *Floating Nanospheres*

✓ Prepared using amphiphilic polymers (e.g., PEG, PDMS).
✓ Possess low density and remain buoyant in gastric fluid.
✓ Provide prolonged retention and controlled drug release.[52,53,54]

- *Dendrimer Nanocarriers*

✓ Highly branched polymers with high drug-loading capacity.
✓ Enable controlled and targeted drug delivery.
✓ Surface functional groups influence biocompatibility.[55]

➢ *Design Considerations for GRDDS*

- Drug properties: Should be stable in acidic pH and preferably soluble in gastric fluid.
- Formulation design: Proper selection of polymers and excipients to achieve desired retention mechanism.
- Retention mechanism: Based on floating, swelling, or bioadhesion principles.
- Gastric factors: pH, motility, food intake, and circadian rhythm affect system performance.
- Drug release mechanism: Occurs via diffusion, erosion, or osmotic processes.
- Manufacturing aspects: Process should be reproducible, scalable, and suitable for industrial production.
- Patient compliance: Dosage form should be easy to administer and reduce dosing frequency.
- Safety and regulation: Components must be biocompatible and meet regulatory standards.
- Cost-effectiveness: Formulation should be economical without compromising performance.
- Targeted delivery: Enables site-specific drug release in the stomach or upper GIT.[31]

➢ *Evaluation Methods for GRDDS:*

Evaluation of gastroretentive drug delivery systems (GRDDS) is crucial to ensure optimal formulation performance, gastric retention efficiency, and controlled drug release behavior. These assessments are broadly categorized into pre-compression studies, in vitro evaluation, and in vivo evaluation.

- *Pre-Compression Studies (Powder Blend Evaluation)*

✓ Performed to assess flowability and packing characteristics of the powder blend prior to compression.
✓ Angle of Repose: Reflects powder flow behavior; lower values indicate superior flow properties.
✓ Bulk Density: Defines mass per unit bulk volume (including void spaces); influences compressibility and content uniformity.
✓ Porosity (%): Indicates the extent of void spaces within the powder bed, affecting packing, tablet hardness, and drug release profile.[24]

- *In Vitro Evaluation of GRDDS:*

Conducted under simulated gastric conditions to predict in vivo performance and drug release characteristics.

✓ *Drug Release Studies*

- Performed using USP dissolution apparatus (Type I or II) in simulated gastric fluid (pH 1.2).
- Determines the release pattern (immediate, sustained, or controlled).
- Drug release kinetics are analyzed using models such as zero-order, first-order, and Higuchi models to elucidate the release mechanism.

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✓ *Swelling Studies*

- Evaluate the hydration and expansion behavior of swellable systems.
- Swelling index is calculated based on weight gain after immersion in gastric fluid.
- Indicates the system's ability to maintain prolonged gastric residence.

✓ *Buoyancy Studies*

- Assess floating lag time and total floating duration of the dosage form.
- Adequate buoyancy is essential for ensuring extended gastric retention and sustained drug release.

✓ *Bioadhesion Testing*

- Determines the adhesive strength of the formulation to gastric mucosa.
- Typically performed using excised tissue and instruments such as texture analyzers.

✓ *Particle Size and Surface Characterization*

- Particle size distribution analyzed using optical microscopy.
- Surface morphology and internal structure examined using scanning electron microscopy (SEM).

- *Evaluation of Tablets:*

Ensures dosage uniformity, mechanical integrity, and durability of the formulation.

✓ *Weight Variation*

- Evaluates uniformity of tablet weight in accordance with pharmacopeial specifications.
- Deviations from the average weight are calculated.[32]

✓ *Hardness and Friability*

- Hardness: Measures mechanical strength using devices such as Monsanto or Pfizer testers.
- Friability: Assesses resistance to abrasion using a Roche friabilator.
- Acceptable weight loss is generally maintained within 0.5–1%.[33]

- *In Vivo Evaluation:*

Provides direct assessment of gastric retention, drug absorption, and overall therapeutic performance.

✓ *X-ray / Gamma Scintigraphy*

- Utilized to monitor in vivo position and transit of the dosage form within the GIT.
- X-ray imaging employs radio-opaque markers, whereas gamma scintigraphy uses γ-emitting radionuclides for precise tracking.

✓ *Pharmacokinetic Studies of GRDDS*

- Pharmacokinetic evaluation is performed to assess the absorption profile and systemic availability of the drug from GRDDS.
- Key parameters such as maximum plasma concentration (Cmax), time to reach peak concentration (Tmax), and area under the plasma concentration–time curve (AUC) are analyzed to determine the rate and extent of drug absorption.
- These studies provide insight into how effectively the formulation maintains therapeutically relevant plasma drug levels over an extended period.
- GRDDS are specifically designed to prolong gastric residence time, which can lead to enhanced drug absorption, particularly for drugs with a narrow absorption window in the upper gastrointestinal tract.
- In comparison to conventional dosage forms, gastroretentive systems often exhibit delayed Tmax, sustained Cmax, and increased AUC, reflecting prolonged and controlled drug release.
- Such improvements contribute to reduced dosing frequency, minimized plasma level fluctuations, and improved patient compliance.
- For example, floating formulations of verapamil have demonstrated higher Tmax and AUC values than immediate-release tablets, indicating enhanced bioavailability and sustained therapeutic action.[8]

III. MECHANISM OF DRUG RELEASE

Drug release from controlled drug delivery systems is primarily governed by a combination of dissolution and diffusion processes. At the initial stage, the drug present on the surface of the dosage form dissolves in the surrounding medium, leading to the formation of a concentration gradient.

This process can be explained by the Noyes–Whitney equation:

$$dM/dt = KS\,(Cs - Ct)$$

Where Cs represents the saturation solubility of the drug and Ct denotes the drug concentration at a given time t. Under sink conditions, where the drug concentration in the medium remains significantly lower than its solubility, the dissolution rate reaches its maximum.[66] Following dissolution, the drug molecules diffuse across the diffusion boundary layer into the bulk medium. This step is described by the Nernst–Brunner modification of Fick's law, where the rate of diffusion depends on parameters such as the diffusion coefficient and the thickness of the boundary layer.

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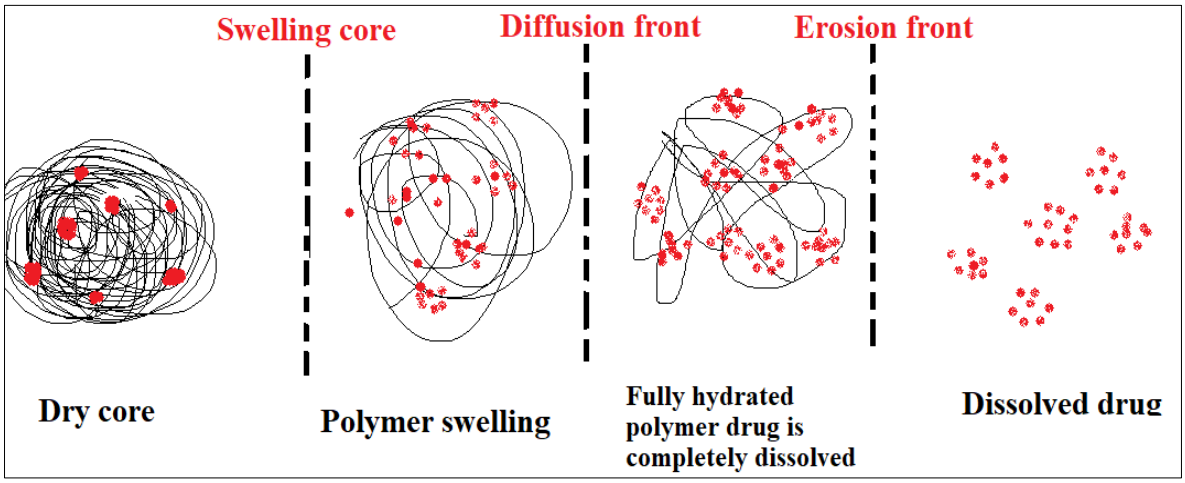

Fig 11 Mechanism of Drug Release

In gastroretentive drug delivery systems, additional mechanisms such as polymer hydration and swelling also play a crucial role. When the dosage form comes into contact with gastric fluid, the polymer matrix absorbs water and forms a viscous gel layer on its surface. This hydrated barrier regulates the movement of drug molecules and contributes to sustained drug release. As the process continues, the drug gradually diffuses through the gel layer into the surrounding medium. At the same time, the outer polymer matrix undergoes slow erosion, which further facilitates drug release. The overall release profile is therefore controlled by the interplay between diffusion through the gel and erosion of the polymer structure. Moreover, GRDDS are specifically designed to remain in the gastric region for an extended period. Floating systems achieve this through gas generation, maintaining buoyancy, while bioadhesive systems adhere to the gastric mucosa. These characteristics ensure prolonged retention at the site of action, thereby enhancing drug absorption and therapeutic effectiveness.

In summary, drug release from GRDDS is a result of multiple simultaneous processes, including dissolution, diffusion, swelling, and erosion, which together provide controlled and sustained drug delivery.[67,68,69]

IV. ADVANTAGES OF GRDDS

- Reduced dosing frequency: - GRDDS minimize the need for frequent drug administration by releasing the drug over an extended period. This is especially beneficial in long-term therapies, as it improves patient convenience and adherence to treatment.
- Prolonged gastric residence time: - Due to their floating or low-density nature, these systems remain in the stomach for a longer duration. This extended retention increases the time available for drug release and absorption in the gastric region.
- Improved efficacy of short half-life drugs: - Drugs that are rapidly eliminated from the body can maintain effective plasma levels for a longer time through sustained release provided by GRDDS, thereby enhancing therapeutic performance.[34]
- Site-specific drug delivery: - GRDDS are designed to deliver drugs directly to the stomach and upper gastrointestinal tract. This targeted approach ensures that the drug is released at the optimal site for absorption.
- Reduced gastric irritation: - The controlled release of drug from GRDDS prevents sudden exposure of high drug concentration to the gastric mucosa, thereby reducing irritation and improving tolerability.
- Uniform drug release: - Multiparticulate systems distribute the drug in multiple small units, which results in more uniform drug release and reduces the chances of dose dumping or uneven drug distribution.
- Suitable for narrow absorption window drugs: - These systems are highly effective for drugs that are absorbed only in the upper part of the small intestine, as they prolong the drug's presence at the absorption site.
- Enhanced local action in stomach: - GRDDS are particularly useful for drugs intended to act locally in the stomach, such as anti-ulcer agents, as prolonged retention improves their therapeutic effect.
- Increased bioavailability: - By maintaining the drug in the upper gastrointestinal tract for a longer time, GRDDS enhance drug absorption, leading to improved bioavailability.
- Targeted therapy for GI disorders: - GRDDS provide a focused drug delivery approach for diseases of the upper gastrointestinal region, resulting in improved treatment outcomes.[4]

V. CHALLENGES /LIMITATIONS IN GRDDS DEVELOPMENT

- Floating systems need enough gastric fluid to remain buoyant, so proper water intake is necessary.
- While lying down, such as during sleep, floating forms may be displaced by gastric contractions; thus, bedtime administration is not ideal.
- Drugs unstable in acidic conditions, poorly soluble at low pH, or irritating to the stomach lining are unsuitable.
- Bioadhesive systems may be less effective due to rapid mucus turnover and thick mucus layers.

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- Swellable systems must quickly expand beyond the pyloric opening and withstand strong gastric peristalsis.
- Gastric retention may vary due to factors such as motility, pH changes, and food intake.
- Continuous mucus renewal can reduce the adhesion time of bioadhesive forms.
- There is a potential risk of bioadhesive systems sticking to the esophagus.
- Drugs with poor stability or solubility in the GI tract are generally unsuitable for gastroretentive delivery.[2]

VI. THERAPEUTIC APPLICATION OF GRDDS

- Treatment of gastrointestinal infections: - GRDDS are useful in managing infections such as Helicobacter pylori, as they retain antibiotics in the stomach for a longer duration. This helps maintain higher local drug concentration, improving bacterial eradication and therapeutic efficiency.
- Diabetes management: - These systems provide sustained release of antidiabetic drugs like metformin, helping to maintain stable plasma glucose levels and reduce fluctuations during therapy.[35]
- Hypertension treatment: - GRDDS allow controlled delivery of antihypertensive drugs such as losartan and amlodipine, ensuring consistent absorption and better regulation of blood pressure.[36]
- Chronic pain management: - They are used for extended release of analgesics, including NSAIDs and opioids, which helps maintain steady drug levels and reduces side effects associated with peak concentrations.[37]
- GERD and peptic ulcer disease: - GRDDS enhance the effectiveness of proton pump inhibitors and antacids by prolonging their gastric residence time, leading to improved acid suppression and faster healing of the gastric mucosa.[38]
- Cardiovascular diseases: - Controlled delivery of drugs such as statins and anticoagulants are possible with GRDDS, which helps maintain therapeutic drug levels for longer durations and improves treatment outcomes.[39]
- Localized gastric infections: - By retaining antimicrobial agents in the stomach, GRDDS improve treatment of localized infections while minimizing systemic exposure and associated side effects.
- Nutraceuticals and herbal formulations: - GRDDS enhance the bioavailability of nutraceuticals and herbal drugs that have poor solubility or stability in the gastrointestinal tract by prolonging their retention time.
- Cancer therapy: - These systems enable localized and sustained delivery of anticancer drugs in the stomach and upper gastrointestinal tract, improving drug effectiveness and reducing systemic toxicity.
- Controlled drug delivery systems: - GRDDS provide a predictable and sustained release pattern, which helps maintain stable plasma drug levels, reduces dosing frequency, and minimizes fluctuations-related side effects.[36]

VII. INDUSTRIAL APPLICATION OF GRDDS

- In the pharmaceutical sector, gastroretentive drug delivery systems are applied to create dosage forms capable of maintaining drug presence in the stomach for an extended duration, which supports prolonged therapeutic activity.[2,12]
- These delivery systems are especially considered during formulation of drugs that are preferentially absorbed in the upper gastrointestinal region, as they help improve drug absorption efficiency and reduce premature elimination.[3]
- On an industrial level, multiple formulation approaches such as buoyant tablets, floating capsules, and multiparticulate carriers (including pellets and microspheres) are designed to ensure reproducible performance and consistent drug release.[12]
- GRDDS technology is widely applied in the development of antibiotic and anti-ulcer formulations, where maintaining the drug within the stomach region improves treatment effectiveness.[23,37]
- Pharmaceutical companies also employ these systems in producing extended-release medications for long-term conditions, ensuring steady drug levels and reducing the need for frequent dosing.[3,12]
- In formulation design, GRDDS contributes to the development of safer gastric delivery systems, as controlled drug release can help reduce irritation caused by conventional dosage forms.[2]
- The approach is increasingly being explored in the nutraceutical and herbal sector, where prolonged gastric residence enhances the absorption of poorly soluble active constituents.[2]
- From a production viewpoint, emphasis is placed on scalable manufacturing methods, process optimization, and strict quality control to maintain uniformity between batches.[21]
- Ongoing advancements in materials and formulation strategies are further supporting the commercial development and large-scale production of GRDDS-based products.[23]

➢ *Marketed Product of GRDDS*

Table 7 Some of the Marketed Formulations Available as GRDDS[5]

Sr No.	Brand name	Delivery Approach	Drug Category	Company name
1.	Topalkan®	Alginate-based Floating liquid	Aluminium-Magnesium (Antacid)	Pierre Fabre, France
2.	Conviron®	In-situ gel-forming System	Ferrous sulphate (Iron supplement)	Ranbaxy, India

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3.	Cifran OD®	Effervescent buoyant tablet	Ciprofloxacin (Antibacterial)	Ranbaxy, India
4.	Valrelease®	Gastroretentive capsule	Diazepam (Sedative)	Roche, USA
5.	Madopar®	Controlled-release floating capsule	Levodopa+Benserazide (Parkinson's therapy)	Roche products, USA

➢ *Regulatory Aspects*

- The regulatory approval of gastroretentive drug delivery systems (GRDDS) is complex due to their hybrid nature, as they exhibit characteristics of both conventional dosage forms and device-like systems.[70]
- There is a growing need for well-defined and harmonized regulatory guidelines specifically tailored for GRDDS to ensure uniformity in evaluation and approval processes.[70]
- Safety evaluation is a critical requirement, with particular emphasis on gastric retention mechanisms such as floating, swelling, and bioadhesion, to prevent risks like gastric obstruction or unintended retention.
- Demonstration of a robust in vitro–in vivo correlation (IVIVC) is essential to establish a predictable relationship between laboratory drug release data and actual in vivo performance.[71,72]
- Regulatory authorities require comprehensive data on formulation stability, mechanical integrity, and reproducibility to ensure consistent product performance throughout its shelf life.
- The influence of physiological variables such as gastric pH, motility, and fed or fasted state must be thoroughly evaluated, as these factors can significantly affect the behavior of GRDDS.
- Advanced characterization techniques and in vivo studies are often required to validate gastric residence time and confirm therapeutic effectiveness.
- Intellectual property plays a significant role in GRDDS development, with increasing patent activity in technologies such as floating systems, mucoadhesive formulations, and expandable systems.[73,74,75]
- Detailed regulatory documentation, including safety, efficacy, quality control, and performance data, is mandatory for successful product approval and commercialization.[76]

VIII. FUTURE PERSPECTIVE

- Development of advanced polymers: - Future research is focused on designing novel polymers with improved floating, swelling, and bioadhesive properties. These materials can enhance gastric retention and provide more precise control over drug release. Smart polymers responsive to pH or temperature are also being explored.[40]
- Integration of nanotechnology: - The use of nanoparticles, nanofibers, and nanocomposites in GRDDS is gaining attention, as they can improve drug stability, targeting efficiency, and bioavailability, particularly for poorly soluble drugs.[41]
- Personalized drug delivery systems: - GRDDS may be tailored according to individual patient factors such as gastric motility, pH, age, and disease condition. This personalized approach can optimize therapeutic outcomes and reduce variability in drug response.[50]
- Combination of retention mechanisms: - Future systems may combine multiple approaches such as floating, swelling, and bioadhesion within a single formulation. This hybrid strategy can provide more reliable and prolonged gastric retention.[42]
- Application of 3D printing technology: - 3D printing offers precise control over dosage form design, including shape, density, and drug distribution. This technology can be used to develop customized GRDDS with predictable and reproducible drug release profiles.[43]
- Improved IVIVC (In vitro–in vivo correlation): - Advancements in IVIVC models will help in accurately predicting in vivo drug behavior from in vitro studies, thereby reducing the need for extensive animal and clinical trials.[44]
- Expansion to biologics and peptides: - GRDDS are being explored for delivering sensitive molecules such as peptides, proteins, and biologics. Prolonged gastric retention along with protective strategies may enhance their stability and absorption.[45]
- Enhanced safety and regulatory acceptance: - Future studies will focus on establishing standardized evaluation methods and safety profiles, which are essential for gaining regulatory approval and wider clinical acceptance.
- Commercialization and large-scale production: - Efforts are being directed toward developing cost-effective and scalable manufacturing techniques, which will support the commercial availability of GRDDS in the pharmaceutical market.[46]

IX. CONCLUSION

Gastroretentive drug delivery systems (GRDDS) have emerged as an effective strategy to overcome the shortcomings associated with conventional oral dosage forms. These systems are specifically designed to remain in the stomach for an extended duration, which enhances drug absorption and improves overall bioavailability. This approach is particularly beneficial for drugs that are absorbed mainly in the upper gastrointestinal tract or those intended for localized gastric action. A key advantage of GRDDS is their ability to provide controlled and site-specific drug release, which helps in maintaining consistent drug levels, reducing dosing frequency, and improving patient adherence to therapy. Several formulation strategies, including floating systems, mucoadhesive systems, expandable systems, high-density systems, raft-forming systems, and magnetic approaches, have been developed to achieve effective gastric retention. Each of these techniques offers distinct benefits depending on the physicochemical properties of the drug and therapeutic needs. With ongoing advancements in

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pharmaceutical technology, the future of GRDDS appears highly promising. Innovations such as the development of novel functional polymers, application of nanotechnology, use of 3D printing, and the concept of personalized drug delivery are expected to further improve their performance. In addition, combining multiple retention mechanisms and establishing better in vitro–in vivo correlations will enhance their reliability and clinical applicability. In conclusion, GRDDS represent a significant advancement in oral drug delivery, offering improved therapeutic efficacy, enhanced safety, and greater precision in drug administration, thereby contributing to more effective modern pharmacotherapy.

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