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Review Article

Development and Evaluation of *Ganoderma lucidum* Polysaccharide-Based Floating Gastroretentive Tablets: A Comprehensive Review

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ABSTRACT

Ganoderma lucidum (Leyss. ex Fr.) Karst. is a highly valued medicinal mushroom in traditional Asian medicine, recognized for its vast reservoir of bioactive compounds—most notably its polysaccharides (GLPs). GLPs are naturally occurring high-molecular-weight β-D-glucan-rich biopolymers with well-documented immunomodulatory, antitumor, antioxidant, anti-inflammatory, antidiabetic, and hepatoprotective pharmacological properties. Despite this formidable therapeutic profile, conventional oral dosage forms of GLPs are constrained by inadequate gastric residence time and inconsistent site-specific absorption, leading to suboptimal bioavailability and unpredictable clinical outcomes. Floating gastroretentive drug delivery systems (FGRDDS) represent an innovative and scientifically validated strategy to overcome these limitations by maintaining the dosage form buoyant on gastric contents for an extended period, enabling controlled and sustained drug release in the stomach and proximal gastrointestinal tract. The present review comprehensively examines the botanical and phytochemical characteristics of G. lucidum, the structural determinants and pharmacological spectrum of GLPs, and the physicochemical and physiological rationale for employing floating gastroretentive tablet technology. Formulation considerations—encompassing polymer selection (HPMC, carbopol, sodium alginate), gas-generating effervescent systems (sodium bicarbonate, citric acid), and manufacturing approaches (direct compression, wet granulation, hot melt extrusion)—are discussed systematically. Comprehensive evaluation methodologies including pre- and post-compression characterization, floating lag time, total floating duration, swelling index, in vitro drug release kinetics modeling, ex vivo mucoadhesion, in vivo pharmacokinetics, and ICH-compliant stability testing are reviewed. The integral roles of Quality by Design (QbD) methodology, regulatory compliance for botanical drug

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products, and current translational challenges are addressed. Emerging future directions including three-dimensional printing, nanoparticle-embedded floating matrices, combination therapy platforms, and artificial intelligence-assisted formulation optimization are highlighted. This review serves as a comprehensive scientific reference to guide researchers toward the development of quality-assured, clinically translatable GLP-based floating gastroretentive tablet formulations.

INTRODUCTION

Ganoderma lucidum *(Leyss. ex Fr.) Karst.* belonging to the family Ganodermataceae, order Polyporales, subdivision Basidiomycotina, is a saprophytic and occasionally parasitic basidiomycete fungus that has occupied a pre-eminent position in traditional Chinese, Japanese, and Korean medicine for over two millennia. Commonly referred to as Lingzhi (China), Reishi (Japan), Yeongji (Korea), or the 'Mushroom of Immortality,' *G. lucidum* has been venerated as a symbol of longevity, vitality, and spiritual harmony, with clinical applications encompassing immunity enhancement, tumor suppression, cardiovascular protection, anti-aging, and hepatic disorders. Its recognition has expanded from traditional pharmacopoeia into mainstream pharmaceutical and nutraceutical sciences, propelled by modern biochemical investigations that have validated many of its traditional therapeutic claims at the molecular and cellular levels.[1,2]

The fungus is morphologically distinguished by its kidney- or fan-shaped pileus with a distinctive glossy, lacquered reddish-brown to purplish-brown surface, a lateral or eccentric woody stipe, and white to pale-yellow lower pore surface. *G. lucidum* is widely distributed across tropical, subtropical, and temperate zones of Asia, Europe, North America, and Africa, typically growing on decaying hardwood stumps. Modern cultivation techniques employing oak logs, sawdust substrates, and liquid fermentation have enabled large-scale commercial production to meet pharmaceutical and nutraceutical demands.[3]

The chemical architecture of *G. lucidum* is remarkable in its diversity. More than 400 bioactive compounds have been isolated and characterized, organized into primary classes: polysaccharides (notably β-D-glucans and glycoproteins), triterpenic acids (ganoderic acids A–Z, lucidenic acids), steroids (ergosterol, ergosterol peroxide), proteins and lectins (LZ-8), nucleosides (adenosine), fatty acids, and trace elements including germanium and selenium. The relative abundance of each bioactive class is profoundly influenced by fungal strain genotype, cultivation substrate (wood species, agricultural waste), developmental stage at harvest, geographic and environmental conditions, and post-harvest processing methodology (drying temperature, extraction solvent).[4,5]

Among all bioactive constituents, Ganoderma lucidum polysaccharides (GLPs) have attracted the most intense scientific scrutiny and represent the primary therapeutic entity. GLPs are naturally occurring biopolymers of considerable structural complexity, predominantly comprising β-D-glucan backbones with characteristic β-(1→3) main chain glycosidic linkages and β-(1→6) branch points, though heteroglycans incorporating galactose, mannose, xylose, arabinose, and fucose residues are also well-documented. Molecular weights of GLPs range from approximately 4×10^3 to 1×10^6 Da depending on source and extraction conditions. Their tertiary triple-helix conformation, stabilized by inter-strand hydrogen bonds analogous to that of Schizophyllan and lentinan, is considered a critical structural prerequisite for immunostimulatory activity via interaction with Dectin-1 and other pattern recognition receptors on immune cells.[6,7]

The pharmacological activities of GLPs are extensive and well-validated in preclinical and, to a growing degree, clinical settings. Immunomodulation, antitumor activity, antioxidant and free radical scavenging, anti-inflammatory effects, hypoglycemic activity, hepatoprotection, and prebiotic modulation of gut microbiota constitute the principal biological activities.[8,9,10] Particularly noteworthy for pharmaceutical formulation purposes are GLP's documented gastroprotective activity—including protection against ethanol- and NSAID-induced gastric mucosal injury—and its inhibitory effects against *Helicobacter pylori,* the principal etiological agent of peptic ulcers and a WHO Group I carcinogen for gastric cancer. These gastric-targeted activities provide compelling scientific rationale for local delivery of GLPs via a gastroretentive platform.[11]

Notwithstanding its impressive therapeutic profile, the pharmaceutical development of GLP-based oral formulations faces a fundamental challenge: inadequate gastric residence time. Under normal fasting conditions, the stomach empties dosage forms primarily during Phase III of the interdigestive migrating motor complex (IMMC)—the 'housekeeper wave'—resulting in highly variable gastric residence times of 1–4 hours for solid dosage forms. This abbreviated gastric contact period is insufficient for site-specific delivery of GLPs to gastric mucosa and limits the extent of absorption in the proximal small intestine. Conventional oral tablets and capsules, despite ease of administration, cannot overcome this physiological limitation.[12,13]

Floating gastroretentive drug delivery systems (FGRDDS) represent the most extensively studied approach to extend intragastric dosage form residence. By maintaining bulk density below that of gastric fluid (~1.004 g/mL), floating systems remain buoyant on gastric contents for 8–24 hours, releasing drug in a controlled and sustained manner at the preferred absorption site. The technology has been applied successfully to numerous drugs including metformin, ranitidine, furosemide, amoxicillin, ciprofloxacin, and several herbal extracts. Recent advances in polymer science, effervescent technology, process optimization, and quality-by-design methodology have substantially advanced the reliability and reproducibility of FGRDDS.[14,15]

The present review aims to provide a thorough, systematic, and integrated analysis of the development and evaluation of GLP-based floating gastroretentive tablets for publication in a pharmaceutical sciences journal. It encompasses GLP phytochemistry and pharmacology, FGRDDS principles and classification, formulation design and QbD optimization strategies, comprehensive evaluation methodologies, regulatory pathways for botanical drug products, current translational challenges, and future technological perspectives. The review is intended to serve as an authoritative and comprehensive scientific reference that will facilitate the rational development of clinically meaningful GLP-based gastroretentive formulations.

MATERIALS AND METHODS

Literature Search Strategy and Study Selection

A comprehensive and systematic literature search was conducted across major peer-reviewed scientific databases including PubMed/ MEDLINE, ScienceDirect, Scopus, Web of Science, Google Scholar, and the Cochrane Library. The search was conducted up to March 2025 using Boolean operators (AND, OR, NOT) combining the following Medical Subject Headings (MeSH) and free-text keywords:

'Ganoderma lucidum,' 'Lingzhi,' 'Reishi,' 'Ganoderma lucidum polysaccharides,' 'GLP,' 'beta-glucan,' 'floating drug delivery system,' 'gastroretentive drug delivery,' 'floating tablets,' 'HPMC matrix tablets,' 'effervescent floating tablets,' 'controlled drug release,' 'bioavailability enhancement,' 'gastric retention,' 'hydrophilic matrix,' 'sodium bicarbonate effervescent system,' 'pharmacokinetics of polysaccharides,' and 'natural polymer-based drug delivery.'

Inclusion criteria for article selection were: (i) peer-reviewed original research articles, systematic reviews, and comprehensive review articles published in English; (ii) studies addressing GL phytochemistry, GLP structure-activity relationships, GLP pharmacological activities, FGRDDS formulation principles and methods, polymer science relevant to matrix tablets, evaluation methodologies for gastroretentive systems, QbD approaches in tablet formulation, and regulatory considerations for botanical drugs; (iii) publications within the period 2000–2025, with preferential weighting given to studies published in the last decade (2015–2025); and (iv) studies with clearly stated, reproducible methodology. Exclusion criteria included: non-English language publications without adequate English abstracts, conference abstracts without accompanying full-text manuscripts, duplicate reports, and studies with irreconcilable methodological deficiencies.

An initial search yielded over 250 records. After title and abstract screening, 160 full-text articles were assessed for eligibility. Following application of inclusion and exclusion criteria and reference list cross-checking of key included articles, 40 references were selected as most pertinent and are cited in this review. The selection process ensured broad thematic coverage across all major aspects of GLP phytochemistry, gastroretentive technology, formulation science, and evaluation methodology.

RESULTS AND DISCUSSION

1. Botanical Profile and Phytochemistry of Ganoderma lucidum

1.1 Taxonomy and Morphological Characteristics

G. lucidum belongs to the kingdom Fungi, phylum Basidiomycota, class Agaricomycetes, order Polyporales, family Ganodermataceae, and genus Ganoderma. The genus *Ganoderma* comprises over 250 recognized species globally, of which *G. lucidum* sensu lato is the most extensively studied for medicinal properties. The macroscopic structure comprises a fan-shaped to kidney-shaped pileus (cap) measuring 5–30 cm in diameter, with a highly distinctive glossy (lacquered) upper surface ranging from reddish-brown to purplish-black with concentric sulci and a paler margin. The lower surface (hymenophore) is white to cream-colored with fine circular pores (4–5 per mm). The stipe (stem) is lateral, cylindrical, and 5–20 cm long. The entire basidiocarp has a woody, corky texture due to dimitic hyphal system composition.[1,3]

Cultivation of *G. lucidum* is conducted commercially using wood log inoculation (traditional, 12–18 months), sawdust bag cultivation (3–6 months), and submerged liquid fermentation for mycelium production. Cultivation substrate profoundly influences chemical composition—fruiting bodies from hardwood substrates contain higher polysaccharide and triterpene concentrations, while liquid-fermented mycelium provides standardizable, large-scale GLP production. The fruiting body, at maturity, has the highest medicinal compound content.[5]

1.2 Chemical Composition of Ganoderma lucidum

Proximate analysis of the *G. lucidum* fruiting body reveals: carbohydrates (21.83–27.78%), dietary fiber (59–65%), crude proteins (7–8%), lipids (1.1–8.3%), and ash (0.72–1.77%). More than 400 distinct bioactive compounds have been isolated and characterized from various parts of the organism. The principal bioactive classes and their pharmacological significance are summarized in Table 1.[4,5]

Table 1: Major Bioactive Constituents of *Ganoderma lucidum* and Their Primary Pharmacological Activities

Constituent Class	Representative Compounds	Part of Fungus	Primary Pharmacological Activity
Polysaccharides (GLPs)	β-D-glucans (GLP-1, GLP-2), heteroglycans, glycoproteins, GL-PP	Fruiting body, spore, mycelium	Immunomodulation, antitumor, antioxidant, anti-inflammatory, antidiabetic, hepatoprotection
Triterpenes	Ganoderic acids A–Z, ganoderols A & B, lucidenic acids A–N	Fruiting body (lacquered surface)	Anti-inflammatory, hepatoprotective, anti-HIV, cytotoxic, cholesterol synthesis inhibition
Proteins / Lectins	LZ-8 immunomodulatory protein, laccases, proteases	Fruiting body, mycelium	Immunosuppression / stimulation, hemagglutination, free radical oxidation
Steroids	Ergosterol, ergosterol peroxide (5α,8α), β-sitosterol	Fruiting body	Anticancer, antiviral, drug resistance reversal
Nucleosides	Adenosine, uridine, guanosine, inosine	Fruiting body	Platelet aggregation inhibition, cardiovascular protection, vasodilation
Fatty Acids	Oleic (18:1), linoleic (18:2), stearic, palmitic acids	Spore oil	Anti-inflammatory, membrane modulation
Trace Elements	Selenium (Se), germanium (Ge), zinc (Zn), iron (Fe)	Fruiting body	Antioxidant cofactors, immune support, enzyme activation

1.3 Structure and Physicochemical Properties of GLPs

GLPs are structurally heterogeneous, and this diversity is a primary determinant of their biological activity. The most potent and widely studied GLPs are β-D-glucans with a linear (1→3)-linked β-D-glucopyranose backbone bearing single (1→6)-linked β-D-glucopyranose branches at varying frequencies. The degree of branching (DB), defined as the ratio of branching residues to total residues, typically ranges from 0.20 to 0.33 for immunologically active GLPs. The triple-helix tertiary conformation, observable by X-ray diffraction and circular dichroism spectroscopy and analogous to lentinan (from *Lentinus edodes*) and schizophyllan (from *Schizophyllum commune,*), is formed by three glucan chains wound around a common axis stabilized by extensive inter-chain hydrogen bonding. This ordered tertiary structure is required for Dectin-1 receptor binding and downstream NF-κB and MAPK pathway activation in innate immune cells.[6,7]

Molecular weight of GLP fractions varies widely (4×10^3 to $>1 \times 10^6$ Da) and is a critical activity determinant: intermediate MW fractions (5×10^4–5×10^5 Da) are generally most potent immunomodulators, while very high MW fractions exhibit increased viscosity but reduced cellular uptake. Monosaccharide composition

analysis by gas chromatography-mass spectrometry (GC-MS) post-hydrolysis reveals glucose as the predominant sugar (60–90% of total monosaccharides in homoglucans), with varying proportions of galactose, mannose, xylose, fucose, arabinose, and rhamnose in heteroglycans.[4,7]

Key physicochemical properties relevant to pharmaceutical formulation include: (a) high water retention capacity and ability to form viscous gels upon hydration, which can synergize with HPMC in matrix tablet formation; (b) susceptibility to acid-catalyzed hydrolysis at gastric pH (1.2–2.0), requiring protective formulation strategies for long gastric exposure; (c) sensitivity to oxidative degradation requiring antioxidant protection or inert atmosphere packaging; and (d) variable solubility—water-soluble GLP fractions (wGLP) constitute 20–40% of total polysaccharide content, with the remainder being water-insoluble or alkali-soluble fractions.[4,6]

1.4 Pharmacological Activities of GLPs: Evidence from Preclinical and Clinical Studies

Immunomodulatory Activity: GLPs stimulate innate and adaptive immune responses through multiple mechanisms. They activate macrophages (increased phagocytic activity, superoxide production, nitric oxide release, cytokine secretion: TNF-α, IL-1β, IL-6, IL-12), promote dendritic cell maturation and antigen presentation (MHC-II upregulation), enhance NK cell cytotoxicity (upregulation of NKG2D receptor and its ligands MICA/MICB), and modulate T helper cell balance (Th1/Th17 promotion, Treg suppression). These effects are mediated through binding of β-glucan structures to Dectin-1, TLR-2, TLR-4, and CR3 receptors. Clinical evidence from randomized controlled trials demonstrates that Ganopoly (a standardized GLP extract) significantly improved immune function (NK cell activity, T-lymphocyte counts) in advanced cancer patients receiving chemotherapy.[8,9,16]

Antitumor Activity: GLPs demonstrate direct and immunologically mediated antitumor activities documented against gastric, hepatocellular, colorectal, lung, breast, and cervical cancers. Direct mechanisms include: mitochondria-dependent apoptosis (Bcl-2 downregulation, cytochrome c release, caspase-3/9 activation), G0/G1 cell cycle arrest, anti-proliferative effects (PCNA and Ki-67 reduction), and antiangiogenic activity (VEGF and CD31 suppression). A Cochrane systematic review of 5 randomized controlled trials (n = 373 cancer patients) concluded that *G. lucidum* supplementation alongside standard oncological therapy significantly improved the one-year survival rate and tumor response rate compared with standard therapy alone.[17]

Antioxidant Activity: GLPs scavenge hydroxyl radicals (·OH), superoxide anion radicals ($O^{2\cdot-}$), DPPH radicals, and ABTS radicals in a concentration-dependent manner. In vivo, they upregulate superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities while reducing malondialdehyde (MDA) levels as markers of oxidative stress.[10] Anti-Inflammatory Effects: GLPs inhibit the NF-κB signaling cascade, reduce phosphorylation of IκBα, suppress COX-2 and iNOS expression, reduce prostaglandin E2 and leukotriene production, and attenuate NLRP3 inflammasome activation—collectively reducing systemic and local inflammation.[18]

Gastroprotective and *H. pylori* Inhibitory Activity: This activity provides direct pharmacological rationale for the gastric delivery approach. Ganoderan suppresses ROS-mediated oxidative damage to gastric mucosal cells, reduces inflammatory cytokine expression in gastric

cancer cell lines, and augments mucosal defense mechanisms by increasing gastric mucin secretion and upregulating prostaglandin synthesis. *G. lucidum* extracts inhibit *H. pylori* urease activity and adhesion to gastric epithelium. These gastroprotective effects are maximally manifested when drug contact with gastric mucosa is prolonged—precisely what FGRDDS achieves.[11]

Antidiabetic Activity: GLPs lower blood glucose through insulin secretagogue effects on pancreatic β-cells, enhancement of peripheral insulin sensitivity (GLUT4 upregulation), and inhibition of α-glucosidase and α-amylase enzymes. GLP-mediated modulation of gut microbiota—increasing Bifidobacterium and Lactobacillus, reducing Bacteroides and Firmicutes/Bacteroidetes ratio—contributes to improved glycemic control and reduced intestinal permeability. Hepatoprotective Activity: GLPs reduce hepatic lipid peroxidation, lower serum AST/ALT/ALP levels, attenuate hepatic fibrosis (via TGF-β1 suppression and hepatic stellate cell inhibition), and protect hepatocytes against CCl4- and D-galactosamine-induced injury in rodent models.[19,20]

2. Floating Gastroretentive Drug Delivery Systems: Principles and Physiological Rationale

2.1 Physiological Basis for Gastric Retention

The oral route is the most preferred for systemic drug delivery due to patient convenience, non-invasiveness, self-administration capability, and cost-effectiveness. However, the gastrointestinal tract imposes significant barriers to reliable drug delivery through complex and variable motility patterns. The interdigestive migrating motor complex (IMMC) governs GI motility in the fasted state and cycles approximately every 90–120 minutes through four phases: Phase I (quiescence, 45–60 min), Phase II (irregular contractions, 30–45 min), Phase III (strong 'housekeeper' peristaltic waves, 5–15 min), and Phase IV (transition). Solid non-disintegrating dosage forms are emptied from the stomach primarily during Phase III, resulting in highly variable gastric residence times of 1–4 hours in the fasted state and 4–8 hours in the fed state.[12,13]

Several drug categories particularly benefit from prolonged gastric retention: (a) drugs with narrow absorption windows in the proximal GI tract (riboflavin, levodopa, captopril); (b) drugs poorly soluble at intestinal pH but soluble at gastric pH; (c) drugs acting locally in the stomach (antacids, anti-*H. pylori* agents, gastroprotective agents, gastric antineoplastics); (d) drugs extensively metabolized by first-pass metabolism with gastric absorption bypassing portal circulation; and (e) drugs requiring sustained plasma levels for chronic therapy. GLPs qualify for categories (c), (d), and (e), making FGRDDS a physiologically rational delivery platform.[12,14]

2.2 Classification and Mechanisms of Gastroretentive Systems

Table 2: Classification of Gastroretentive Drug Delivery Systems with Comparative Features

System Type	Retention Mechanism	Key Excipients	Floating Duration	Advantages	Limitations
Effervescent Floating	CO_2 gas entrapment in polymer matrix (density < 1.004 g/mL)	$NaHCO_3$, citric acid, HPMC	8–12 h	Rapid onset, well characterized, scalable	Acid-base incompatibility risk, CO_2 loss over time

Non-Effervescent Floating	Low-density polymers/ porous structure/ sublimation agents	HPMC, EC, volatile agents	8–24 h	No gas generation, stable	Slower FLT, complex manufacture
Bioadhesive / Mucoadhesive	Adhesion to gastric mucosa via hydrogen bonding and electrostatic interaction	Carbopol, HPMC, chitosan	Mucosa-dependent	Dual retention mechanism	Variable due to mucus turnover
Swelling / Expandable	Expansion > pyloric aperture (~12 mm)	PEO, cross-linked polymers, coiled springs	Until erosion / deformation	Very long retention possible	Risk of obstruction, patient acceptability
Magnetic	External magnet applied abdominally	Iron oxide particles	Duration of magnet application	Controllable retention	Impractical for ambulatory patients
High Density / Sinking	Lodging in gastric rugae folds	$BaSO_4$, ZnO dense particles (density > 2.5 g/mL)	Variable	Fasted state retention	Unreliable, position-dependent

Floating systems are the most extensively developed GRDDS due to their scientific tractability, ease of in vitro characterization, scalability, and substantial body of clinical evidence. Their mechanism—buoyancy based on reduced bulk density—operates independently of gastric pH (important for drugs with pH-sensitive solubility) and is compatible with fed and fasted state physiology. The effervescent floating mechanism is particularly amenable to tablet formulation, combining established direct compression or wet granulation manufacturing with well-understood polymer matrix technology.[14,15]

2.3 Factors Influencing Gastric Retention of Floating Systems

Physiological variables critically modulating in vivo gastric retention of floating tablets include: (a) Fed vs. fasted state—the fed state prolongs gastric residence significantly; GLP floating tablets should ideally be administered with or shortly after meals to maximize retention; (b) Posture—upright posture accelerates gastric emptying; recumbent posture prolongs retention; (c) Gender—females have slower gastric emptying than males; (d) Age—elderly subjects exhibit slower gastric emptying; (e) Disease state—gastroparesis, diabetes, Parkinson's disease, and hypothyroidism delay emptying, while hyperthyroidism accelerates it; (f) Caloric content and viscosity of co-ingested food—high-fat, high-calorie meals extend gastric residence substantially; and (g) Drug effects—anticholinergics, prokinetics, and opioids alter gastric motility.[13,15]

Formulation variables influencing floating performance include: polymer type and concentration (HPMC viscosity grade and quantity determining gel layer formation rate and strength), gas-generating agent concentration and particle size (determining CO_2 evolution rate and FLT), tablet size and geometry (larger tablets empty more slowly), and tablet density prior to hydration. Optimization of these interdependent variables through QbD-based experimental design is essential for robust FGRDDS performance.[15,22]

3. Formulation Development of GLP-Based Floating Gastroretentive Tablets

3.1 Rationale for GLP Formulation as Floating Tablets

The convergence of GLP pharmacology with FGRDDS technology is supported by multiple compelling rationales. First, GLP's documented gastroprotective and anti-*H. pylori* activities require sustained local contact with gastric mucosa to achieve therapeutically relevant drug concentrations at the target tissue. Second, high-molecular-weight polysaccharides are absorbed primarily in the upper GI tract through specialized transcytosis mechanisms, and extended residence in this region maximizes absorption opportunity. Third, GLP's intrinsic gel-forming and mucoadhesive properties (β-glucan chains interact with mucin via hydrogen bonding) provide supplementary gastric retention capacity that synergizes with the floating mechanism—creating a dual-retention system. Fourth, chronic administration for cancer prevention, immunotherapy support, or metabolic disease management demands patient-friendly, once- or twice-daily dosing regimens that FGRDDS enables. Fifth, the avoidance of premature release in the upper intestine preserves GLP integrity from alkaline pH-mediated conformational changes that may reduce immunostimulatory potency.[6,11,12]

3.2 Selection and Optimization of Polymers

Hydroxypropyl Methylcellulose (HPMC): HPMC is the most widely employed matrix-forming polymer for floating gastroretentive tablets, and its selection is underpinned by an extensive body of formulation science evidence. Upon contact with aqueous gastric fluid, HPMC undergoes rapid surface hydration forming a coherent viscous hydrogel layer (gel boundary) that simultaneously (a) controls drug diffusion through the matrix by increasing the path length for drug molecules; (b) swells progressively, contributing to reduced bulk density and enhanced buoyancy; (c) provides mechanical integrity preventing tablet disintegration during the floating period; and (d) governs the erosion rate of the outer gel layer, which determines overall matrix drug release.[15,22]

The selection of HPMC viscosity grade profoundly affects performance: HPMC K4M (nominal viscosity 4,000 cP at 2% aqueous solution) is suitable for 6–8 hour sustained release profiles; K15M (15,000 cP) achieves 10–14 hour profiles; K100M (100,000 cP) enables 16–24 hour profiles. Higher viscosity grades create denser, more erosion-resistant gel layers with slower drug diffusion. The optimal HPMC concentration in floating tablets typically ranges from 20 to 40% w/w; below 20% w/w the gel layer may be insufficient to prevent rapid drug release and maintain floating integrity, while above 40% w/w tablet hardness may compromise and friability increase.[22]

Carbopol 934P (cross-linked polyacrylic acid): At concentrations of 0.5–2% w/w, carbopol provides bioadhesive capacity through formation of hydrogen bonds and electrostatic interactions with gastric mucus glycoproteins. Combination of HPMC with carbopol (typically HPMC:carbopol 95:5 to 85:15 by weight) creates tablets with dual retention—floating via low density and mucoadhesion via polymer-mucin interaction. This combination consistently demonstrates superior in vivo gastric retention over HPMC alone in scintigraphic studies.[24] Sodium Alginate: An anionic linear polysaccharide composed of β-D-mannuronate and α-L-guluronate residues, sodium alginate forms robust gels in acidic gastric conditions through protonation of carboxylate groups (pKa ~3.5), making it inherently suitable for gastric matrix applications. Its natural

polysaccharide composition makes it chemically compatible with GLP and enables development of an entirely bio-derived floating matrix.[25]

Ethylcellulose (EC): A water-insoluble hydrophobic polymer incorporated at 5–20% w/w to (a) reduce the hydration rate of the matrix and slow drug release, (b) increase mechanical strength of the tablet, and (c) reduce friability. EC acts as a retardant layer interspersed with the HPMC gel network. Guar Gum and Xanthan Gum: These natural polysaccharide polymers have been explored as cost-effective, biodegradable, and GRAS-classified HPMC replacements or co-excipients. Their high molecular weight and strong gel-forming capacity are favorable for matrix tablet applications, though their performance consistency is less well-established than pharmaceutical-grade HPMC.[26]

Table 3: Polymers Employed in Floating Gastroretentive Tablet Formulations: Properties and Selection Criteria

Polymer	Type	Conc. Range (% w/w)	Primary Role	Viscosity / MW	Special Advantage
HPMC K4M	Hydrophilic semisynthetic	20–40	Gel formation, drug release control	4,000 cP (2%)	6–8 h sustained release; well characterized
HPMC K15M	Hydrophilic semisynthetic	20–40	Sustained release matrix	15,000 cP (2%)	10–14 h extended release profile
HPMC K100M	Hydrophilic semisynthetic	20–35	Ultra-sustained release matrix	100,000 cP (2%)	16–24 h; highest gel strength
Carbopol 934P	Cross-linked polyacrylic acid	0.5–2	Bioadhesion, viscosity enhancement	High MW	Dual floating + mucoadhesion; acidic pH active
Sodium Alginate	Natural anionic polysaccharide	5–20	Co-matrix, pH-gelling	Varied	Natural source; pH-dependent gelation
Ethylcellulose	Water-insoluble cellulosic	5–20	Release retardation	~100 cP (5% in EtOH)	Improves mechanical integrity
Xanthan Gum	Natural microbial polysaccharide	5–15	Matrix co-polymer	High (1% aq: ~1200 cP)	GRAS, eco-friendly, mucoadhesive
Guar Gum	Natural galactomannan	5–15	Matrix co-polymer, binder	High MW ($1–2 \times 10^6$ Da)	Inexpensive, biodegradable

3.3 Effervescent and Non-Effervescent Floating Systems

Effervescent System Design: The effervescent system is the most widely employed approach for GLP floating tablets due to its rapid FLT and well-characterized performance. Sodium bicarbonate ($NaHCO_3$, 5–20% w/w) reacts with citric acid (5–15% w/w) in gastric fluid according to: $3NaHCO_3 + C_6H_8O_7 \rightarrow Na_3C_6H_5O_7 + 3H_2O + 3CO_2$. The CO_2 generated becomes entrapped within the hydrated HPMC gel network, displacing water and reducing bulk density below 1.004 g/mL. The $NaHCO_3$:citric acid molar ratio is critical: stoichiometric ratio (1:0.56 by weight) provides maximal CO_2 generation efficiency. Sub-stoichiometric acid results in residual $NaHCO_3$ raising tablet pH (potentially destabilizing GLP); excess acid reduces tablet pH and may accelerate polysaccharide hydrolysis.[14,15]

Non-Effervescent System Design: Non-effervescent approaches achieve buoyancy through inherent low-density polymer incorporation (polyethylene oxide, hypromellose foam, low-density polyethylene beads), porous structure generation via sublimation of volatile co-processed agents (menthol, ammonium carbonate, camphor, borneol), or hollow microsphere incorporation. The sublimation technique, recently validated for theophylline floating matrix tablets, employs sublimable agents mixed into the tablet mass prior to compression; upon storage or exposure to mild heat, the volatile agent sublimes creating a porous, low-density matrix without the potential acid-base incompatibility of effervescent systems. This approach may be particularly advantageous for GLP formulations where acid-base reactions could degrade sensitive polysaccharide chains.[21]

3.4 Manufacturing Methods and Process Optimization

Direct Compression (DC): DC is the preferred method for GLP floating tablet manufacture when the polysaccharide fraction exhibits adequate compressibility (Carr's Index < 25%) and flowability (angle of repose < 40°). The key process steps involve: (a) size reduction of GLP (micronization or controlled milling to target D50 of 50–150 µm); (b) geometric blending with HPMC, $NaHCO_3$, citric acid, MCC, and glidant in a double-cone or V-blender (15–20 minutes, 10–15 rpm); (c) addition of lubricant (magnesium stearate) and final blend (3–5 minutes); (d) compression on a single-punch or rotary tablet press at optimized compression force (5–15 kN). Critical process parameters for DC include blending time and speed (affecting content uniformity), compression force (affecting hardness, porosity, and floating performance), and punch geometry.[26,27]

Wet Granulation: Indicated when the GLP fraction exhibits poor flowability or compressibility. A binder solution (PVP K30, 2–5% w/w in 70:30 isopropanol:water to minimize moisture exposure) is added to the GLP-HPMC-filler mixture with thorough mixing in a planetary mixer or high-shear granulator. Granules are dried in a fluidized bed dryer (40°C inlet temperature, LOD endpoint ≤ 2%) and sieved (16/30 mesh). The dried granules are blended with effervescent agents, glidant, and lubricant, then compressed. Critical parameters include binder concentration and addition rate, granulation endpoint moisture, drying temperature (avoiding HPMC thermal gelation at > 50°C), and milling speed. The principal risk of wet granulation for GLP formulations is moisture-induced polysaccharide hydrolysis or gelation and partial effervescent agent neutralization.[26]

Hot Melt Extrusion (HME): An advanced, solvent-free continuous manufacturing technique applicable to thermostable GLP fractions (verified by thermogravimetric analysis). GLP and HPMC or HPMC-AS are co-extruded through a heated barrel (temperature 140–180°C depending on polymer Tg) and twin-screw at controlled screw speed. The resultant extrudate is milled to granules and compressed. HME creates molecularly homogeneous GLP-polymer solid dispersions with potentially improved dissolution rate and content uniformity. Its solvent-free nature eliminates moisture-induced polysaccharide degradation risk.[27]

3.5 Quality by Design (QbD) Approach to Formulation Optimization

ICH Q8(R2), Q9, and Q10 guidelines mandate QbD principles in modern pharmaceutical development. For GLP floating tablets, QbD implementation follows a structured workflow. The Quality Target Product Profile (QTPP) defines the ideal product: FLT ≤ 5 minutes, TFD ≥

10 hours, GLP release ≥ 80% at 12 hours, hardness 6–10 kg/cm², friability < 1%, content uniformity 98–102%, and shelf life ≥ 24 months.[28]

Risk assessment using Failure Mode Effects Analysis (FMEA) and Ishikawa (fishbone) diagrams identifies Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) that affect Critical Quality Attributes (CQAs). CMAs include HPMC viscosity grade and concentration, $NaHCO_3$ concentration and particle size, citric acid concentration, GLP particle size distribution and moisture content, and MCC grade. CPPs include compression force, blending time and speed, granulation moisture endpoint, and drying temperature.

Experimental designs such as Box-Behnken Design (BBD), Central Composite Design (CCD), or D-Optimal Design are applied to systematically explore the formulation space. For a three-factor BBD (HPMC concentration, $NaHCO_3$ concentration, citric acid concentration), 17 experimental runs including 3 center-point replicates map the quadratic response surfaces for CQAs. RSM-derived polynomial equations model CQA relationships with CMAs, identify critical inflection points, and define the design space—a multidimensional combination of CMAs and CPPs proven to assure quality. Overlay plots of desirability functions enable simultaneous multi-response optimization. Validation through 3–5 confirmation runs within the design space confirms model predictability.[28,29]

Table 4: Quality By Design Elements for GLP-Based Floating Gastroretentive Tablet Development

QbD Element	Component	Target / Specification
QTPP	Floating Lag Time (FLT)	≤ 5 minutes
QTPP	Total Floating Duration (TFD)	≥ 10 hours
QTPP	Drug Release at 12 h	≥ 80% (cumulative)
QTPP	Tablet Hardness	6–10 kg/cm²
QTPP	Friability	< 1% w/w
QTPP	Content Uniformity	98.0–102.0%
CQA	Swelling Index at 8 h	≥ 150% (indicative of adequate hydration)
CQA	Floating Force	Positive buoyancy throughout TFD
CMA	HPMC K15M Concentration	20–40% w/w (most critical)
CMA	$NaHCO_3$ Concentration	10–20% w/w
CMA	GLP Particle Size (D90)	< 250 µm
CPP	Compression Force	8–12 kN
CPP	Blending Time	15–20 min at 12 rpm
CPP	Granule LOD (wet gran.)	≤ 2.0%

4. Evaluation Parameters for GLP-Based Floating Gastroretentive Tablets

4.1 Pre-compression Powder Characterization

Comprehensive pre-compression characterization of the GLP-excipient blend is essential to predict tableting behavior and ensure content uniformity. Bulk density (BD) is determined by measuring the volume occupied by a known mass of powder poured gently into a graduated cylinder. Tapped density (TD) is measured after 100 taps from a standardized height (USP Tap Density Apparatus). Carr's Compressibility Index (CCI = [(TD−BD)/TD] × 100) provides a measure of inter-particulate interaction: CCI < 15% indicates excellent flow; 15–20%: good; 20–25%: fair (direct compression acceptable); > 25%: granulation recommended. Hausner's Ratio (HR =

TD/BD) < 1.25 indicates adequate flow for direct compression.[29,30]

Angle of repose (θ), measured by the fixed funnel method, quantifies powder flow dynamically: θ < 25° excellent; 25–35° good; 35–45° fair; > 45° poor flow. Particle size distribution, determined by sieve analysis or laser diffraction (Malvern Mastersizer), confirms GLP milling consistency and affects dissolution rate, content uniformity, and compressibility. Loss on drying (LOD) by infrared moisture analyzer or Karl Fischer titration must be ≤ 2% w/w to prevent premature polysaccharide gelation during storage and effervescent agent degradation. Drug (GLP) content in the blend is verified at multiple stratified sampling points to confirm homogeneity (RSD ≤ 2% is acceptable).[29]

4.2 Post-compression Physical Tablet Evaluation

Standard physical evaluation per USP/BP/IP specifications encompasses: (a) Weight Variation—20 tablets individually weighed on an analytical balance; acceptable per USP if ≤ 2 tablets deviate from mean by > 5% (for tablets > 324 mg) or > 7.5% (for tablets 130–324 mg); (b) Hardness—Monsanto or Erweka hardness tester; target 6–10 kg/cm² balancing mechanical integrity with porosity requirements for floating; excessive hardness (> 12 kg/cm²) may delay CO_2 diffusion and impair FLT; (c) Friability—Roche friabilator, 6.5 cm drum diameter, 100 revolutions at 25 rpm; acceptable < 1% weight loss; tablets pre-dusted and individually weighed before and after; (d) Thickness—digital Vernier calipers, mean ± SD of 10 tablets; (e) Drug content—validated phenol-sulfuric acid colorimetric method (λmax 490 nm) after acid hydrolysis of GLP to reducing sugars, referenced against standard glucose calibration curve; acceptable 98–102% of label claim; (f) Content Uniformity per USP <905>—10 individual tablets assayed; acceptable if all 10 values fall within 85–115% and RSD ≤ 6%.[29,31]

4.3 Floating Performance Evaluation

In vitro floating behavior is the most critical and discriminating test for FGRDDS quality. The standard test employs 900 mL of simulated gastric fluid (SGF, 0.1 N HCl, pH 1.2, prepared per USP) maintained at 37 ± 0.5°C in a USP Dissolution Apparatus II (paddle, 50 rpm). A single tablet is carefully placed on the surface without initial disturbance and observed continuously. Floating Lag Time (FLT) is precisely recorded as the elapsed time from tablet introduction to the moment it rises to the surface and remains continuously buoyant. Total Floating Duration (TFD) is recorded from FLT to the moment the tablet sinks, disintegrates, or ceases to maintain buoyancy.[14,22]

FLT < 5 minutes is the accepted clinically relevant threshold, as the gastric MMC Phase III 'housekeeper wave' occurs approximately every 90–120 minutes under fasting conditions and lasts 5–15 minutes. A tablet achieving FLT < 5 minutes will be floating before the next housekeeper wave and is unlikely to be swept into the small intestine. FLT is primarily governed by gas generation rate—higher $NaHCO_3$ and citric acid concentrations and smaller particle sizes generate CO_2 more rapidly, reducing FLT. TFD ≥ 10–12 hours ensures effective coverage of a full fed-state period (typically 6–8 hours) plus a safety margin. TFD is governed by the durability of the HPMC gel matrix—higher viscosity grades and concentrations maintain gel integrity longer, extending TFD.[15,22]

Buoyancy force measurement, using a Texture Analyzer or modified balance system, provides quantitative floating force data as a function of time. Positive floating force throughout the

intended floating duration is required. Some researchers employ the 'floating efficiency' metric—ratio of actual TFD to nominal 12-hour test period—expressed as percentage. For GLP tablets, floating efficiency ≥ 80% (TFD ≥ 9.6 hours in a 12-hour test) is a meaningful performance benchmark.[22]

4.4 Swelling Index and Water Uptake

Swelling behavior is mechanistically linked to both drug release and floating performance. Pre-weighed tablets (W_0) are placed in SGF (pH 1.2, 37°C) and removed at predetermined intervals (0.5, 1, 2, 4, 6, 8, 12 h). After careful surface blotting to remove adherent fluid, tablets are immediately reweighed (W_t). Swelling Index (SI%) = $[(W_t - W_0)/W_0] \times 100$. The SI–time profile characterizes three phases: (i) initial rapid hydration phase (0–2 h): HPMC surface hydration forms gel layer, CO_2 generation occurs; (ii) progressive swelling phase (2–8 h): gel layer expansion, matrix maintenance; (iii) erosion phase (> 8 h): outer gel layer erodes, releasing inner matrix material. An optimized formulation shows progressive SI increase to 200–350% at 8 hours, indicative of robust gel layer formation and sustained matrix integrity.[26,29]

4.5 In Vitro Drug Release Studies and Kinetics Modeling

In vitro dissolution testing is conducted in USP Apparatus II (paddle, 50–75 rpm) in 900 mL SGF (0.1 N HCl, pH 1.2, 37 ± 0.5°C). Six replicates per formulation are required for statistical validity. Sample aliquots (5–10 mL) are withdrawn at intervals (0.5, 1, 2, 4, 6, 8, 10, 12 h) with immediate replacement of equal volume of fresh dissolution medium to maintain sink conditions (drug concentration < 10% of saturation solubility throughout). GLP concentration in each aliquot is quantified by the phenol-sulfuric acid colorimetric assay (5% phenol solution + concentrated H_2SO_4, λmax 490 nm), validated per ICH Q2(R1) for linearity ($r^2 > 0.999$), precision (RSD < 2%), accuracy (recovery 98–102%), LOQ, and LOD.[30,31]

Cumulative GLP release (%) is plotted against time for each formulation. An ideal release profile for the GLP floating tablet demonstrates: release < 20% at 1 hour (indicating absence of burst release), release of 50 ± 10% at 6 hours (indicating sustained first-half release), and cumulative release ≥ 80% at 12 hours (indicating completeness). Comparison of profiles between formulations uses the f_1 (difference factor) and f_2 (similarity factor) metrics per FDA guidance: $f_2 \geq 50$ indicates equivalent profiles.

Release kinetics are characterized by non-linear least-squares fitting to mathematical models. The most commonly applicable models for HPMC-based floating matrix tablets are summarized in Table 5.

Table 5: Mathematical Models for In Vitro Drug Release Kinetics of GLP Floating Matrix Tablets

Model	Equation	Parameters	n or Exponent Value	Mechanistic Interpretation	Typical Fit for GLP HPMC Matrix
Zero Order	$Q_t = Q_0 + K_0 t$	K_0 = zero-order rate constant	—	Constant release rate independent of concentration; ideal controlled release	Possible with very high HPMC K100M concentration
First Order	$\ln(1 - Q_t/Q_\infty) = -K_1 t$	K_1 = first-order rate constant	—	Release rate proportional to remaining drug;	Less common for polymer matrix systems

				typical for soluble drugs	
Higuchi	$Qt = KH \cdot \sqrt{t}$	KH = Higuchi diffusion constant	—	Diffusion-controlled release from a matrix; Fick's first law applies	Applies for lower HPMC grades; early-phase kinetics
Korsmeyer-Peppas	$Mt/M\infty = K \cdot t^n$	K = rate constant; n = diffusion exponent	n < 0.45: Fickian; 0.45–0.89: anomalous; n = 0.89: Case II; n > 0.89: Super Case II	Power law capturing combined diffusion and swelling/erosion mechanisms	Best fit for most GLP HPMC floating matrices; n = 0.5–0.85 typical
Hixson-Crowell	$W_0^{(1/3)} - Wt^{(1/3)} = KHC \cdot t$	KHC = dissolution rate constant	—	Surface area and diameter change with time during dissolution	Applicable for eroding matrix tablets
Baker-Lonsdale	$3/2[1 - (1 - Mt/M\infty)^{(2/3)}] - Mt/M\infty = Kt$	K = rate constant	—	Drug diffusion from spherical matrix; microsphere adaptation	Applicable to matrix granules before compression

For the majority of HPMC-based GLP floating matrix formulations, the Korsmeyer-Peppas power law model with anomalous (non-Fickian) diffusion exponent n in the range 0.5–0.89 provides the best fit (highest $R^2 > 0.98$, lowest AIC). This reflects the superimposed contribution of Fickian diffusion through the hydrated gel layer and polymer chain relaxation/matrix erosion at the gel-fluid interface—the hallmark release mechanism of HPMC matrix tablets. Higher HPMC viscosity grades and concentrations shift n toward 0.89 (Case II transport, approaching zero-order), while lower concentrations yield n closer to 0.45 (Fickian diffusion dominant). Hixson-Crowell model may provide secondary fit for erosion-dominated formulations.[22,32]

4.6 Mucoadhesion Studies

For formulations incorporating carbopol or chitosan, ex vivo mucoadhesive strength is quantified using the wash-off method or texture analyzer. In the wash-off method, a pre-hydrated tablet is attached to excised goat gastric mucosa (mounted on a glass slide) using a small adhesive pressure, then placed in a tilted (45°) USP dissolution apparatus with SGF flowing at 50 rpm; percentage tablets remaining adherent at 2-hour intervals is recorded over 8 hours. Tensile strength measurement employs a TA-XT2 Texture Analyzer with a 5-mm cylindrical probe; after 2-minute contact with wetted mucosal tissue (2 N contact force), the maximum detachment force (N) is the mucoadhesive strength. GLP-carbopol (1:0.05 w/w) combinations in early formulation studies demonstrate mucoadhesive force of 0.8–1.6 N, significantly exceeding HPMC-only tablets (0.2–0.4 N), confirming the benefit of dual-retention strategies.[24]

4.7 In Vivo Pharmacokinetic Evaluation

In vivo pharmacokinetic evaluation in appropriate animal models (Sprague-Dawley rats, New Zealand albino rabbits) is conducted following single oral dose administration of the optimized GLP floating tablet formulation vs. an equivalent dose of GLP conventional tablet or aqueous

suspension as the reference standard. Blood samples are collected at predetermined intervals (0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24 h) via retro-orbital or jugular cannula (rats) or marginal ear vein (rabbits). GLP plasma concentrations are quantified using validated ELISA (β-glucan-specific antibody) or HPLC-UV methods post-protein precipitation.[33]

Key pharmacokinetic parameters derived by non-compartmental analysis (NCA) include: AUC0-t and AUC0-∞ (area under the plasma concentration-time curve, reflective of total drug exposure and relative bioavailability), Cmax (peak plasma concentration), Tmax (time to peak concentration), t1/2 (elimination half-life), MRT (mean residence time), and relative bioavailability (Frel = AUCFGRDDS/AUCreference × 100%). A successful GLP FGRDDS demonstrates significantly higher AUC (improved bioavailability, target ≥ 150% of conventional tablet), lower Cmax (reduced peak-dose side effects), delayed Tmax (consistent with controlled release), and extended MRT (reflecting prolonged absorption from gastric mucosa).[33]

Gamma Scintigraphy: The gold standard for in vivo intragastric retention confirmation in human volunteers is gamma scintigraphy. Tablets are radiolabeled with ^{99m}Tc (technetium-99m, t1/2 = 6 h, γ energy 140 keV) by incorporation into the tablet core as ^{99m}Tc-DTPA. Sequential anterior and posterior gamma camera images are acquired at 0, 1, 2, 4, 6, 8, 12 h post-dose. Center of mass position tracking and region of interest (ROI) analysis confirm intragastric retention and document the timing of gastric emptying. Optimized HPMC-based floating tablets typically demonstrate gastric retention ≥ 5 hours in fasted volunteers and ≥ 8 hours in fed state—confirming that the floating mechanism translates effectively from in vitro to in vivo.[34]

4.8 Stability Testing

Stability studies follow ICH Q1A(R2) guidelines for Zone IVb (hot and humid climates: 30 ± 2°C/75 ± 5% RH as long-term; 40 ± 2°C/75 ± 5% RH as accelerated), most appropriate for the Indian subcontinent. Parameters evaluated at 0, 1, 3, and 6 months (accelerated) and 0, 3, 6, 9, 12, and 24 months (long-term) include: GLP content (colorimetric/HPLC, acceptable ≥ 95% of initial), FLT and TFD (acceptable if within ± 2 min of initial FLT; TFD within ± 1 h), drug release profile at 6 and 12 h ($f_2 \geq 50$ vs. t=0 reference), tablet hardness and friability, appearance (color, surface texture), and moisture content (Karl Fischer, acceptable ≤ 3% w/w for packed tablets).[35]

GLP stability is particularly sensitive to: (a) moisture (accelerates polysaccharide hydrolysis and promotes effervescent agent premature neutralization—primary packaging must provide moisture barrier); (b) oxidative degradation (β-glucan backbone susceptible to •OH attack—use of antioxidants such as BHA 0.1% w/w or tocopherol, and nitrogen gas purging during manufacture and packaging); (c) thermal degradation (extended exposure to > 45°C degrades HPMC gel properties—storage at controlled room temperature). Nitrogen-flushed aluminium/aluminium (Al/Al) blister packaging is strongly recommended over HDPE bottles or PVC/Al blisters for GLP floating tablet packaging, with desiccant sachets in secondary packaging. Any decrease > 5% in GLP content, significant change in dissolution profile ($f_2 < 50$), or degradation in floating performance during stability testing constitutes a formulation failure requiring reformulation.[35]

5. Regulatory Considerations for GLP-Based Floating Tablets

The regulatory framework for GLP-based floating tablets varies by jurisdiction and depends on the intended therapeutic claim, dosage level, and manufacturing standards. In India, which is a relevant regulatory territory given the traditional use of *G. lucidum* in Ayurvedic and traditional medicine, GL-based formulations may be classified as: (a) Herbal/Ayurvedic products under the Drugs and Cosmetics Act (1940), Schedule E1 (prohibited in certain forms) and AYUSH Ministry guidelines, requiring compliance with Ayurvedic Pharmacopoeial standards; or (b) Modern pharmaceutical products (Schedule M/GMP) if specific therapeutic claims are made, requiring submission of a new drug application to the Central Drugs Standard Control Organisation (CDSCO). The classification determination hinges on the nature of the health claim and the concentration of active GLP fraction.[36]

In the United States, GLPs from *G. lucidum* may qualify for the botanical drug product pathway under the FDA Guidance for Industry: Botanical Drug Development (2016). This pathway requires comprehensive characterization of the botanical raw material (BRM) and botanical drug substance (BDS) using a combination of chromatographic fingerprinting (HPLC, TLC), monosaccharide composition analysis (GC-MS post-hydrolysis), molecular weight distribution (GPC-MALS), β-glucan content (enzymatic BG-assay), and biological activity markers (in vitro macrophage stimulation index). The innovative nature of the gastroretentive dosage form may trigger additional FDA guidance on modified-release solid oral dosage forms (FDA, 2014) and IVIVC guidances.[36,37]

Key regulatory documentation requirements for a GLP floating tablet New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) include: (i) Module 2: Quality Overall Summary (QOS); (ii) Module 3.2.S: Drug Substance characterization, specification, analytical methods, and validation (ICH Q2(R1)), manufacturing process, and stability data (ICH Q1A(R2)); (iii) Module 3.2.P: Drug Product formulation development (ICH Q8(R2)), specification, analytical methods, manufacturing process validation (ICH Q7), container-closure system, and stability; (iv) Module 5: Clinical pharmacology data including pharmacokinetic studies, bioavailability data, and IVIVC; (v) For QbD submissions: QTPP, CQA identification, risk assessment, design space definition, and control strategy documentation in Module 3.2.P.2.

6. Challenges and Future Perspectives

6.1 Current Challenges

GLP Standardization and Quality Control: The foremost challenge in GLP pharmaceutical development is the significant inter-batch variability in molecular weight distribution, monosaccharide composition, degree of branching, and biological activity arising from differences in fungal strain genotype, cultivation substrate, geographic origin, and extraction/purification methodology. This variability confounds dose-response relationships and makes reproducible formulation development difficult. Development of internationally harmonized reference standards, validated bioassay methods (standardized macrophage activation assay), and molecular fingerprinting techniques using multi-angle light scattering (MALS) and nuclear magnetic resonance (NMR) spectroscopy is urgently required.[4,7]

Polysaccharide Stability in Gastric Conditions: GLPs exposed to acidic gastric conditions (pH 1.2–2.0) for extended durations (8–24 h in FGRDDS) are susceptible to acid-catalyzed hydrolysis of glycosidic bonds, leading to

progressive molecular weight reduction and disruption of the triple-helix tertiary structure—both associated with reduced immunostimulatory potency. The magnitude of this degradation under actual intragastric conditions has not been thoroughly characterized, and appropriate protective formulation strategies (microencapsulation, coating, acid-resistant carrier systems) require systematic investigation. Clinical Evidence Deficit: Despite extensive preclinical pharmacology data, rigorously designed randomized controlled clinical trials demonstrating the pharmacokinetic and clinical superiority of GLP FGRDDS over conventional oral formulations in defined patient populations are absent. This evidence gap represents the critical bottleneck for regulatory approval and clinical adoption.[11,17]

Process Scalability: The complex interdependency of HPMC hydration kinetics, effervescent gas evolution, and GLP polysaccharide behavior during manufacturing at industrial scale (100,000+ tablets/batch) creates significant PAT (Process Analytical Technology) implementation challenges. NIR spectroscopy for real-time blend uniformity monitoring, Raman spectroscopy for crystalline/amorphous state tracking, and acoustic emission for granulation endpoint determination are emerging PAT tools applicable to GLP floating tablet manufacture but require validation for this specific application. Fed/Fasted State Variability: Floating tablet performance—FLT, TFD, and drug release—differs substantially between the fed state (viscous gastric contents, elevated gastric volume, prolonged residence) and the fasted state (aqueous gastric fluid, small volume, rapid MMC emptying). Formulations must demonstrate adequate performance under both conditions, which may require separate optimization or pharmacokinetic bridging studies.[37]

6.2 Future Perspectives

Three-Dimensional (3D) Printing Technology: Additive manufacturing modalities including fused deposition modeling (FDM), direct powder extrusion (DPE), stereolithography (SLA), and inkjet printing offer unprecedented ability to engineer precise tablet geometry, porosity architecture, and multi-compartment drug loading configurations unachievable by conventional compression. For GLP floating tablets, 3D printing enables design of tablets with precisely calibrated internal pore networks (optimizing both FLT and TFD independently), personalized drug loading based on patient body weight or pharmacogenomic profile, and complex multiphasic release architectures (immediate-release outer layer + sustained-release core). Recent studies on 3D-printed gastroretentive floating tablets of conventional drugs demonstrate FLT < 2 min and TFD > 12 h with excellent reproducibility, setting a benchmark for GLP applications.[38]

Nanoparticle-Embedded Floating Matrix Systems: The integration of GLP-loaded polymeric nanoparticles (PLGA, 200–500 nm) or lipid nanoparticles (solid lipid nanoparticles, nanostructured lipid carriers, 100–300 nm) into a conventional HPMC floating matrix represents a powerful 'nano-in-macro' strategy. Nanoencapsulation protects GLP from acid-catalyzed hydrolysis during gastric residence, improves uptake by gastric mucosal epithelial cells and M cells via endocytosis, enables controlled intracellular release, and potentially facilitates transcytosis for systemic absorption. Chitosan-coated GLP nanoparticles are particularly promising given chitosan's mucoadhesive properties, which provide additional gastric retention capacity.[39]

Combination Gastroretentive Formulations: Co-delivery of GLPs with synergistically acting

therapeutic agents in a single floating tablet platform amplifies therapeutic outcomes. Clinically relevant combinations include: (a) GLP + amoxicillin + proton pump inhibitor for locally acting triple therapy of *H. pylori,* eliminating the need for separate antibiotic floating tablets; (b) GLP + 5-fluorouracil adjuvant for gastric cancer chemoprevention (GLP's immunostimulatory activity may counteract 5-FU-induced immunosuppression); (c) GLP + metformin for type 2 diabetes management (GLP's antidiabetic activity is additive to biguanide therapy). Each combination requires careful investigation of drug compatibility, differential release requirements, and potential pharmacokinetic interactions.[11,20]

Artificial Intelligence (AI) and Machine Learning (ML) in Formulation Development: The multidimensional, non-linear formulation space of floating tablets—involving numerous interdependent CMAs, CPPs, and CQAs—is particularly amenable to ML-assisted optimization. Deep neural network (DNN), random forest, and Gaussian process regression models trained on historical formulation datasets can predict CQAs from CMAs/CPPs with high accuracy, reducing experimental burden by up to 70% compared with conventional RSM approaches. AI-assisted formulation tools such as Chemotion ELN integrated with ML prediction modules are increasingly available to pharmaceutical scientists and hold significant promise for accelerating GLP FGRDDS development from laboratory to clinic.[40]

Biopolymer-Based Floating Systems: The inherent physicochemical properties of GLPs—high molecular weight, gel-forming capacity, mucoadhesive potential, and biological activity—can be exploited to develop entirely biopolymer-based floating tablet matrices in which GLP itself functions as the primary matrix polymer. This approach would eliminate the need for HPMC and other synthetic/semisynthetic polymers, improve the biocompatibility and environmental sustainability of the formulation, and potentially create a self-reinforcing therapeutic platform where the matrix material contributes to the pharmacological action. Proof-of-concept for biopolymer-only floating matrices has been demonstrated with sodium alginate-guar gum blends and merits investigation with GLP fractions as matrix-forming excipients.[25,26]

CONCLUSION

Ganoderma lucidum polysaccharides (GLPs) are pharmacologically compelling natural biopolymers whose extensive array of immunomodulatory, antitumor, antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, and gastroprotective activities positions them as highly valuable candidates for pharmaceutical formulation. The fundamental limitation of conventional oral GLP delivery—inadequate and unpredictable gastric residence time—can be effectively addressed through floating gastroretentive drug delivery technology.

Floating gastroretentive tablets employing effervescent mechanisms (sodium bicarbonate/ citric acid) in combination with hydrophilic HPMC matrix systems provide a scientifically rigorous and technically scalable platform for GLP delivery with floating lag times achievable below 5 minutes, total floating durations extending to 12 hours or more, and sustained controlled-release profiles well-modeled by the Korsmeyer-Peppas power law with anomalous transport exponents. The formulation development process is optimally guided by QbD principles—from QTPP definition through CQA identification, risk assessment, experimental design-based optimization using BBD or CCD, and design space validation—to ensure robust, reproducible product quality.

Comprehensive evaluation through pre-compression characterization, physical tablet testing, in vitro floating behavior assessment, swelling index profiling, validated dissolution testing with kinetics modeling, ex vivo mucoadhesion studies, in vivo pharmacokinetic evaluation in animal models, gamma scintigraphy for intragastric retention confirmation, and ICH Q1A(R2)-compliant stability testing constitutes the full quality evidence package required for regulatory submission. Regulatory pathways for GLP-based botanical drug products require particular attention to GLP characterization and standardization, analytical method validation, and clinical bioavailability demonstration.

Current challenges—notably GLP standardization, polysaccharide gastric stability, clinical evidence generation, and manufacturing scale-up—represent tractable problems for the pharmaceutical community equipped with modern analytical, process analytical, and clinical research tools. Emerging technologies including 3D printing, nanoparticle-embedded floating matrices, AI-assisted formulation optimization, and biopolymer-only floating matrices promise to substantially advance the development landscape over the coming decade. The convergence of classical botanical medicine with modern pharmaceutical science and engineering in the development of GLP-based floating gastroretentive tablets represents a significant and exciting frontier, with genuine potential to deliver the full therapeutic value of this remarkable natural polysaccharide to patients in a quality-assured, reliable, and patient-friendly oral dosage form.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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