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Review

Polymeric Innovations in Gastroretentive Drug Delivery Systems: An Updated Review

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Abstract

Gastroretentive Drug Delivery Systems (GRDDS) are specifically engineered to enhance gastric residence time, thereby improving the bioavailability of drugs characterized by a narrow absorption window, reduced solubility under alkaline conditions, or those requiring local gastric action. Among the various GRDDS approaches, floating drug delivery systems are extensively investigated, primarily due to their capacity to remain buoyant in gastric fluids without significantly altering gastric emptying rates. Polymers play a pivotal role in the successful design of GRDDS, contributing to buoyancy, swelling behavior, mucoadhesion, and controlled drug release. A wide range of polymeric materials has been employed. Natural polymers, such as chitosan, guar gum, xanthan gum, sodium alginate, and pectin, offer biocompatibility, gel-forming properties, and adhesion capabilities. Semi-synthetic polymers like hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and sodium carboxymethyl cellulose (NaCMC) enhance swelling, matrix integrity, and release control. Synthetic polymers, including polyvinyl alcohol (PVA), Eudragit® grades, and polyvinylpyrrolidone (PVP), provide structural strength, pH-dependent release, and improved solubility. Through strategic selection and combination of these polymers, researchers can achieve predictable gastric retention and finely tuned release profiles, establishing GRDDS as a versatile and effective approach for oral controlled drug delivery.

Keywords: Gastroretentive drug delivery systems, Mucoadhesive, Eudragit, Chitosan, Sodium alginate.

INTRODUCTION

Oral administration is the most common and preferred route for drug delivery because of its convenience, cost-effectiveness, and high level of patient compliance. It eliminates the need for invasive procedures, is simple to manufacture, and ensures better acceptance compared to parenteral routes. Despite these advantages, conventional oral dosage forms frequently exhibit limitations, the most significant being the unpredictable gastric emptying time. Variations in gastric motility often lead to premature drug transit into the intestine, resulting in incomplete drug release and reduced systemic bioavailability. This problem is particularly critical for drugs that exhibit a narrow absorption window in the upper gastrointestinal tract, are poorly soluble under alkaline pH conditions, are chemically unstable in intestinal fluids, or require local delivery to the stomach. To overcome these barriers, Gastroretentive Drug Delivery Systems (GRDDS) have been developed. These systems are specifically designed to extend gastric residence time, thereby improving drug absorption and maintaining sustained therapeutic levels in plasma. By delaying the transition of dosage forms from the stomach to the intestine, GRDDS can optimize the pharmacokinetic profile of drugs, reduce fluctuations in drug concentration, minimize dosing frequency, and ultimately improve patient adherence. Their value is especially evident in the treatment of chronic conditions where consistent therapeutic coverage is essential.[1]

Multiple approaches have been investigated to achieve gastroretention, including floating, swelling, mucoadhesive, high-density, and expandable systems. Of these, Floating Drug Delivery Systems (FDDS) have attracted the greatest attention due to their relatively simple design and clinical feasibility. The principle of FDDS lies in maintaining a bulk density lower than gastric fluid, allowing the dosage form to remain buoyant on the stomach contents for several hours, without interfering with normal gastric emptying mechanisms. During this floating period, the drug is released gradually at a controlled rate, ensuring localized retention and improving therapeutic efficiency.[2]

FDDS are broadly categorized as effervescent and non-effervescent systems. Effervescent formulations incorporate gas-generating agents such as sodium bicarbonate, citric acid, or tartaric acid—which react with gastric fluid to liberate carbon dioxide. The gas becomes trapped within the hydrated polymer matrix, lowering density and promoting buoyancy. Non-effervescent FDDS, on the other hand, rely on swellable polymers or gel-forming excipients (e.g., hydrocolloids, alginates, or cellulose derivatives) that expand and form a viscous gel layer upon hydration. This swollen matrix decreases dosage form density, thereby sustaining floatation while releasing the drug in a controlled manner. Overall, GRDDS and particularly FDDS, represent a promising platform for overcoming the limitations of conventional oral systems. Through rational formulation design and appropriate polymer selection, these systems improve the bioavailability of drugs restricted to upper GI absorption or requiring prolonged gastric residence, making them an effective strategy for controlled oral delivery.[3]

CRITERIA FOR CHOOSING A DRUG FOR GRDDS

- **Narrow absorption window:** Drugs absorbed only in the upper GIT (stomach/duodenum) benefit from prolonged gastric residence. Example: Levodopa, Gabapentin, Riboflavin, Furosemide.[4]
- **Low solubility at higher pH:** Drugs are more soluble in acidic pH than alkaline pH (intestinal pH). Example: Verapamil, Diazepam, Ketoconazole. Drugs that dissolve better in gastric pH (1.2) than in intestinal pH (6.8). Example: Itopride, Atorvastatin.[5]
- **Local action in the stomach:** Drugs that act locally in the stomach for ulcers, reflux, H. pylori, etc. Example: Antacids, Misoprostol, Sucralfate, Clarithromycin.[6]
- **Drug stability in acidic pH:** Drugs that remain stable in stomach pH (~1.2) and are not degraded. Example: Propranolol, Metformin, Atenolol.[7]
- **Short half-life**: Drugs with a short plasma half-life benefit from sustained/controlled release via GRDDS. Example: Propranolol, Ranitidine, Captopril.[8]
- **Need for prolonged release**: To reduce dosing frequency and improve patient compliance. Example: Diltiazem, Nifedipine, Verapamil.[9]
- **Poor colonic absorption:** Drugs that are not absorbed in the colon should be retained in the stomach or upper GIT. Example: Riboflavin, Atenolol.[10]
- **Low bioavailability due to limited GIT transit:** GRDDS can increase bioavailability by increasing residence time. Example: Alendronate, Metformin.[11]
- **Floating or swelling capability of the dosage form:** For dosage forms that need to float or expand to prolong gastric retention. Example: Ciprofloxacin, Domperidone.[12]
- **Molecular weight:** Should be low to moderate (<500–600 Da) for better gastric absorption. Example: Levodopa (MW 197 Da).
- **pKa value:** weakly basic drugs with pKa> 5 are often ideal because they are poorly soluble in intestinal pH but highly soluble in acidic gastric pH, benefiting most from prolonged gastric retention. Example: Ketoconazole (pKavalue is 6.5, more soluble in the stomach).

- **Hydrophilic/Lipophilic character:** Moderate lipophilicity (Log P 1–3) balances solubility and permeability. Example: Atorvastatin (Log P ~2.1). [13]

POLYMERS USED IN GRDDS

Polymers in Gastroretentive Drug Delivery Systems (GRDDS) are natural, semi-synthetic, or synthetic macromolecules incorporated into formulations to regulate drug release and modify system properties by imparting buoyancy, swelling, bioadhesion, or density control, these polymers extend gastric residence, optimize therapeutic retention, and significantly improve drug bioavailability.

NATURAL POLYMER

Natural polymers in GRDDS are biocompatible, biodegradable macromolecules obtained from plant, animal, or microbial sources that aid in floating, swelling, mucoadhesion, or controlled drug release to prolong gastric retention.

A) Chitosan

Source: Obtained by deacetylation of chitin, which is a structural polysaccharide found in crustacean shells (e.g., shrimp, crab, lobster).

Structure: Linear cationic polysaccharide composed of β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units.

Properties: It is one of the few naturally occurring cationic polymers.Biodegradable and biocompatible. pKa value 6.5, meaning it becomes positively charged in acidic environments like the stomach.Forms viscous gels in acidic pH due to protonation of amino groups. Can form films, hydrogels, microspheres, and nanoparticles. [14]

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Mucoadhesion-Cationic amino groups interact electrostatically with negatively charged sialic acid residues in gastric mucin,resulting in prolonged gastric residence time.

Floating Capability-Can entrap gas bubbles within its gel structure in effervescent systems, aiding buoyancy.[15]

Controlled Drug Release-Forms a dense gel matrix that slows drug diffusion. Ex; Chitosan–Chitosan-alginate multilayer beads for controlled release of ampicillin.[16]

B) Guar gum

Source: Extracted from the seeds of Cyamopsistetragonoloba (cluster bean plant), mainly grown in India and Pakistan**.**

Structure: High-molecular-weight galactomannan polysaccharide composed of a mannose backbone (β-1→4 linkages) with galactose side chains (α-1→6 linkages).

Properties: Hydrophilic and highly swellable in water.Forms viscous gels at low concentrations.Non-ionic, hence stable over a wide pH range (including gastric pH).[17]

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Swelling / Expandable Systems-Rapid water uptake and high swelling index increase size, preventing pyloric passage**.**It is suitable forswelling-type systems of drugs with narrow absorption windows.E.g.,Riboflavin (Vitamin B_2) – narrow absorption window in upper GIT.

Controlled Drug Release-Gel layer acts as a barrier, slowing drug diffusion and sustaining release.[18]

Floating Systems-When combined with effervescent agents, guar gum gels can entrap CO_2 and provide buoyancy.E.g.,Floating tablets of ciprofloxacin using guar gum + HPMC for prolonged gastric retention.

Mucoadhesion-Hydroxyl groups form hydrogen bonds with mucin, aiding moderate adhesion.Eg:Mucoadhesive microspheres of metformin using guar gum as matrix.[19]

C) Xanthan gum

Source: Extracellular polysaccharide produced by the bacterium Xanthomonas campestris during fermentation of carbohydrate substrates (e.g., glucose, sucrose).

Structure:

Backbone: β-(1→4)-D-glucose units (cellulose-like).

Side chains: Trisaccharide units containing mannose–glucuronic acid–mannose, often with acetyl and pyruvate groups.

Properties: It is a cream-white powder, soluble in both hot and cold water. Highly hydrophilicswells quickly in water to form a viscous gel.Stable across wide pH range (pH 1–13) and in presence of gastric acid.Pseudoplastic rheology (shear-thinning)viscosity decreases with stirring but recovers when at rest.Biodegradable and biocompatible.[20]

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Floating Systems-Swells and forms a hydrated gel barrier that can entrap CO2 (in effervescent systems), aiding buoyancy.Floating tablets of metformin using xanthan gum + sodium bicarbonate.

Mucoadhesion-Hydroxyl groups in xanthan gum can form hydrogen bonds with gastric mucin.

Synergistic Gelling-Often combined with other natural gums (e.g., guar gum, locust bean gum) for a stronger gel network.

Controlled Drug Release-Gel matrix slows drug diffusion, enabling sustained release in gastric conditions. Matrix tablets for ciprofloxacin and other antibiotics to prolong gastric retention.[21]

D) Sodium alginate

Source: Extracted from the cell walls of brown seaweeds (Phaeophyceae), such as Laminaria, Macrocystis, and Ascophyllum species.

Structure: Linear **anionic polysaccharide** composed of two uronic acid monomers:

- **β-D-mannuronic acid (M)**
- **α-L-guluronic acid (G)**

- The **M/G ratio** determines gel strength and flexibility.

Properties: Water soluble in sodium salt form.Gel formation occurs in the presence of divalent cations (especially Ca^{2+}) or acidic environments (gastric pH). Remains gelled in acidic gastric pH, ensuring structural integrity until it enters higher pH environments.Biodegradable, biocompatible, and FDA "Generally Recognized as Safe".[22]

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Floating Systems-In effervescent GRDDS, sodium alginate forms a gel barrier upon contact with gastric acid, trapping CO_2 bubbles and reducing density, allowing the dosage form to float.

Example

- **Floating beads** for drugs like amoxicillin, metronidazole, clarithromycin (used in H. pylori eradication).
- **Floating-mucoadhesive tablets** for drugs with narrow absorption windows (e.g., propranolol HCl, metformin).
- **Ionotropic gelation** with calcium chloride to form buoyant beads or microspheres.

Mucoadhesion-Carboxyl groups in alginate chains form hydrogen bonds and electrostatic interactions with mucin glycoproteins in gastric mucus, prolonging gastric residence.

Controlled Drug Release-The gel matrix slows water penetration and drug diffusion, allowing sustained release in the stomach.[23]

E) Pectin

Source: Pectin is a water-soluble polysaccharide found in the primary cell walls and middle lamella of plants,especially citrus peels (orange, lemon) and apple pomace.

Structure: Composed mainly of α-(1→4)-linked D-galacturonic acid units, partially methyl-esterified.

Types:

High-methoxyl pectin (HMP): >50% methyl esterification; gels in acidic pH with high sugar concentration.

Low-methoxyl pectin (LMP): <50% methyl esterification; gels in presence of calcium ions (Ca^{2+}).

Properties: Highly hydrophilic, forming viscous gels in aqueous media.Biodegradable and biocompatible.Gelation can be triggered by pH changes or divalent cations.Swells significantly in gastric fluid, forming a barrier to drug release.[24]

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Mucoadhesion-Carboxyl and hydroxyl groups interact via hydrogen bonding with gastric mucin that increases gastric residence time.Example:Bioadhesive microspheres for gastric delivery of metformin or propranolol.

Controlled/Sustained Drug Release-Swelling of pectin gel slows drug diffusion → maintains therapeutic drug levels over time.

Floating Systems-In combination with gas-generating agents, pectin gels can entrap CO_2 bubbles, lowering density and allowing floatation. Floating-mucoadhesive tablets for drugs with narrow absorption windows (e.g., ciprofloxacin HCl).

Targeted Delivery-Pectin is resistant to gastric enzymes but degraded by colonic microflora; in GRDDS it mainly serves as a swelling and mucoadhesive polymer, but can be tailored for colon targeting after gastric retention.[25]

Table 1: Functions of natural polymer

Polymer	Floating	Swelling	Mucoadhesion	Controlled Release
Guar Gum	Low	High	Low	High

Xanthan Gum	High	High	Low	High
Sodium Alginate	High	High	Moderate	High
Pectin	Moderate	Moderate	High	High
Chitosan	Moderate	Moderate	High	High

SEMISYNTHETIC POLYMER

Semi-synthetic polymers in GRDDS are chemically modified natural polymers that provide swelling, gel formation, and controlled release to prolong gastric retention. Example; HPMC, ethyl cellulose, NaCMC.

A) Hydroxypropyl methylcellulose (HPMC)

Origin: Derived from cellulose (a natural polymer) through chemical substitution with methyl and hydroxypropyl groups.

Properties: Semi-synthetic, non-ionic, hydrophilic polymer.White to off-white, odorless, tasteless powder. Swells and disperses in cold water to form colloidal solutions; insoluble in hot water but reversible gelation occurs. Stable over pH 3–11. Density 1.26–1.31 g/cm³ (true density). Moisture content- ≤5%. Glass transition temperature is 170–180 °C.[26]

Table 2: Different grades of HPMC and their functions

HPMC Grades	Viscosity(cps)	Role in Floating GRDDS
HPMC K4M	~4,000	Forms moderate gel layer,supports buoyancy for 6–8 h, provide medium release control.
HPMCK15M	~15,000	Thickergellayer, stronger matrix integrity, floats for 8–10 h, slower drug release.
HPMCK100M	~100,000	Very strong gel, excellent swelling, maintains floatation for>12h,ideal for sustained release.[27]

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Swelling-HPMC rapidly hydrates in gastric fluid to form a 3D gel network. Increases the size of the dosage form and prevents early passage through the pylorus.

Controlled Release-Gel barrier slows drug diffusion & polymer erosion. Maintains steady plasma levels for prolonged periods.

Mucoadhesion-Hydrogen bonding with gastric mucosa. Further prolongs gastric retention.[28]

B) Ethyl cellulose (EC)

Origin: Derived from cellulose via ethyl etherification of hydroxyl groups.

Properties: Permeable to water vapor and certain drugs, but not water-soluble. Hydrophobicity helps in buoyancy.Compatibility with solvent evaporation methods for floating microsphere preparation. Non-toxic and FDA-approved for oral use.

Polymeric Roles and Mechanistic Impact in Gastroretentive Systems

Controlled Drug Release-Forms a hydrophobic barrier that slows water penetration and drug diffusion.[29]

Film Coating -Used as a sustained-release coating on tablets/pellets Prevents dose dumping, controls dissolution.

Matrix Former-Used in combination with hydrophilic polymers to form floating matrices.Balances floatation with controlled release.

Floating Microsphere Formation-Low density and hydrophobic nature help create hollow microspheres with trapped air.Maintains buoyancy in gastric fluid for prolonged periods.Example; floating clarithromycin microsphere formulation, EC was used as the primary polymer via solvent evaporation, producing microspheres that floated for over 12 hours and released drug in a controlled manner.[30]

C) Sodium carboxymethyl cellulose (NACMC)

Structure: Cellulose backbone with carboxymethyl (-CH_2–COOH) groups substituted on the hydroxyl sites; degree of substitution ~0.6–0.95.

Properties

Anionic, water-soluble cellulose ether. Swells and dissolves in water forming a highly viscous solution.NaCMC is rarely used alone in GRDDS. it's typically combined with HPMC, polyethylene oxideor gas-generating agents ($NaHCO_3$ + citric acid) to achieve both longer float time and controlled release.

Floating system- floating tablets, NaCMC is combined with gas-generating agents (e.g., sodium bicarbonate) to trap CO_2 in the swollen matrix. Enhances floatation and prevents burst release.Examples:Floating Mucoadhesive

Tablets of Propranolol HCl: NaCMC was used with HPMC to enhance swelling, mucoadhesion, and floatation time (>12 h).
Floating Beads: NaCMC coated beads showed better buoyancy due to gel formation.
Mucoadhesive Polymer -The anionic carboxyl groups form hydrogen bonds and ionic interactions with the gastric mucin layer. Prolongs gastric residence time by adhering to stomach lining.
Swelling Agent- Upon contact with gastric fluid, NaCMC hydrates rapidly, absorbing water. increases bulk volume and decreases density, helping the dosage form remain buoyant.[31]

SYNTHETIC POLYMER

Synthetic polymers in GRDDS are man-made macromolecules designed to provide buoyancy, structural integrity, and controlled or pH-dependent drug release e.g., polyvinyl alcohol, Eudragit®, and polyvinylpyrrolidone.

A) Polyvinyl alcohol
Structure: Repeating vinyl alcohol units –(CH_2–CHOH)–
Properties: Water-soluble. Goodfilm-former, adhesive, flexible, chemically stable.Non-toxic, FDA-approved for oral use.it can be crosslinked for slower dissolution and also compatible with hydrophilic and hydrophobic drugs.[32]
Floating System

- **Microsphere-**PVA adsorbs at the oil–water interface during preparation (e.g., solvent evaporation method), preventing droplet coalescence.it Ensures uniform particle size and spherical shape of floating microspheres. Example: Floating PVA microspheres of Metformin HCl – PVA as stabilizer & coating polymer improved buoyancy (>12 h) and sustained release.[33]
- **Microsponges-**The porous, low-density microsponges formed in presence of PVA trap air/gas.Prolongs floatation time in gastric fluid. example;Floating Microsponges of Ketoprofen – PVA used as an emulsifier in quasi-emulsion solvent diffusion; resulted in porous microsponges with >12 h buoyancy and sustained release.[34]

Matrix Former- PVA hydrates and swells to form a gel network that can entrap gas, reducing system density.
Binder-Improves mechanical strength of floating tablets, preventing disintegration before prolonged float.[35]

B) Eudragit
Source: Eudragit® is a brand name for a series of synthetic copolymers of methacrylic acid and its esters, developed by Evonik Industries AG (Germany).
Chemical basis: Made from methacrylic acid, methyl methacrylate, and/or other alkyl methacrylates in varying ratios.
Properties-Synthetic, non-biodegradable, film-forming polymers. Charge can be neutral, cationic, or anionic depending on grade. Solubility is pH-dependent or pH-independent (depending on functional groups). Thermal stability-Stable up to ~150–200 °C, enabling processing by hot-melt extrusion. Excellent film forming. High tensile strength, resists rupture in gastric fluid.[36]

Table 3: Different grades of Eudragit and its function

Eudragit Grade	Solubility / Permeability	Function in GRDDS
EudragitRL 100 / RL PO	Insoluble, but highly permeable due to high content of quaternary ammonium groups.	Sustained drug release with good swelling; maintains buoyancy.
EudragitRS 100 / RS PO	Insoluble, low permeability	Slower drug release than RL; provides stronger matrix for prolonged retention.
Eudragit NE 30 D	Insoluble, low permeability	Film-forming polymer for coating floating pellets; controls drug diffusion without pH dependence.
EudragitE100	Soluble below pH 5.0.	pH-dependent release in stomach; can improve gastric solubility of poorly soluble drugs.[37,38]

- ✓ RL and RS are the most common in floating DDS because they are pH-independent, insoluble, but permeableideal for sustained release in the stomach.
- ✓ The **ratio of RL:RS** determines drug release rate (more RL → faster release, more RS → slower release).
- ✓ **NE 30 D** is useful for film coating floating multiparticulates to control release without affecting buoyancy.[39]

C) Polyvinyl pyrrolidine

Origin: Produced by free radical polymerization of N-vinylpyrrolidone.

Properties: White to light yellow hygroscopic powder.Freely soluble in water, ethanol, and many organic solvents.Non-ionic, chemically stable.Film-forming ability is Good and forms transparent, flexible films.Hygroscopic; absorbs water readily.Non-toxic, non-irritant, pharmaceutically accepted.Higher concentrations can increase drug release rate by improving wettability.[40]

PVP Grades-PVP grades are classified by **K-value** (a measure of molecular weight and solution viscosity).

- **Low K value** → Low molecular weight → Low viscosity, faster dissolution.
- **High K value** → High molecular weight → High viscosity, stronger binding

Table 4: Different grades of PVP and its function

Grade	Key Properties	Function in GRDDS
PVP K-12	Verylow viscosity, high solubility	Solubilizer for poorly soluble drugs in floating systems; reduces tablet density
PVP K-17	Low viscosity, quick hydration	Pore former in floating tablets and films; enhances buoyancy
PVP K-25	Moderate viscosity, good binding	Binder in floating matrix tablets; aids gas entrapment
PVP K-30	Widely used grade, strong binder, good solubilizer	Combines binding and pore-forming; improves wettability and buoyancy
PVP K-60	High viscosity, strong film former	In floating films, improves structural integrity and drug dispersion
PVP K-90	Very high viscosity, high gel strength	Swelling agent in floating systems; prolongs gastric residence

- **Low MW grades (K-12, K-17)** → Better for **solubilization** and **pore formation**.
- **Mid MW grades (K-25, K-30)** → Ideal for **binding** and **porosity control** in floating tablets.
- **High MW grades (K-60, K-90)** → Useful as **swelling agents** and **film formers** for long gastric retention.[41]

CONCLUSION

Gastroretentive drug delivery systems (GRDDS), especially floating drug delivery systems (FDDS), are designed to improve the bioavailability of drugs with narrow absorption windows or targeted gastric action by prolonging their gastric residence time. Polymers play a pivotal role in optimizing these systems by providing critical functionalities such as swelling, buoyancy, mucoadhesion, and controlled drug release. Natural polymers, including chitosan, guar gum, xanthan gum, sodium alginate, and pectin, are favoured for their biocompatibility and ability to promote swelling and mucoadhesion, ensuring that the dosage form remains in the stomach for extended periods. These polymers help maintain buoyancy and form a gel matrix that supports controlled drug delivery. Semi-synthetic polymers like hydroxypropyl methylcellulose (HPMC), particularly the K4M to K100M grades, contribute to sustained floatation exceeding 12 hours by forming a robust gel layer, which also allows for gradual drug release. This prolonged retention enhances therapeutic efficacy and reduces dosing frequency. Synthetic polymers such as polyvinyl alcohol (PVA), Eudragit®, and polyvinylpyrrolidone (PVP) strengthen the dosage form's structural integrity and facilitate precise control over drug release profiles through pH-responsive and sustained mechanisms. By strategically selecting and combining these polymers, GRDDS achieves predictable gastric retention and tailored release kinetics, representing an effective approach to oral drug delivery with improved patient outcomes

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