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Gastroretentive Drug Delivery Systems: Principles, Designs, Recent Advances and Future Perspectives

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.Abstract

Gastroretentive drug delivery systems (GRDDS) are engineered oral formulations designed to prolong gastric residence time (GRT) and provide controlled drug release in the stomach or proximal small intestine. GRDDS are particularly valuable for drugs with a narrow absorption window, local gastric action, instability in intestinal/colonic pH, or low solubility at higher pH. This review summarizes stomach physiology relevant to GRDDS, discusses the main gastroretentive approaches (floating, mucoadhesive, expandable/swellable, high-density, superporous hydrogels, raft systems, magnetic and 3D-printed systems), formulation strategies and polymers, evaluation methods, clinical applications, advantages and limitations, recent technological trends (including 3D printing and shape-memory polymers), manufacturing and regulatory considerations, and future directions. A critical appraisal of challenges and opportunities is provided.

(Keywords: gastroretentive, floating, mucoadhesive, swellable, 3D printing, polymers.)

1. Introduction

Oral delivery remains the most convenient route for systemic and local drug therapy. However, variable gastric emptying and gastrointestinal transit often compromise therapeutic performance for drugs with narrow absorption windows or gastric site-specific actions. Gastroretentive drug delivery systems (GRDDS) aim to extend the residence time of dosage forms in the stomach, thereby improving bioavailability, reducing dosing frequency, and enabling localized therapy. Interest in GRDDS has grown substantially, with numerous formulation strategies and emerging manufacturing technologies such as 3D printing and shape-memory materials**.**

1.1 Physiology of the stomach :-

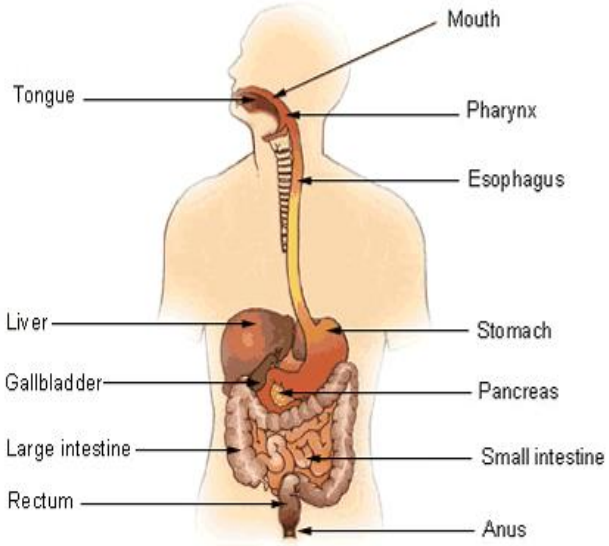

Figure 1: General Gastrointestinal tract

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds calledrugae. There are 4 major types of secretory a epithelial cell that covers the stomach and extends into gastric pits and glands.

1. Mucous cells- secrete alkaline mucus
2. Parietal cells – secrete HCL
3. Chief cells- secrete pepsin
4. G cells- secrete hormone gastrin.[1]

1.2 Need for GRDDS 2 :- Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and major draw-back is non-site specificity. • Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site. • Pharmaceutical field is now focusing towards such drugs which require site specificity. • Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine

2. Stomach physiology and factors affecting gastric retention

Understanding gastric anatomy and motility is essential for designing GRDDS. The stomach performs storage, grinding, and controlled emptying. Gastric emptying is influenced by fed/fasted state (migrating motor complex (MMC) cycles), meal composition, posture, age, disease states, and concurrent medications. Dosage form size, density, shape, gastric pH, and excipient interactions also determine retention. The fed state generally prolongs gastric residence compared with fasted conditions because phase III MMC contractions are suppressed. Formulation design must therefore consider physiological variability and patient factors. [2]

3. Rationale: Which drugs benefit from GRDDS?

GRDDS are well-suited for:

1. Drugs with a narrow absorption window in the stomach or upper small intestine (e.g., levodopa, riboflavin).
2. Drugs that are primarily absorbed in the stomach or proximal small intestine (e.g., furosemide, metformin — depending on formulation specifics).
3. Drugs unstable in intestinal or colonic environment (acid-labile drugs with protection needs).
4. Drugs intended for local gastric action (e.g., antacids, eradication of Helicobacter pylori).
5. Drugs with low solubility at higher pH, where prolonged exposure to gastric fluid enhances dissolution.[3]

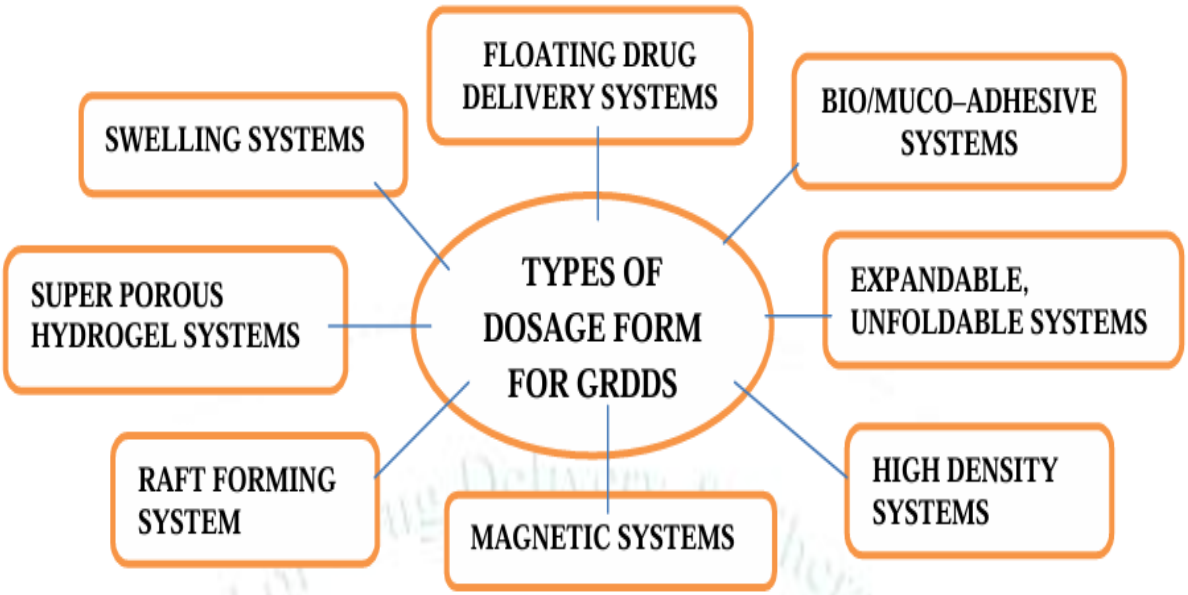

Figure 2: Gastroretentive Techniques [4]

4. Major gastroretentive approaches.

4.1 Floating (hydrodynamic) systems

Floating systems are the most widely researched GRDDS. These remain buoyant on gastric contents by reducing density (≤1.0 g/mL), often via gas-generating agents (e.g., effervescent CO_2 generators) or hollow/foam matrices. Designs include single-unit floating tablets and multi-unit floating beads/ microspheres. Key formulation challenges include achieving reliable buoyancy in varying gastric volumes and ensuring controlled drug release while maintaining floatation.[5]

4.2 Mucoadhesive (bioadhesive) systems

Mucoadhesive systems adhere to the gastric mucosa using polymers that interact with mucin (hydrogen bonding, electrostatic interactions, chain interpenetration). Common mucoadhesive polymers include chitosan, carbomers, sodium alginate, and polycarbophil. These systems can provide intimate contact with the absorption site but are challenged by mucus turnover and shear forces from gastric motility.

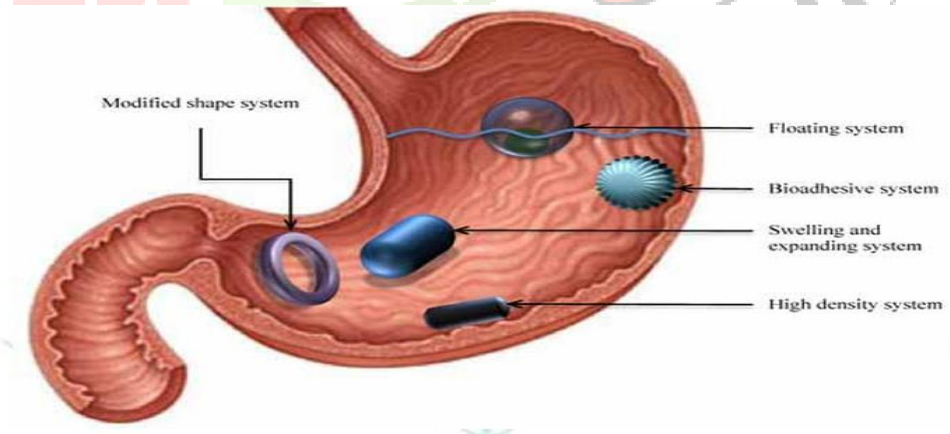

Figure 3: Bio-adhesion System.[6]

4.3 Swellable / expandable systems

Swellable systems (also called hydrophilic or expandable systems) rapidly increase in size upon contact with gastric fluids to dimensions that prevent passage through the pylorus. Superporous hydrogels fall into this category, allowing quick swelling to large volumes. Design must balance swelling kinetics and mechanical resilience to withstand gastric contractions. [3]

4.4 High-density systems

High-density systems (density > 1.0 g/mL) tend to sink and resist gastric emptying. These have been less widely applied due to poor patient acceptability and formulation challenges but can be useful when sinking behavior is advantageous.

4.5 Raft-forming systems

Raft systems form viscous cohesive gels (rafts) on contact with gastric fluids; used mainly for reflux disease where the raft acts as a barrier to reflux. They can also serve as gastroretentive vehicles for local therapy. [7]

4.6 Magnetic systems

Magnetic systems contain an internal magnet and require an external magnetic field to retain the dosage form in the stomach. Limited by practicality and patient acceptability; mostly investigated in proof-of-concept studies.

4.7 3D-printed and shape-memory systems

3D printing enables complex geometries (e.g., hollow lattices, multi-compartment devices) and personalized release profiles. Shape-memory polymers and devices can expand after ingestion to larger forms, offering novel routes for gastric retention. Recent studies highlight 3D-printed floating and expandable devices with tunable buoyancy and release kinetics. [8]

5. Polymers and excipients used in GRDDS:-

Hydrophilic polymers (HPMC, polyethylene oxide, sodium alginate), lipophilic matrix formers, gas-generating agents (sodium bicarbonate), effervescent acids, and mucoadhesive materials (chitosan, carbomers) are commonly used. Choice depends on desired mechanism (e.g., HPMC for swelling and controlled release; sodium alginate for raft formation). Superporous hydrogels use cross-linked hydrophilic monomers to achieve rapid swelling. Polymers must be GRAS, scalable, and compatible with the drug. [9]

6. Formulation strategies and manufacturing

Common dosage forms include single-unit tablets, capsules (hollow systems), multiparticulates (beads, pellets) and in situ gelling liquids. Manufacturing methods vary: direct compression (tablets), wet/dry granulation, ionotropic gelation (alginate beads), hot-melt extrusion, and 3D printing (FDM, semi-solid extrusion). Scale-up of complex geometries (e.g., 3D-printed devices) remains a challenge for commercial translation. [10]

7. Evaluation and characterization (In-Vivo Evaluation

1) **Radiology:** Barium Sulphate is widely used as Radio Opaque Marker. X-ray is used for examination of internal body systems. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view gastric retention.[11]

2) Gastroscopy: Gastroscopy is used to inspect visually the effect of prolongation in stomach. **3) Scintigraphy:** Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99 Tc.

4) Ultrasonography: It is not used generally because it is not traceable at intestine.

5**) Magnetic Marker Monitoring:** This technique is radiation less and so not hazardous. In this technique, dosage form is magnetically marked by **incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment.8. Advantages and limitations.[12]]**

1.Improved bioavailability for narrow-window drugs.

Reduced dosing frequency and improved patient compliance.

2.Localized gastric therapy (e.g., eradication of H. pylori).

Potential reduction of systemic side effects by targeted release.

3. Gastric residence duration is extended by buoyancy

4. Drugs with short half-lives have better therapeutic effects

5. Drug distribution to the stomach can be site-specific.

6. By creating sustained release, gastric discomfort can be prevented.

7. There is no chance of dose dumping when a single floating unit, like a microsphere, elivers medication consistently.

8. Administration of medications having a limited window of absorption in the small intestine.

9. For local action in the upper portion of the small intestine, such as the treatment of peptic ulcer disease, a longer residence period in the stomach may be beneficial.

10. Drugs like cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, and others that are easily absorbed after being released in the GI tract should have improved bioavailability.[13]

Limitations and challenges

1. Inter- and intra-subject variability in gastric motility and pH.
2. Risk of dose dumping if matrix integrity fails.
3. Potential gastric irritation from certain polymers or prolonged retention.
4. Complex manufacturing and scale-up issues for advanced devices (3D-printed/shape-memory).
5. Regulatory hurdles for novel materials/devices lacking precedence. [14]

9. Clinical and therapeutic applications — selected examples

GRDDS have been investigated for a variety of drugs and indications:

- Antibiotics and combination regimens for H. pylori eradication.
- Anti-ulcer agents and local gastric actives.
- Narrow absorption window agents such as levodopa analogues and certain peptides.
- Controlled release of drugs like metformin and ciprofloxacin (formulation dependent). Clinical translation has been limited for some drug classes due to variability and manufacturability challenges. [15]

10. Recent advances and research trends

10.1 3D printing and personalized GRDDS

3D printing allows fabrication of intricate, patient-specific geometries with multi-material capability and staged release profiles. Recent systematic reviews highlight the potential for personalized floating devices with programmable buoyancy and release [16]

10.2 Shape-memory and stimulus-responsive systems

Shape-memory polymers that change conformation after ingestion (e.g., expand to prevent pyloric passage) provide a promising route to stable gastric retention with compact swallowable forms. Early studies show feasibility but clinical translation requires safety and biodegradation validation.[17]

10.3 Superporous hydrogels and rapid swelling matrices

Superporous hydrogels show very fast swelling rates enabling rapid increase in size and retention. Their compressive strength and resilience under gastric contractions are key focus areas.[18]

10.4 Manufacturing and scale-up innovations

Hybrid manufacturing (combining extrusion, printing and conventional tableting) and continuous processing approaches are being explored to improve reproducibility and scale-up for complex GRDDS. [19]

11. Regulatory, safety and commercial considerations

Commercialization of GRDDS must demonstrate consistent gastric retention, predictable release, and robust safety data. Regulatory agencies expect standardization of in vitro–in vivo correlations (IVIVC), stability, biocompatibility of novel polymers, and clear demonstration of clinical benefit versus conventional formulations. Devices using new materials or magnets need thorough toxicological and mechanical testing. [20]

12. Future perspectives

Key directions for the field include:

- Greater use of personalized GRDDS (3D printing) for individual pharmacokinetics.
- Integration of imaging biomarkers and real-time monitoring to better predict retention.
- Development of biodegradable shape-memory materials with proven safety.
- Improved IVIVC frameworks for GRDDS to streamline regulatory approval.
- More clinical studies comparing GRDDS to conventional formulations, focusing on hard endpoints (efficacy, adherence, side effects). [21]

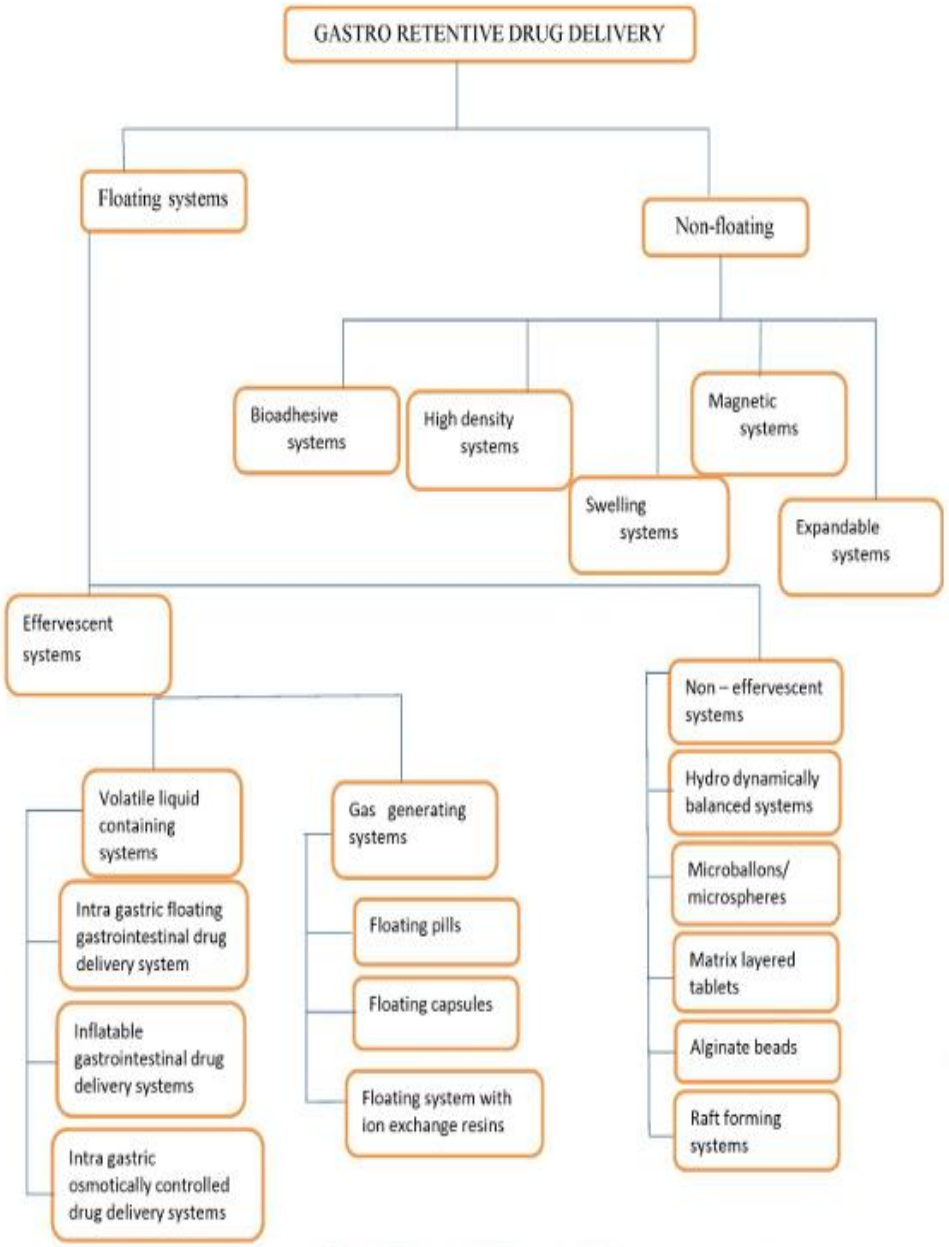

Figure 4 : Flowchart showing different approaches for gastro retentive drug delivery systems

13. Conclusion.

GRDDS continue to evolve from concept-stage designs to more sophisticated, manufacturable systems. They have real potential to improve therapy for drugs that are limited by narrow absorption windows or need local gastric action. However, physiological variability, formulation complexity, and regulatory hurdles remain significant. Advances in materials science (shape-memory polymers), manufacturing (3D printing), and better in vivo evaluation tools will shape the next generation of clinically successful GRDDS

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