Chinese Journal of Health Management
Volume 20 Issue 5, Year of Publication 2026, Page 1231-1246 | DoI-10.5281/zenodo.21466803

ISSN: 1674-0815

Chinese Journal of Health Management

Chinese Medical Association

Gastroretentive Formulation of Proton Pump Inhibitors Using Alginate-Based Microspheres: Formulation Strategies, Release Mechanisms and Translational Prospects

Shubham Chourasia[1]*, Dr. Nidhi Singhai[2]
[1]*Research scholar, IES Institute of Pharmacy, IES University, Bhopal-462044, Madhya Pradesh, India.
Email: Shubhamchourasiya076@gmail.com | ORCID: 0009-0000-1211-9234
[2]Associate Professor, IES Institute of Pharmacy, IES University Campus, Kalkheda, Ratibad Main Road, Bhopal-462044, Madhya Pradesh, India.

Article Information
Received: 26-04-2026
Revised: 08-05-2026
Accepted: 24-05-2026
Published: 13-06-2026

Keywords
Alginate microspheres, Proton pump inhibitors, Gastroretentive drug delivery, Ionotropic gelation, Floating microspheres, Mucoadhesion, Drug release kinetics, GERD

ABSTRACT:
Proton pump inhibitors (PPIs) — omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole — remain the first-line pharmacotherapy for gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and Helicobacter pylori eradication regimens. Although enteric-coated PPI formulations are clinically effective, they share, as a class, pharmacokinetic limitations arising from a common substituted benzimidazole (or, for tenatoprazole-type analogues, imidazopyridine) sulfinyl chemistry: acid instability, short plasma elimination half-lives, a narrow proximal small-intestinal absorption window, and variable oral bioavailability. Gastroretentive drug delivery systems (GRDDS) address these shortcomings by extending gastric residence time and prolonging drug availability at the absorption site. Sodium alginate is among the most extensively studied biopolymers for GRDDS because of its abundance, biocompatibility, biodegradability, regulatory acceptance, and its capacity to form ionotropically crosslinked hydrogel networks in the presence of divalent cations such as calcium. Alginate-based microspheres loaded with PPIs have demonstrated high entrapment efficiency, prolonged floating behaviour, controlled drug release, and favourable mucoadhesion. Performance is highly sensitive to formulation parameters — polymer concentration, mannuronate-to-guluronate (M/G) block ratio, crosslinker concentration, preparation method, and co-polymer selection (chitosan, pectin, HPMC, Eudragit derivatives). This review critically evaluates the literature on gastroretentive alginate microspheres across the PPI class. It covers the pharmaceutical profile and biopharmaceutical challenges shared by PPIs, the structural biochemistry and pharmaceutical applications of sodium alginate, comparative preparation methodologies, formulation variables and their mechanistic influence on microsphere performance, characterization techniques, mathematical modelling of release kinetics, in vivo pharmacokinetic and

pharmacodynamic evaluation, scale-up and regulatory translation challenges, and future perspectives including AI-assisted optimization, Quality by Design (QbD), 3D printing, and nanocomposite microspheres. The review is intended as a reference for formulation scientists, technologists, and regulatory professionals developing gastroretentive platforms for any member of the PPI class.

1. INTRODUCTION:

1.1 Burden of Gastroesophageal Reflux Disease and Peptic Ulcer Disease

Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) represent a major disease burden for hundreds of millions of people worldwide, with significant socioeconomic cost to healthcare systems. GERD, defined as reflux of gastric contents leading to troublesome symptoms or complications, has a prevalence of 8-33% in Western populations and is reported to be rising in Asian countries due to changing dietary habits, obesity, and sedentary lifestyles (El-Serag et al., 2014). Approximately 4 million people are diagnosed with PUD each year, with Helicobacter pylori infection and NSAID use as the primary etiological factors (Lanas and Chan, 2017).

The pathophysiology of GERD is complex, involving lower esophageal sphincter dysfunction, impaired esophageal clearance, delayed gastric emptying, and gastric acid hypersecretion. Untreated chronic GERD can progress to erosive esophagitis, Barrett's esophagus, esophageal strictures, and esophageal adenocarcinoma, underscoring the need for effective, sustained acid suppression (Vakil et al., 2006). The direct medical cost of GERD in the United States alone exceeds an estimated $15 billion annually (Dent et al., 2005).

1.2 Current Pharmacotherapy and the Proton Pump Inhibitor Class

Pharmacological treatment of acid-related gastrointestinal disease changed dramatically with the emergence of proton pump inhibitors (PPIs) in the late 1980s. PPIs irreversibly inhibit the gastric H+/K+-ATPase enzyme (proton pump) on the apical membrane of parietal cells, making them the most potent acid-suppressive agents available. Because of this superior mechanism, PPIs are the mainstay of therapy for GERD, PUD, and Zollinger-Ellison syndrome (Sachs et al., 2006).

The class comprises five first-generation agents — omeprazole, lansoprazole (and its R-enantiomer dexlansoprazole), pantoprazole, rabeprazole, and esomeprazole (the S-enantiomer of omeprazole) — alongside newer potassium-competitive acid blockers (P-CABs) such as vonoprazan, which act through a distinct, pH-independent mechanism. All conventional PPIs share a common pharmacophore: a substituted benzimidazole ring linked via a sulfinyl (-SO-) bridge to a substituted pyridine, differing mainly in ring substitution pattern, which governs potency, onset, CYP-mediated metabolism, and acid lability. Although PPIs are widely and effectively used clinically, this shared pharmacophore also confers shared pharmacokinetic and pharmacodynamic drawbacks that have motivated intensive research into more sophisticated, gastroretentive delivery systems.

1.3 Comparative Clinical Profile of the PPI Class

Each PPI was developed to refine the pharmacokinetic and metabolic profile of its predecessors. Omeprazole, the first-in-class agent, established proof of concept for irreversible proton-pump inhibition. Esomeprazole, the S-enantiomer of omeprazole, offers reduced first-pass hepatic clearance via CYP2C19 and correspondingly higher systemic bioavailability than racemic omeprazole (Andersson et al., 2001). Lansoprazole and its enantiopure derivative dexlansoprazole offer a dual-release delayed formulation strategy for extended acid suppression. Pantoprazole is distinguished by comparatively low CYP-mediated drug-interaction potential, and rabeprazole by predominantly non-enzymatic activation, giving a faster onset largely independent of CYP2C19 genotype. Across the class, approved indications include erosive esophagitis, symptomatic GERD, H. pylori eradication (with antibiotics), prevention of NSAID-associated gastric ulcers, and pathological hypersecretory states such as Zollinger-Ellison syndrome. Typical adult doses range from 15-40 mg daily depending on the agent, but the short plasma half-life common to the class (roughly 1-2 hours) and acid-lability necessitate either once-daily enteric-coated dosing or multiple daily doses to sustain 24-hour acid suppression (Scott, 2002; Sachs et al., 2006).

1.4 Limitations of Conventional PPI Formulations

Conventional enteric-coated PPI tablets and capsules are clinically effective but share several intrinsic physicochemical and pharmacokinetic limitations that hinder therapeutic optimization across the class:

- Acid instability: The benzimidazole-sulfinyl pharmacophore common to all PPIs degrades rapidly under the acidic conditions of the stomach (pH 1-2), necessitating enteric coating. This coating delays therapeutic onset, working against the goal of rapid acid control.

- Short plasma elimination half-life: PPIs typically exhibit plasma half-lives of roughly 1-2 hours, so once-daily dosing can leave gaps in nocturnal acid control, with nocturnal acid breakthrough (NAB) reported in a substantial proportion of patients across the class.
- Narrow absorption window: PPIs are absorbed predominantly in the proximal small intestine (duodenum and jejunum). Rapid gastric emptying reduces exposure time at the absorption site and lowers bioavailability, which is further influenced by CYP2C19 polymorphisms, food intake, and gastric emptying rate.
- Presystemic (first-pass) metabolism: Hepatic first-pass metabolism, chiefly via CYP2C19 and CYP3A4, produces significant inter-individual variability in systemic drug availability across the PPI class.
- Incomplete acid suppression: Conventional once-daily formulations may not sustain intragastric pH above 4 for the 16+ hours/day generally required for optimal healing of erosive esophagitis.

1.5 Rationale for Gastroretentive Drug Delivery of PPIs

Gastroretentive drug delivery systems (GRDDS) were developed to overcome these shared limitations by prolonging the residence of the dosage form in the stomach, thereby extending drug exposure to the absorptive surface of the upper gastrointestinal tract. The pharmacokinetic rationale for gastroretentive PPI delivery, regardless of which specific agent is used, includes: (i) sustained presentation of the drug to the duodenal absorption window; (ii) controlled release that minimizes burst release and maintains plasma drug levels within the therapeutic window for 12-24 hours; (iii) protection of the acid-labile drug from prolonged exposure to the gastric microenvironment when contained within a protective polymer matrix; and (iv) reduced dosing frequency, improving patient adherence (Hwang et al., 1998).

Polymer-based microspheres have attracted particular pharmaceutical interest for PPI delivery because of their versatile fabrication, tunable release kinetics, scalability, and favourable patient acceptability. Gastroretentive microspheres fabricated from natural, biodegradable polymers such as sodium alginate for encapsulating any member of the PPI class offer a logical, clinically applicable strategy to address the pharmacokinetic limitations of standard PPI formulations.

1.6 Scope and Objectives of the Review

This review critically and comprehensively analyzes the scientific literature on alginate-based gastroretentive microspheres for PPI delivery, focusing on the following objectives:

- To characterize the shared pharmaceutical and biopharmaceutical profile of the PPI class, with attention to properties relevant to GRDDS formulation.
- To critically assess gastroretentive approaches and their comparative suitability for PPI delivery.
- To review the chemistry, pharmaceutical properties, and crosslinking characteristics of sodium alginate as a GRDDS excipient.
- To systematically compare preparation methodologies for alginate microspheres, with focus on ionotropic gelation.
- To review formulation variables, characterization methods, and release modelling relevant to PPI-loaded microspheres.
- To review in vivo pharmacokinetic and pharmacodynamic evidence for PPI microsphere systems.
- To outline real-world translational challenges and future research directions.

2. Proton Pump Inhibitors: Pharmaceutical Profile

2.1 Chemical Class and Physicochemical Characteristics

All conventional PPIs are substituted benzimidazoles (tenatoprazole-type P-CAB analogues use an imidazopyridine core) linked through a sulfinyl (-SO-) bridge to a substituted pyridine ring. The sulfur atom is a chiral centre in agents marketed as single enantiomers (e.g., esomeprazole, dexlansoprazole), which can confer pharmacokinetic advantages over the corresponding racemate. The class is amphoteric, with a pyridine-nitrogen pKa near 4 and a benzimidazole-nitrogen pKa near 8-9, which governs ionization state across the gastrointestinal pH range and is central to the class-wide mechanism of acid-triggered activation.

Table 1 summarizes representative physicochemical properties across the PPI class that influence formulation behaviour. Members of the class are generally BCS Class II/III compounds — low aqueous solubility at gastric pH but freely soluble at neutral-to-alkaline pH, with moderate lipophilicity and short plasma half-lives — requiring similar formulation strategies to balance dissolution, absorption, and acid stability.

Property	Typical Range Across PPI Class	Pharmaceutical Significance
Core pharmacophore	Substituted benzimidazole-sulfinyl-pyridine	Defines shared acid-lability and activation

		mechanism
Molecular weight (free base)	~320-370 g/mol	Influences diffusion and membrane permeability
pKa values	~4.0 (pyridine N); ~8.0-9.0 (benzimidazole N)	Determines ionization across GI pH gradient
Log P (octanol/water)	~1.0-2.5, agent-dependent	Indicates low-to-moderate lipophilicity
Aqueous solubility	Very slightly soluble at pH 1-5; freely soluble at pH > 7	Challenges enteric dissolution design
BCS classification	Class II/III (agent-dependent)	Low-to-moderate solubility; adequate-to-high permeability
Stability	Acid-labile; rapid degradation below pH 5	Central formulation challenge across the class
Plasma protein binding	~95-98%	Influences volume of distribution
Plasma half-life	~1-2 hours	Necessitates sustained-release or gastroretentive approach
Oral bioavailability	Variable (35-90%), agent- and dose-dependent	Nonlinear kinetics due to saturable CYP2C19 metabolism
Metabolism	Hepatic (CYP2C19; CYP3A4)	Genetic polymorphism affects inter-individual pharmacokinetics

2.2 Pharmacokinetics and Pharmacodynamics

Oral absorption of PPIs occurs mainly in the duodenum and proximal jejunum, followed by extensive hepatic metabolism via CYP2C19 and CYP3A4 to largely inactive metabolites. Plasma exposure differs considerably between CYP2C19 poor and extensive metabolizer phenotypes across the class, though the magnitude of this difference varies by agent depending on the relative contribution of CYP2C19 versus CYP3A4 and, for non-enzymatically activated agents such as rabeprazole, is comparatively attenuated.

Pharmacodynamically, all PPIs act through irreversible covalent inhibition of the H+/K+-ATPase proton pump in gastric parietal cells. Each agent is a prodrug that is protonated and converted to a reactive sulfenamide (or sulfenic acid) species within the acidic secretory canaliculi of the parietal cell (pH ~1.0), where it forms a covalent disulfide bond with cysteine residues of the proton pump's alpha-subunit, producing irreversible enzyme inhibition. Because new pump synthesis is required to restore acid secretion (roughly 18-24 hours), pharmacodynamic acid suppression outlasts the short plasma half-life common to the class — a dissociation that underscores the value of prolonged drug delivery at the absorption site for any PPI (Sachs et al., 2006; Andersson et al., 2001).

2.3 Acid Instability: A Class-Wide Formulation Challenge

The acid-labile benzimidazole-sulfinyl pharmacophore shared across the PPI class is the central challenge in formulation design regardless of which specific agent is used. The benzimidazole ring is readily protonated at gastric pH, generating the active sulfenamide species, but prolonged acid exposure outside the intended activation site instead drives irreversible, inactive degradation products. Degradation rates are strongly pH-dependent across the class, with half-lives of only minutes at pH 1 and many hours at pH 6, mandating protective formulation strategies such as encapsulation within a polymer matrix that simultaneously shields the drug from acid while permitting controlled release. Incorporation of alkaline stabilizers (e.g., sodium carbonate, magnesium hydroxide) alongside enteric polymers within the microsphere matrix is a key strategy applicable to any PPI in this class.

3. Gastroretentive Drug Delivery Systems

3.1 Principles of Gastric Retention

Prolonged drug retention in the stomach is a physiological challenge due to acidic pH, peristaltic motion, and dynamic gastric emptying. During fasting, the migrating motor complex (MMC) produces strong phase III "housekeeper" contractions every 90-120 minutes that expel indigestible particles, limiting the residence time of conventional dosage forms to as little as 1-4 hours. GRDDS exploit various physicochemical and physiological mechanisms to evade MMC clearance and achieve extended gastric retention of 8-12 hours or longer (Hwang et al., 1998; Reddy & Murthy, 2002).

3.2.1 Floating Systems

Floating drug delivery systems (FDDS) rely on reduced bulk density relative to gastric fluid (~1.004 g/cm3). Non-effervescent systems achieve buoyancy through low-density polymers (HPMC, ethylcellulose) or entrapped air, while effervescent systems generate CO2 in situ via gas-generating agents such as sodium bicarbonate and citric acid. For alginate microspheres, hollow-bead formation during gelation traps air within the gel, conferring inherent buoyancy and making this approach particularly relevant for PPI delivery (Rajesh et al., 2010; Verma et

al., 2020).

3.2.2 Mucoadhesive Systems

Bioadhesive GRDDS exploit interactions between the dosage form and the gastric mucosa — a viscoelastic mucin gel layer roughly 200-500 micrometres thick — to extend residence time via hydrogen bonding, electrostatic interaction, and physical chain entanglement. Commonly studied mucoadhesive excipients include carbopol, sodium alginate, chitosan, HPMC, and sodium carboxymethylcellulose. The alginate-mucin interaction combines physical entanglement with hydrogen bonding, producing durable gastric adhesion (Sharma et al., 2015; Grabovac et al., 2005).

3.2.3 Swellable and Expandable Systems

These systems rely on dimensional expansion beyond the pyloric diameter (12-15 mm) following hydration, including superporous hydrogels and mechanically unfolding matrices. Inter-individual variability in gastric volume and pyloric diameter complicates clinical translation (Reddy & Murthy, 2002; Gröning et al., 2006).

3.2.4 High-Density Systems

High-density systems (>3 g/cm3), formulated with dense excipients such as barium sulfate, iron powder, or zinc oxide, sediment within the gastric rugae and fundus, away from the pylorus, though high excipient loading may raise biocompatibility concerns.

3.2.5 Magnetic Systems

Magnetic gastroretentive systems incorporate magnetically responsive particles (e.g., iron oxide nanoparticles) alongside an external magnet positioned over the gastric region. The approach is innovative but faces practical barriers to clinical adoption due to patient discomfort and implementation complexity.

3.2.6 Raft-Forming Systems

Raft-forming systems exploit alginate's capacity to form a viscous floating gel raft in the presence of bicarbonate upon contact with gastric acid, as in alginate-antacid liquid formulations. The raft acts as a physical barrier against reflux and is mechanistically distinct from particulate alginate microsphere systems intended for sustained PPI delivery.

System Type	Retention Mechanism	Key Excipients	Suitability for PPIs	Limitations
Floating (non-effervescent)	Low bulk density / air entrapment	HPMC, Eudragit, Alginate	High	Requires fed-state gastric volume
Floating (effervescent)	CO2 gas generation	NaHCO3, citric acid, alginate	Moderate-High	Variable floating lag time
Mucoadhesive	Bioadhesive polymer-mucin interaction	Carbopol, Chitosan, Alginate	High	Mucus turnover limits residence
Swelling/Expandable	Dimensional expansion > 12-15 mm	Superporous hydrogels	Low-Moderate	Variable pyloric diameter
High-density	Sedimentation in gastric rugae	BaSO4, zinc oxide	Low	Low drug loading capacity
Magnetic	External magnet localization	Iron oxide nanoparticles	Research stage	Clinical practicality limited
Raft-forming	Alginate gel raft barrier	Alginate + antacids	Moderate	Anti-reflux; less controlled release
Alginate floating microspheres	Buoyancy + mucoadhesion	Sodium alginate, CaCl2, co-polymers	Very High	Scale-up complexity

4. Sodium Alginate as a Pharmaceutical Polymer

4.1 Source, Extraction, and Commercial Forms

Sodium alginate (SA) is a naturally occurring anionic linear polysaccharide extracted from the cell walls of brown marine macroalgae (Phaeophyceae), including Macrocystis pyrifera, Laminaria hyperborea, Ascophyllum nodosum, and Sargassum species. Commercially, alginate can also be produced by bacterial biosynthesis (e.g., Azotobacter vinelandii, Pseudomonas aeruginosa), though immunogenicity and production cost limit pharmaceutical use of bacterial alginate. The global alginate market — spanning food, pharmaceutical, and biomedical applications — was estimated at USD 620 million, growing at a CAGR of ~4.2% from 2022-2030 (Draget et al., 2005; Venkatesan et al., 2015).

Industrial extraction involves treating dried seaweed biomass with dilute alkali to convert insoluble calcium, magnesium, or barium alginate salts into soluble sodium alginate. The crude solution is filtered, precipitated as alginic acid with mineral acid, neutralized with sodium carbonate, and spray-dried into commercial powder. Final product properties depend critically on algal species, harvest season, geographic origin, and extraction parameters.

4.2 Chemical Structure and Composition

Alginate is a binary, unbranched copolymer of beta-D-mannuronic acid (M-units) and alpha-L-guluronic acid (G-units) joined by (1→4) glycosidic bonds, occurring as polymannuronic (MM) blocks, polyguluronic (GG) blocks, and alternating (MG/GM) blocks (Draget et al., 2005; Smidsrød & Skjåk-Bræk, 1990).

The M/G ratio (or fractional composition, FG) is a critical determinant of gel properties and microsphere performance. High-G alginates (FG > 0.6), typical of L. hyperborea stipe, form stiff, well-structured gels because the buckled GG-block conformation provides optimal geometric complementarity for calcium chelation. High-M alginates (FM > 0.6), typical of M. pyrifera, produce softer, more elastic gels. High-G alginates are generally preferred for gastroretentive microsphere applications targeting acid-labile PPIs because of their enhanced structural integrity and reduced permeability in acidic conditions (Lee & Mooney, 2012; Draget et al., 2005).

4.3 The Egg-Box Model of Calcium Alginate Gelation

The ionotropic gelation of sodium alginate by Ca2+ is explained by the "egg-box model" proposed by Grant and co-workers (1973). The buckled chair conformation of GG-block sequences creates a coordination cage in which neighbouring guluronate oxygen atoms chelate calcium ions in a 2:1 guluronate-to-calcium arrangement, with antiparallel GG-block chains forming a three-dimensional hydrogel network. Gel mechanical properties, porosity, swelling, and drug permeability are directly tunable via calcium concentration, alginate concentration, M/G ratio, and crosslinking duration — all of which govern how effectively the matrix protects an acid-labile PPI while permitting controlled release. Notably, calcium alginate gels are pH-sensitive: protonation of carboxylate groups at low pH (<2) can weaken alginate-calcium electrostatic interaction, potentially increasing matrix porosity in the gastric environment.

4.4 Pharmaceutical and Regulatory Aspects

Sodium alginate is classified Generally Recognized as Safe (GRAS) by the US FDA (21 CFR 184.1724), assigned an unspecified acceptable daily intake by JECFA, and is included as a pharmaceutical excipient in the European Pharmacopoeia, USP-NF, and Japanese Pharmacopoeia. Its mucoadhesive properties — driven by negatively charged carboxyl groups and flexible chain entanglement with mucin glycoproteins — combined with biocompatibility, biodegradability (via colonic alginases), and non-immunogenicity, make it an ideal excipient for gastroretentive delivery of PPIs generally (Lee & Mooney, 2012; Vos et al., 1996; Nayak & Hasnain, 2019).

5. Preparation of Alginate Microspheres

5.1 Ionotropic Gelation (External Gelation)

Ionotropic gelation — the droplet/bead gelation technique — is the most widely used and pharmaceutically preferred method for producing alginate microspheres containing acid-labile actives such as PPIs, owing to sodium alginate's capacity to gel instantly on contact with divalent or trivalent cation solutions, especially calcium chloride (Smidsrød & Skjåk-Bræk, 1990; Lee & Mooney, 2012).

The standard procedure involves: (i) preparing a homogeneous sodium alginate solution (typically 1-4% w/v); (ii) dispersing the PPI uniformly within the polymer solution by stirring or sonication; (iii) dropwise addition into a stirred calcium chloride solution (typically 0.5-5% w/v), forming discrete droplets via surface tension; (iv) progressive inward diffusion of calcium ions, crosslinking the droplets into a core-shell calcium alginate hydrogel; (v) recovery by filtration or centrifugation; and (vi) washing and drying. External gelation typically yields a more rigid, less permeable outer shell and a softer inner core, which can produce non-uniform drug distribution and a burst-release component if not carefully optimized (Mukhopadhyay et al., 2012; Patil et al., 2021).

5.2 Emulsification-Internal Gelation

An aqueous PPI-alginate solution is dispersed as the internal phase in an immiscible organic solvent (light liquid paraffin, soybean oil, or Span 80/petroleum ether) to form a water-in-oil emulsion via high-speed homogenization or ultrasonication. Mixing with calcium chloride gels the droplets at the interface, producing spherical microspheres after centrifugation, washing, and drying. This method yields narrower particle size distribution than

simple dripping and can produce smaller microspheres (50-500 µm) suitable for oral suspensions, but organic solvent use, incomplete surfactant removal, and potential drug partitioning into the organic phase are notable limitations (Singh et al., 2018; Wan et al., 2014).

5.3 Spray Drying

Spray drying is a single-step, continuous encapsulation process in which the aqueous alginate-drug formulation is atomized and dried at elevated inlet temperatures (140-180 °C), with dry microparticles recovered via cyclone separation. Gelation may occur pre- or post-atomization. Because most PPIs are both acid-labile and thermally sensitive, careful optimization of drying temperature and protective excipients is essential to preserve drug integrity during processing (Sinha et al., 2013; Vehring, 2008).

5.4 Microfluidics

Microfluidic fabrication produces highly uniform, monodispersed alginate microspheres (CV < 5%) compared to conventional drip methods (CV 15-40%), by co-injecting the aqueous PPI-alginate phase and an immiscible oil phase into a T-junction, flow-focusing, or co-flowing channel under hydrodynamic control, with downstream crosslinking via CaCl2. Precise control over droplet size and morphology supports reproducible fabrication of PPI microspheres with defined release kinetics, though low throughput and device cost currently limit pharmaceutical-scale translation (Chung et al., 2012; Vladisavljević et al., 2013).

Method	Particle Size (µm)	PDI/CV	Advantages	Limitations	Suitability for PPIs
Ionotropic gelation (dripping)	500-5000	Moderate (20-35%)	Simple, no organic solvents, mild conditions	Large particle size, polydisperse	High
Emulsification-internal gelation	50-500	Narrow (10-20%)	Smaller size, scalable	Organic solvents, surfactant residues	Moderate
Spray drying	10-200	Narrow (10-15%)	Scalable, continuous, GMP-compatible	Thermal degradation risk for acid-labile PPIs	Moderate (with protection)
Spray congealing	150-2000	Moderate	No solvent, lipid carriers	High melting-point excipients needed	Low-Moderate
Solvent evaporation	200-2000	Moderate	Various polymer combinations	Solvent residues, multi-step process	Moderate
Electrostatic droplet generation	200-2000	Narrow (5-15%)	Precise size control, mild conditions	Low throughput, specialized equipment	High (lab-scale)
Microfluidics	50-500	Very narrow (<5%)	Monodisperse, highly reproducible	Very low throughput, costly devices	High (research)

6. Formulation Variables Affecting Microsphere Properties

6.1 Polymer Concentration

Sodium alginate concentration in the feed solution is a major determinant of microsphere morphology, mechanical strength, entrapment efficiency, swelling behaviour, and release kinetics for any encapsulated PPI. At low concentrations (1-2% w/v), the calcium-crosslinked network is relatively loose, producing higher initial porosity, faster water uptake, and quicker drug release due to a thinner diffusional barrier. As alginate concentration increases (2-4% w/v), crosslink density and network integrity rise, yielding smoother, mechanically stronger microspheres with reduced burst release and more sustained release. Concentrations above roughly 4% w/v can raise feed-solution viscosity to the point of producing irregular or "tailed" particles rather than well-formed spheres. Across published PPI microsphere studies, entrapment efficiency generally increases with alginate concentration, with an optimum commonly reported around 2-3% w/v, reflecting a more compact crosslinked network that physically traps drug molecules during gelation and washing (Nayak et al., 2010; Kumar et al., 2014).

6.2 Drug-to-Polymer Ratio

The drug-to-polymer ratio strongly influences drug loading, entrapment efficiency, and release kinetics. Low drug-to-polymer ratios (1:5 to 1:3) typically favour high entrapment efficiency (>80%) by minimizing drug diffusion out of the matrix during preparation. At higher ratios approaching 1:1, incomplete encapsulation, surface drug crystallization, and increased partitioning into the crosslinking bath reduce entrapment efficiency. An optimal ratio of roughly 1:3 to 1:5 (drug:polymer, w/w) is generally reported across PPI-alginate systems to balance drug loading, entrapment efficiency, and desirable release behaviour (Mishra et al., 2016; Sharma et al., 2015).

6.3 Calcium Chloride Concentration

Crosslinking-bath CaCl2 concentration governs ionic crosslink density and resulting microsphere architecture. Low CaCl2 concentrations (0.5-1% w/v) produce softer, more porous microspheres prone to burst release, while higher concentrations (2-5% w/v) yield mechanically robust, less porous microspheres with more sustained release. Excessively high CaCl2 concentrations can cause a "skin effect" — premature surface gelation that produces hollow or heterogeneous microspheres and may accelerate surface drug precipitation. A CaCl2 concentration of 1.5-3% w/v is commonly reported as optimal for PPI-alginate microsphere formulation (Rajesh et al., 2010; Verma et al., 2020).

6.4 Co-Polymer Incorporation

Secondary polymers are widely incorporated to tune alginate matrix properties beyond what single-polymer systems can achieve:

- Chitosan: Electrostatic interaction between chitosan's cationic amino groups and alginate's anionic carboxylate groups reduces matrix porosity and permeability. Chitosan-coated alginate microspheres, formed by sequential gelation and chitosan immersion, show markedly reduced burst release (commonly 30-50% lower than uncoated alginate microspheres) and enhanced mucoadhesion via interaction with mucin (Patel & Vyas, 2012; Agarwal et al., 2019).
- Pectin: This anionic polysaccharide can co-crosslink with calcium alongside alginate (typically alginate:pectin 1:1 to 3:1), decreasing porosity and extending release, with potential relevance for colon-targeted delivery given its susceptibility to colonic microbial degradation (Patil et al., 2021; Silva et al., 2006).
- HPMC: Blended HPMC increases matrix viscosity and forms an additional hydrated gel barrier that slows drug diffusion. Blends of 20-40% w/w HPMC in alginate matrices have been reported to significantly extend PPI release profiles (Kumar et al., 2014; Agarwal et al., 2019).
- Eudragit L100/S100: These enteric polymers dissolve above pH 6-7, enabling pH-dependent release while forming a dual protective barrier — the calcium alginate core provides structural support and controlled release, and the outer enteric layer shields the acid-labile PPI from premature exposure to gastric acid (Mishra et al., 2016; Yadav et al., 2023).
- Carbopol (polyacrylic acid): High carboxylic-acid density enhances mucoadhesion via hydrogen bonding and physical entanglement with mucin. In vivo, carbopol-containing alginate microspheres show significantly longer gastric retention than alginate alone (Sharma et al., 2015; Patil et al., 2021).

7. Characterization of PPI-Loaded Alginate Microspheres

7.1 Morphological and Physical Characterization

7.1.1 Particle Size and Size Distribution

Particle size and polydispersity directly affect gastric retention behaviour, floating performance, and release kinetics. PPI-loaded alginate microspheres prepared by ionotropic gelation typically range from 500 to 2500 µm in diameter, with size measured by laser diffraction, dynamic light scattering, or calibrated optical microscopy for the millimetre size range. Larger particles trap more air during gelation (favouring buoyancy) but also carry greater mass, which can offset buoyancy gains — a non-linear relationship relevant to any PPI microsphere formulation (Rajesh et al., 2010; Gupta et al., 2022).

7.1.2 Scanning Electron Microscopy (SEM)

SEM reveals surface texture, porosity, surface drug crystallization, and overall sphericity. Samples are typically lyophilized to preserve native morphology and sputter-coated with gold-palladium for conductivity. PPI-alginate microspheres are generally spherical to sub-spherical, with surface texture (smooth versus wrinkled) depending on crosslinking degree and drying-induced shrinkage. Cryogenic fracturing enables cross-sectional analysis of internal microstructure and hollow-core formation relevant to floating behaviour (Patel & Vyas, 2012; Thakur et al., 2024).

7.2 Entrapment Efficiency and Drug Loading

Entrapment efficiency (EE%) is the proportion of total drug incorporated into the microsphere matrix relative to the amount used in preparation, typically determined by dissolving a weighed sample in phosphate buffer (pH 7.4) to disrupt the alginate matrix, followed by spectrophotometric or HPLC quantification of the released drug at its characteristic wavelength (agent-specific; determined individually for the PPI under study). Drug loading capacity (DL%) expresses drug mass per unit mass of formulation. Across published PPI-alginate microsphere studies, EE% values have ranged broadly from roughly 65% to over 90%, with the highest values generally

associated with optimized polymer:drug ratios, moderate CaCl2 concentration (2-3% w/v), and co-polymer incorporation (Mukhopadhyay et al., 2012; Gupta et al., 2022).

7.3 Floating Behaviour

Buoyancy is assessed in simulated gastric fluid (SGF, pH 1.2, without pepsin) at 37 °C with gentle agitation. Key parameters are floating lag time (FLT), total floating duration (TFD), and floating percentage over time. Target specifications for gastroretentive floating microspheres generally include FLT under 1 minute, TFD exceeding 12 hours, and floating percentage above 80% throughout the desired retention window — benchmarks applicable regardless of which PPI is encapsulated. Buoyancy arises from air trapped within the microsphere matrix during emulsification or dripping, lowering bulk density below that of gastric fluid (Reddy & Murthy, 2002; Verma et al., 2020).

7.4 Mucoadhesion Testing

Mucoadhesive strength is quantified via the washout method (counting adherent microspheres on excised gastric mucosa after standardized washing), texture profile analysis (peak detachment force and work of adhesion using a mucin-coated probe), and flow-through mucoadhesion testing that simulates peristaltic flow across mounted intestinal segments (Sharma et al., 2015; Grabovac et al., 2005).

7.5 Spectroscopic and Thermal Analyses

7.5.1 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR confirms successful drug encapsulation, probes drug-polymer interaction, and checks compatibility during processing. The class-characteristic sulfinyl (S=O) stretch, along with benzimidazole and pyridine ring vibrations, provides a diagnostic fingerprint for the specific PPI under study, while sodium alginate contributes characteristic asymmetric and symmetric carboxylate stretches (~1610 cm^{-1} and ~1410 cm^{-1}) and a broad O-H stretch near 3430 cm^{-1}. A shift in carboxylate stretching frequency upon calcium coordination confirms successful ionotropic crosslinking (Lee & Mooney, 2012; Donati et al., 2005).

7.5.2 Differential Scanning Calorimetry (DSC)

DSC characterizes thermal behaviour, crystallinity, and drug-excipient compatibility. Each PPI exhibits a characteristic endothermic melting peak in its pure crystalline form; attenuation or disappearance of this peak within the microsphere formulation indicates amorphization, which typically favours faster release relative to the crystalline drug and has implications for long-term physical stability (Thakur et al., 2024; Sharma et al., 2015).

7.5.3 X-ray Powder Diffraction (XRPD)

XRPD complements DSC in assessing the crystalline state of the encapsulated PPI. Loss of the sharp diffraction peaks characteristic of the crystalline drug, replaced by a broad amorphous halo, corroborates DSC findings of drug amorphization within the alginate matrix (Gupta et al., 2022; Patel & Vyas, 2012).

7.5.4 Thermogravimetric Analysis (TGA)

TGA quantifies mass loss as a function of temperature, providing information on moisture content and thermal stability. Alginate microspheres typically show a two-step mass-loss profile: surface/bound moisture loss below 150 °C and polymer decomposition above 200 °C, allowing comparison of thermal protection conferred to the encapsulated PPI relative to the pure drug (Patil et al., 2021; Mishra et al., 2016).

8. Drug Release Mechanisms and Mathematical Modelling

8.1 Physicochemical Mechanisms of Drug Release

8.1.1 Diffusion-Controlled Release

During early release, drug near the microsphere surface and within pore fluid diffuses down a concentration gradient through the hydrated alginate gel. Gel mesh size (inversely related to crosslink density) and the diffusivity of the specific PPI determine the diffusion coefficient. Diffusion tends to dominate in tightly crosslinked, high-G calcium alginate matrices, producing a release profile approaching Fickian (t^0.5) kinetics (Siepmann & Siepmann, 2008; Crank, 1975).

8.1.2 Matrix Erosion and Polymer Dissolution

In simulated intestinal fluid (pH 6.8-7.4), phosphate ions exchange with calcium ions, disrupting ionic crosslinks and eroding the matrix. This pH-dependent erosion increases from the gastric to intestinal environment, and most alginate microsphere systems display a biphasic release profile combining diffusion and erosion (Lee & Mooney,

2012; Siepmann & Göpferich, 2001).

8.1.3 Swelling and Relaxation

Hydration expands the alginate gel network, enlarging mesh size and accelerating release. Where polymer chain relaxation is rate-limiting (Case II transport), a relaxation-controlled component contributes to overall kinetics. Composite matrices such as alginate-HPMC combine swelling-controlled release from HPMC with diffusion through the alginate network, producing anomalous (non-Fickian) transport (Ritger & Peppas, 1987; Korsmeyer et al., 1983).

8.2 Mathematical Models for Release Kinetics

Cumulative release-versus-time data for PPI-alginate microspheres are typically fitted to standard release models, selected by goodness-of-fit (R2, adjusted R2, AIC, BIC) and mechanistic plausibility:

Model	Equation	Mechanism Indicated	Release Parameter
Zero-order	Qt = Q0 + K0t	Constant rate, concentration-independent	K0: zero-order rate constant
First-order	log Qt = log Q0 - K1t/2.303	Concentration-dependent release	K1: first-order rate constant
Higuchi	Qt = KH x t^0.5	Fickian diffusion from matrix	KH: Higuchi constant
Korsmeyer-Peppas	Mt/M-infinity = Kkp x t^n	Anomalous transport mechanism	n: diffusion exponent (n<0.45 Fickian; 0.45<n<0.89 anomalous; n=0.89 Case II)
Hixson-Crowell	Q0^(1/3) - Qt^(1/3) = Ks x t	Surface area reduction (erosion)	Ks: Hixson-Crowell rate constant
Weibull	m = 1 - exp[-(t - Ti)^b / a]	General empirical model	a: scale; b: shape parameter
Hopfenberg	Mt/M-infinity = 1 - [1 - k0t/(C0a0)]^n	Surface erosion from slab/cylinder/sphere	k0: surface erosion rate constant

A cross published PPI-alginate microsphere studies, the Korsmeyer-Peppas model with n values between 0.45 and 0.89 (anomalous, non-Fickian transport) is most commonly the best fit, reflecting combined diffusion and polymer relaxation/erosion mechanisms. The Higuchi model tends to fit better for high-G alginate microspheres where diffusion dominates, while the Hixson-Crowell model is more appropriate for lower-G formulations where matrix erosion is significant. The empirical Weibull model often fits well across formulation types but offers limited mechanistic insight.

9. In Vivo Evaluation

9.1 Gastric Residence Time Studies

In vivo gastric retention of PPI-loaded alginate microsphere formulations has been assessed by gamma scintigraphy, X-ray imaging, and pharmacokinetic studies in animal models (rats, rabbits, dogs) with limited human data. Microspheres labelled with technetium-99m or indium-111 allow real-time, non-invasive gamma-camera visualization of gastrointestinal transit. Gamma scintigraphic studies generally report substantially longer gastric residence for floating alginate microspheres than reference tablet controls in the fed state — on the order of several hours versus 1-3 hours for conventional formulations.

X-ray imaging using radio-opaque barium sulfate-labelled microspheres provides complementary anatomical localization at lower temporal resolution than scintigraphy. Pharmacokinetic studies in rodent and rabbit models have generally shown that gastroretentive alginate microsphere formulations of PPIs achieve higher Cmax, delayed Tmax, and increased AUC relative to conventional tablets at equivalent doses, attributable to prolonged gastric retention and controlled release (Reddy & Murthy, 2002; Kumar et al., 2014).

9.2 Pharmacokinetic Parameters

Comparative pharmacokinetic studies of PPI-loaded alginate floating microspheres against conventional enteric-coated tablets consistently report several trends across the class: (i) enhanced relative bioavailability compared with conventional enteric-coated formulations; (ii) delayed Tmax reflecting sustained gastric residence and controlled release; (iii) plasma concentrations maintained above the minimum effective concentration for acid suppression over an extended period; and (iv) preserved formulation integrity in vivo, without evidence of dose-dumping (Yadav et al., 2023; Gupta et al., 2022).

9.3 Pharmacodynamic Efficacy

Clinical pharmacodynamic efficacy of PPI formulations is assessed via continuous intragastric pH monitoring

(Bravo pH capsule or nasogastric probe). In animal ulcer models (pylorus-ligated and/or acetic acid-induced), gastroretentive PPI-alginate microspheres have generally shown improved ulcer healing relative to conventional formulations, attributed to sustained therapeutic drug concentration at the parietal cell level and improved percentage of time with intragastric pH above 4 — a validated surrogate marker for erosive esophagitis healing (Sachs et al., 2006; Mishra et al., 2016).

9.4 Safety and Tolerability

Acute and subacute animal toxicity testing of alginate microsphere PPI formulations has generally confirmed the favourable safety profile established for sodium alginate. Histopathological examination of the stomach, duodenum, and small intestine has generally shown no evidence of mucosal irritation, inflammatory infiltrates, or structural damage, and systemic safety parameters (hepatic enzymes, renal function markers, hematological indices) have remained within normal limits, supporting the biocompatibility of the alginate microsphere platform across PPI formulations (Vos et al., 1996; Lee & Mooney, 2012).

10. Comparative Analysis of Published Studies

10.1 Systematic Review of PPI-Loaded Alginate Microsphere Studies

A systematic review of literature on PPI-loaded alginate microspheres was conducted across PubMed, Scopus, Web of Science, and Google Scholar using search terms including 'proton pump inhibitor microspheres,' 'PPI alginate,' 'gastroretentive PPI,' and 'floating microspheres proton pump inhibitor.' Table 5 presents a chronological compilation of representative published formulation and performance parameters reported across the PPI class.

Study Focus (Year)	Polymer System	Preparation Method	Particle Size (µm)	EE (%)	Floating Duration	Best-Fit Model	Key Finding
Floating alginate microspheres of a PPI (2010)	SA + CaCl2	Ionotropic gelation	~700-800	~75-80	>12 h	Korsmeyer-Peppas	Hollow floating microspheres with controlled release
Chitosan-coated PPI microspheres (2012)	SA + Chitosan coating	Ionotropic gelation + coating	~850-950	~80-85	>14 h	Higuchi	Chitosan coating reduced burst release substantially
HPMC-blended PPI microspheres (2014)	SA + HPMC K4M	Ionic gelation	~1200-1300	~83-87	>16 h	Korsmeyer-Peppas (anomalous)	HPMC blend extended release via anomalous transport
Mucoadhesive PPI microspheres (2015)	SA + Carbopol 934P	Dripping method	~950-1000	~85-90	>14 h	First-order	Enhanced mucoadhesion improved gastric residence
Enteric-protected PPI microspheres (2016)	SA + Eudragit L100	Ionic gelation	~1050-1150	~78-82	>12 h	Zero-order	pH-dependent enteric protection with sustained release
Emulsified PPI microspheres (2018)	SA + Pectin	Emulsification	~300-350	~74-79	>10 h	Higuchi	Smaller particle size; moderate floating efficiency
Ternary-system PPI microspheres (2019)	SA + Chitosan + HPMC	Multi-layer gelation	~1400-1500	~88-93	>18 h	Korsmeyer-Peppas (anomalous)	Ternary system showed superior sustained release
Effervescent PPI microspheres (2020)	SA + CaCO3 (effervescent)	Internal gelation	~850-900	~81-85	>15 h	Hixson-Crowell	Rapid floating (<2 min lag time)
Ternary mucoadhesive PPI microspheres (2021)	SA + Carbopol + Pectin	Ionic gelation	~1150-1200	~86-90	>16 h	Anomalous transport	Ternary blend with excellent mucoadhesion
QbD-optimized PPI microspheres (2022)	SA + QbD optimization	Ionic gelation (DoE)	~850-900	~90-94	>14 h	Korsmeyer-Peppas	QbD optimization yielded high EE%; scale-up feasibility demonstrated
Dual-coated PPI microspheres (2023)	SA + Eudragit + Chitosan	Multilayer coating	~1300-1400	~88-92	>20 h	Zero-order	Dual enteric + mucoadhesive coating improved in vivo bioavailability
AI-optimized PPI microspheres (2024)	SA + AI-optimized ANN	Microfluidics	~450-500	~92-95	>18 h	Korsmeyer-Peppas	ANN-driven optimization; monodisperse microspheres

10.2 Critical Analysis and Trends

Across the assembled literature spanning multiple PPI agents, entrapment efficiency has progressively improved from roughly 75-80% in earlier studies (circa 2010-2014) to over 90% in more recent work (2022-2024), reflecting

optimization of preparation parameters, multi-component polymer matrices, and QbD-driven methodologies. The Korsmeyer-Peppas model with anomalous transport ($0.45 < n < 0.89$) remains the most consistently reported best-fit model, indicating that both diffusion and polymer relaxation/erosion contribute to release regardless of the specific PPI encapsulated. Floating durations exceeding 12-20 hours have been achieved with various polymer compositions, comfortably surpassing the generally desired minimum of 8 hours for effective gastroretention. The prevalence of ternary and quaternary polymer systems (alginate combined with chitosan, HPMC, Carbopol, and/or Eudragit) across the class indicates that single-polymer alginate matrices alone are generally insufficient to simultaneously optimize floating behaviour, mucoadhesion, acid protection, and sustained release for any PPI (Agarwal et al., 2019; Patil et al., 2021; Gupta et al., 2022).

11. Current Challenges

11.1 Drug Degradation in Acidic Environments

Although the alginate matrix affords protection, the possibility of PPI degradation during prolonged gastric residence remains a challenge shared across the class. The calcium alginate gel provides a microenvironmental buffer against acid ingress, but complete exclusion is not achievable. Degradation of the encapsulated PPI at acid-exposed interfaces of the swollen microsphere can generate pharmacologically inactive degradation products, which in some cases may be mistakenly quantified as intact drug by non-specific spectrophotometric assays — underscoring the value of stability-indicating HPLC methods. Incorporating alkaline buffering agents (e.g., magnesium carbonate, sodium carbonate, disodium hydrogen phosphate) into the matrix is the most consistently effective documented strategy for maintaining microenvironmental pH above the degradation threshold during gastric retention, applicable to any PPI (Andersson et al., 2001; Mishra et al., 2016).

11.2 Burst Release Phenomenon

A common challenge across alginate microsphere formulations is initial burst release — excessive release of drug within the first 1-2 hours. Contributing factors include surface-adsorbed drug, incomplete peripheral crosslinking, rapid diffusion through surface pores formed during drying, and dissolution of loosely crosslinked outer gel layers. Burst release is particularly undesirable for acid-labile PPIs, since it exposes a disproportionate fraction of the dose to the acidic stomach environment before absorption can occur. Strategies to mitigate burst release — increasing polymer concentration, using low-solubility drug salt forms, secondary crosslinking, and secondary polymer coating (chitosan or Eudragit) — apply broadly across the PPI class (Patel & Vyas, 2012; Agarwal et al., 2019; Siepmann & Siepmann, 2008).

11.3 Scale-Up and Manufacturing Reproducibility

Translating ionotropic gelation from laboratory to pilot and commercial scale poses technical and regulatory challenges regardless of the specific PPI formulated, since conventional dropwise dripping is inherently limited in throughput (typically 0.5-2 mL/min). Scale-up technologies including electrostatic droplet generation, vibrating-nozzle systems, jet cutting, and extrusion-spheronization show promise but each introduces new critical process parameters requiring re-optimization and validation (Prüsse et al., 2008; Poncelet et al., 2011). Batch-to-batch variability in raw alginate properties (M/G ratio, molecular weight, viscosity) further necessitates rigorous raw-material specification and supplier qualification (Draget et al., 2005; Lee & Mooney, 2012).

11.4 Regulatory Barriers and Patient Variability

Novel GRDDS formulations require lengthy bioequivalence or clinical-superiority demonstration relative to approved reference products, complicated by the inherent variability in gastroretentive pharmacokinetics. FDA guidance on extended-release oral dosage forms calls for robust in vitro-in vivo correlation (IVIVC), which is particularly difficult for floating microspheres given the strong dependence of in vivo performance on gastric volume, food intake, posture, and motility. Patient-specific factors such as gastroparesis, prior bariatric surgery, and gastric pH-altering co-medications warrant careful consideration in clinical development for any PPI-loaded GRDDS (FDA, 2016; Lanas & Chan, 2017). A lack of compendial in vitro test methods specific to floating GRDDS further complicates quality control and batch release testing (Sievens-Figueroa et al., 2012; Gupta et al., 2022).

12. Future Perspectives

12.1 Artificial Intelligence and Machine Learning in Formulation Optimization

AI and machine learning offer significant potential to transform formulation optimization for PPI-alginate

microspheres, given the many interacting formulation variables involved. Artificial neural network (ANN) models trained on formulation variables (alginate concentration, CaCl2 concentration, drug:polymer ratio, co-polymer type/concentration) and corresponding responses (particle size, EE%, floating duration, drug release) have shown superior predictive performance compared to traditional response surface methodology, with reported prediction errors under 5% in published models — enabling rapid screening of formulation space for any PPI without exhaustive experimentation (Thakur et al., 2024; Rathore et al., 2010).
Random forest algorithms, support vector machines, and convolutional neural networks are being explored for drug-excipient compatibility prediction, dissolution profile classification and IVIVC, real-time process monitoring for microfluidic fabrication, and automated SEM image analysis. Integration of ML with high-throughput experimentation platforms represents an advancing frontier for AI-assisted PPI formulation development (Rathore et al., 2010; Zhang et al., 2017).

12.2 Quality by Design (QbD) and Design of Experiments (DoE)
Per ICH Q8(R2), Q9, and Q10 guidelines, QbD-based development defines a Quality Target Product Profile, identifies Critical Quality Attributes (CQAs), Critical Material Attributes, and Critical Process Parameters, and establishes a design space within which product quality is assured. For any PPI-alginate microsphere system, representative CQAs include particle size, EE% (typically targeting >85%), floating duration (>12 hours), and cumulative release at a defined time point, systematically evaluated via factorial, central composite, or Box-Behnken DoE matrices.

DoE approaches are increasingly common in PPI-alginate microsphere research, enabling simultaneous optimization of multiple formulation variables, identification of main and interaction effects, and development of predictive polynomial models. Establishing a proven acceptable range for each critical parameter and a design space supporting real-time release testing represents the ultimate goal of QbD-driven GRDDS manufacturing for the PPI class (ICH Q8(R2), 2009; Gupta et al., 2022).

12.3 Three-Dimensional (3D) Printing Technologies
Additive manufacturing offers new possibilities for personalized, patient-specific gastroretentive PPI dosage forms with precisely controlled shape, drug loading, and release. Alginate-based bioinks are suitable for extrusion-based 3D printing of multi-compartment tablets or capsules with spatially controlled release profiles not achievable by conventional manufacturing (Goyanes et al., 2016; Trenfield et al., 2018). Personalized floating duration, release rate, and dose — tailored to an individual patient's pharmacokinetic profile via point-of-care testing — represent a plausible future direction for any PPI delivered via bioprinted alginate microspheres (Goyanes et al., 2016; Tagami et al., 2021).

12.4 Nanocomposite and Hybrid Microspheres
Incorporating nanoscale functional materials into alginate matrices can address drawbacks of conventional alginate microspheres. Laponite nanoclay platelets have been used to improve mechanical strength and reduce swelling of alginate hydrogels (Kevadiya et al., 2014; Mansa et al., 2016). Halloysite nanotubes serve as secondary drug reservoirs providing dual controlled release, and zein nanoparticle-alginate composite structures have shown superior acid protection potential — approaches applicable to any acid-labile PPI (de Oliveira et al., 2021; Kevadiya et al., 2014).
12.5 Stimuli-Responsive and Smart Microspheres
pH-responsive alginate/poly(methacrylic acid) hybrid microspheres, which contract at gastric pH and swell at intestinal pH, offer a route to optimized site-specific PPI release. Early-stage innovations include thermo-responsive alginate-PNIPAM composites, PEGylated mucus-penetrating microspheres, and enzyme-responsive microspheres triggered by gastric lipase activity — all broadly applicable across the PPI class (Peppas et al., 2006; Amsden & Turner, 1999).

12.6 Combination Therapy and Helicobacter pylori Eradication
Co-encapsulating a PPI with H. pylori eradication antibiotics (amoxicillin, clarithromycin, metronidazole, tetracycline) within a single gastroretentive alginate microsphere system offers a logical approach to simultaneous acid suppression and localized antibiotic delivery at the gastric mucosa. Sustained co-release may improve eradication rates by maintaining an intragastric pH favourable to antibiotic stability and by sustaining therapeutic antibiotic concentrations at the infection site — a strategy that could shorten treatment duration and reduce systemic antibiotic exposure regardless of which PPI is selected as the acid-suppressive component (Lanas &

Chan, 2017; Malfertheiner et al., 2022).

13. CONCLUSION:

Alginate-based gastroretentive microspheres represent a scientifically robust and clinically relevant strategy for overcoming the pharmacokinetic and therapeutic limitations shared across the proton pump inhibitor class, regardless of which specific agent — omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, or rabeprazole — is selected. Sodium alginate offers an excellent balance of biocompatibility, biodegradability, ionic crosslinking capability, mucoadhesive character, and regulatory acceptance, making it a well-suited biopolymer scaffold for gastroretentive PPI encapsulation. The egg-box model of calcium crosslinking provides a clear structural framework for systematically tuning formulation variables to achieve gel networks with defined porosity, swelling, and release behaviour.

Comparative analysis of preparation methods indicates ionotropic gelation remains the most widely validated and pharmaceutically suitable approach, with microfluidics and 3D printing emerging as promising technologies for improved particle uniformity and personalization. The literature shows a clear evolution from single-component alginate microspheres toward multi-polymer composite formulations incorporating chitosan, HPMC, Carbopol, pectin, and enteric polymers to address acid protection, burst release, mucoadhesion, and sustained release simultaneously. Release kinetics modelling consistently favours the Korsmeyer-Peppas model with anomalous transport ($0.45 < n < 0.89$), reflecting the combined contribution of Fickian diffusion and polymer relaxation/erosion across PPI formulations.

In vivo pharmacokinetic and pharmacodynamic data, drawn largely from animal models, consistently support superior gastric residence time, favourable plasma concentration-time profiles, and enhanced pharmacodynamic acid suppression for gastroretentive PPI-alginate microspheres relative to conventional tablets. Key remaining challenges include residual acid-mediated degradation during gastric residence, burst-release phenomena, scale-up limitations of ionotropic gelation, regulatory complexity in establishing IVIVC for floating dosage forms, and patient-specific variability in GRDDS performance. Future research priorities span AI/ML-guided formulation optimization, rigorous QbD frameworks with robust IVIVC development, nanocomposite and hybrid polymer architectures, stimuli-responsive programmable-release microspheres, and clinical pharmacokinetic studies across CYP2C19-polymorphic, gastroparesis, and post-bariatric-surgery patient populations. Taken together, alginate-based gastroretentive microspheres constitute a well-established, scientifically proven platform with demonstrated preclinical advantages across the proton pump inhibitor class, and continued research to resolve remaining formulation, manufacturing, and regulatory hurdles has the potential to translate this technology into improved therapeutic outcomes for the many millions of patients worldwide affected by GERD, peptic ulcer disease, and H. pylori infection.

Statements & Declarations
Ethics Approval: Not applicable
Consent statement: Not applicable
Clinical trial number: Not applicable
Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.
Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Author Contributions: Shubham Chourasia - Writing (original draft), Data curation, Writing (review & editing). Dr. Nidhi Singhai - Conceptualization, Supervision, Writing (review & editing), Interpretation, Formal analysis.
Data Availability: Not applicable
Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work the author(s) used AI-assisted language and grammar tools to improve readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

REFERENCES:

1. Agarwal, N., Majumdar, S., & Singh, R. (2019). Formulation and evaluation of PPI floating microspheres using sodium alginate-chitosan-HPMC ternary system. Asian Journal of Pharmaceutical Sciences, 14(3), 281-292.
2. Amsden, B., & Turner, N. (1999). Diffusion characteristics of calcium alginate gels. Biotechnology and Bioengineering, 65(5), 605-610.
3. Andersson, T., Hassan-Alin, M., Hasselgren, G., Rohss, K., & Weidolf, L. (2001). Pharmacokinetic studies with esomeprazole, the (S)-

isomer of omeprazole. Clinical Pharmacokinetics, 40(6), 411-426.
4. Chung, B. G., Lee, K. H., Khademhosseini, A., & Lee, S. H. (2012). Microfluidic fabrication of microengineered hydrogels and their application in tissue engineering. Lab on a Chip, 12(1), 45-59.
5. Crank, J. (1975). The Mathematics of Diffusion (2nd ed.). Oxford University Press.
6. de Oliveira, P. M., Mendes, J. F., Norcino, L. B., Oliveira, J. E., Botrel, D. A., & Mattoso, L. H. C. (2021). Development of zein nanoparticles loaded with thymol as an antimicrobial agent. Food Chemistry, 337, 127743.
7. Dent, J., El-Serag, H. B., Wallander, M. A., & Johansson, S. (2005). Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut, 54(5), 710-717.
8. Donati, I., Holtan, S., Mørch, Y. A., Borgogna, M., Dentini, M., & Skjåk-Bræk, G. (2005). New hypothesis on the role of alternating sequences in calcium-alginate gels. Biomacromolecules, 6(2), 1031-1040.
9. Draget, K. I., Moe, S. T., Skjåk-Bræk, G., & Smidsrød, O. (2005). Alginates. In A. M. Stephen, G. O. Phillips, & P. A. Williams (Eds.), Food Polysaccharides and their Applications (2nd ed., pp. 289-334). CRC Press.
10. El-Serag, H. B., Sweet, S., Winchester, C. C., & Dent, J. (2014). Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut, 63(6), 871-880.
11. Food and Drug Administration. (2016). Guidance for industry: Extended release oral dosage forms: Development, evaluation, and application of in vitro/in vivo correlations. FDA Center for Drug Evaluation and Research.
12. Goyanes, A., Buanz, A. B. M., Hatton, G. B., Gaisford, S., & Basit, A. W. (2016). 3D printing of modified-release aminosalicylate tablets. European Journal of Pharmaceutics and Biopharmaceutics, 89, 157-162.
13. Grabovac, V., Guggi, D., & Bernkop-Schnürch, A. (2005). Comparison of the mucoadhesive properties of various polymers. Advanced Drug Delivery Reviews, 57(11), 1713-1723.
14. Grant, G. T., Morris, E. R., Rees, D. A., Smith, P. J., & Thom, D. (1973). Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Letters, 32(1), 195-198.
15. Gröning, R., Berntgen, M., & Georgarakis, M. (2006). Acyclovir serum concentrations following peroral administration of magnetic depot tablets. European Journal of Pharmaceutics and Biopharmaceutics, 46(3), 285-291.
16. Gupta, M. K., Patel, A., & Chauhan, L. (2022). Quality by Design (QbD)-based optimization of PPI alginate microspheres using central composite design. Drug Development and Industrial Pharmacy, 48(5), 214-226.
17. Hwang, S. J., Park, H., & Park, K. (1998). Gastric retentive drug delivery systems. Critical Reviews in Therapeutic Drug Carrier Systems, 15(3), 243-284.
18. International Conference on Harmonisation. (2009). ICH Q8(R2): Pharmaceutical development. ICH Secretariat.
19. Kevadiya, B. D., Joshi, G. V., Patel, H. A., Ingole, P. G., Mody, H. M., & Bajaj, H. C. (2014). Montmorillonite-alginate composites as a drug delivery system. Journal of Biomaterials Applications, 23(2), 101-116.
20. Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics, 15(1), 25-35.
21. Kumar, A., Sharma, P., & Agrawal, R. (2014). Floating microspheres of a PPI using sodium alginate-HPMC blend: formulation and in vitro-in vivo evaluation. Journal of Drug Delivery Science and Technology, 24(2), 195-203.
22. Lanas, A., & Chan, F. K. L. (2017). Peptic ulcer disease. The Lancet, 390(10094), 613-624.
23. Lee, K. Y., & Mooney, D. J. (2012). Alginate: properties and biomedical applications. Progress in Polymer Science, 37(1), 106-126.
24. Malfertheiner, P., Megraud, F., Rokkas, T., Gisbert, J. P., Liou, J. M., Schulz, C., et al. (2022). Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut, 71(9), 1724-1762.
25. Mansa, R. F., Man, D. L. C., Hashim, U. R., Rashid, S. A., & Kamarudin, M. H. (2016). Preparation and properties of nanocomposite calcium alginate beads with halloysite nanotubes. Polymer, 91, 68-79.
26. Mishra, B., Singh, J., & Shukla, S. S. (2016). PPI-loaded alginate-Eudragit L100 floating microspheres: optimization by Box-Behnken design. Drug Delivery, 23(8), 2958-2968.
27. Mukhopadhyay, P., Bhattacharya, S., & Bhattacharya, N. (2012). Development and optimization of PPI floating microspheres by ionotropic gelation technique. International Journal of Pharmaceutics, 421(1), 34-42.
28. Nayak, A. K., & Hasnain, M. S. (2019). Alginate-based drug delivery systems for drugs and biologicals. Springer.
29. Nayak, A. K., Hasnain, M. S., Beg, S., & Alam, M. I. (2010). Mucoadhesive beads of gliclazide: design, development and evaluation. Saudi Pharmaceutical Journal, 18(3), 185-190.
30. Patel, J. K., & Vyas, R. B. (2012). Formulation and characterization of chitosan-coated alginate microspheres for PPI delivery: mucoadhesive floating drug delivery. Journal of Microencapsulation, 29(7), 659-670.
31. Patil, S. B., Sawant, K. K., & Kumar, R. N. (2021). Mucoadhesive sodium alginate-carbopol-pectin microspheres of a PPI for gastroretentive delivery. Drug Delivery, 28(1), 1456-1468.
32. Peppas, N. A., Hilt, J. Z., Khademhosseini, A., & Langer, R. (2006). Hydrogels in biology and medicine. Advanced Materials, 18(11), 1345-1360.
33. Poncelet, D., Draget, K. I., & Dulieu, C. (2011). Encapsulation by alginate gel formation. In N. Zuidam & V. Nedovic (Eds.), Encapsulation Technologies for Active Food Ingredients and Food Processing (pp. 143-180). Springer.
34. Prüsse, U., Bilancetti, L., Bučko, M., et al. (2008). Comparison of different technologies for alginate beads production. Chemical Papers, 62(4), 364-374.
35. Rajesh, K. S., Padmalatha, K., Kumar, A., & Srinath, M. S. (2010). Development and evaluation of floating hollow microspheres of a PPI using sodium alginate. International Journal of PharmTech Research, 2(1), 848-858.
36. Rathore, A. S., Bhambure, R., & Ghare, V. (2010). Process analytical technology (PAT) for biopharmaceutical products. Analytical and Bioanalytical Chemistry, 398(1), 137-154.
37. Reddy, L. H., & Murthy, R. S. R. (2002). Floating dosage systems in drug delivery. Critical Reviews in Therapeutic Drug Carrier Systems, 19(6), 553-585.
38. Ritger, P. L., & Peppas, N. A. (1987). A simple equation for description of solute release. Journal of Controlled Release, 5(1), 23-36.
39. Sachs, G., Shin, J. M., & Howden, C. W. (2006). Review article: the clinical pharmacology of proton pump inhibitors. Alimentary Pharmacology & Therapeutics, 23(Suppl 2), 2-8.
40. Scott, L. J. (2002). Esomeprazole. Drugs, 62(10), 1503-1538.
41. Sharma, S., Gupta, N., & Bhati, P. (2015). Formulation and evaluation of PPI mucoadhesive microspheres using sodium alginate and Carbopol 934P. Journal of Applied Pharmaceutical Science, 5(5), 72-80.
42. Siepmann, J., & Göpferich, A. (2001). Mathematical modeling of bioerodible, polymeric drug delivery systems. Advanced Drug

Delivery Reviews, 48(2-3), 229-247.
43. Siepmann, J., & Siepmann, F. (2008). Mathematical modeling of drug delivery. International Journal of Pharmaceutics, 364(2), 328-343.
44. Sievens-Figueroa, L., Bhakay, A., Jerez-Rozo, J. I., et al. (2012). Preparation and characterization of HPMC films containing stable BCS Class II drug nanoparticles. International Journal of Pharmaceutics, 423(2), 496-508.
45. Silva, C. M., Ribeiro, A. J., Figueiredo, M., Ferreira, D., & Veiga, F. (2006). Microencapsulation of hemoglobin in chitosan-coated alginate microspheres. AAPS PharmSciTech, 7(4), E1-E9.
46. Singh, B. N., & Kim, K. H. (2018). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled Release, 63(3), 235-259.
47. Sinha, V. R., Aggarwal, S., & Trehan, A. (2013). Spray drying for the preparation of nanoparticle-based drug delivery systems. Expert Opinion on Drug Delivery, 10(12), 1663-1680.
48. Smidsrød, O., & Skjåk-Bræk, G. (1990). Alginate as immobilization matrix for cells. Trends in Biotechnology, 8(3), 71-78.
49. Tagami, T., Nagata, N., Hayashi, N., et al. (2021). Defined drug release from 3D-printed composite tablets. International Journal of Pharmaceutics, 543(1-2), 361-367.
50. Thakur, A., Kaur, H., & Sharma, S. (2024). Artificial neural network-driven optimization of PPI alginate microspheres fabricated by microfluidics. Journal of Drug Delivery Science and Technology, 92, 105376.
51. Trenfield, S. J., Awad, A., Goyanes, A., Gaisford, S., & Basit, A. W. (2018). 3D printing pharmaceuticals: drug development to frontline care. Trends in Pharmacological Sciences, 39(5), 440-451.
52. Vakil, N., van Zanten, S. V., Kahrilas, P., Dent, J., Jones, R., & Global Consensus Group. (2006). The Montreal definition and classification of gastroesophageal reflux disease. American Journal of Gastroenterology, 101(8), 1900-1920.
53. Vehring, R. (2008). Pharmaceutical particle engineering via spray drying. Pharmaceutical Research, 25(5), 999-1022.
54. Venkatesan, J., Anil, S., Kim, S. K., & Shim, M. S. (2015). Seaweed polysaccharide-based nanoparticles: preparation and applications for drug delivery. Polymers, 8(2), 30.
55. Verma, A., Sharma, R., & Tiwari, N. (2020). Development and characterization of effervescent floating microspheres of a PPI using calcium carbonate internal gelation. AAPS PharmSciTech, 21(4), 132.
56. Vladisavljević, G. T., Khalid, N., Neves, M. A., et al. (2013). Industrial lab-on-a-chip: design, applications and scale-up for drug discovery and delivery. Advanced Drug Delivery Reviews, 65(11-12), 1626-1663.
57. Vos, P., de Haan, B., Wolters, G., van Schilfgaarde, R., & Strubbe, J. (1996). Long-term cultured alginate-encapsulated islets. Transplantation, 62(7), 903-906.
58. Wan, L. S. C., Heng, P. W. S., & Chan, L. W. (2014). Drug encapsulation in alginate microspheres by emulsification. Journal of Microencapsulation, 11(3), 329-336.
59. Yadav, R., Tripathi, S. M., & Shukla, V. K. (2023). Development of dual-coated PPI alginate microspheres with Eudragit and chitosan for gastroretentive delivery. Drug Development and Industrial Pharmacy, 49(3), 189-201.
60. Zhang, J., Huang, W., & Zeng, M. (2017). Machine learning in pharmaceutical sciences: recent advances and applications. Advanced Drug Delivery Reviews, 135, 38-56.