Buoyant by Design: Gastroretentive Floating Microspheres of Ginger

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***Abstract*—Ginger (Zingiber officinale Roscoe) is among the most heavily used and most thoroughly trialled botanicals in the world, with meta-analytic support for antiemetic activity and a well-documented gastroprotective pharmacology that includes inhibition of H^+,K^+-ATPase and of Helicobacter pylori. Its pungent principles — the gingerols and their dehydration products the shogaols — are nonetheless among the least bioavailable constituents in common therapeutic use. In healthy volunteers given up to 2.0 g of a standardised extract, no free gingerols or shogaol were detectable in plasma: the analytes circulate essentially entirely as glucuronide and sulfate conjugates, with elimination half-lives under two hours. In rats dosed with the pure compounds, oral bioavailability falls below 2%. Two conclusions follow. First, conventional immediate-release oral ginger preparations deliver a short, conjugated and highly variable systemic exposure. Second, and more interesting for formulation, much of ginger's most robust clinical and preclinical activity — antiemetic, antiulcer, anti-Helicobacter — is exerted at or near the gastric mucosa, where systemic exposure is not the relevant variable at all and residence time is. Gastroretentive delivery therefore addresses both problems simultaneously: it prolongs presentation to the upper gastrointestinal absorption window for the systemic indications, and it holds the extract at the site of action for the local ones. This review surveys the phytochemistry and standardisation of ginger extract, assembles the pharmacokinetic evidence that motivates gastroretention, compares the available gastroretentive strategies, and examines multiple-unit floating microspheres — hollow, low-density particles prepared by emulsion solvent evaporation or diffusion — as the architecture best matched to a standardised botanical extract. The formulation variables that govern buoyancy and release are set out, together with the Quality by Design logic needed to optimise them, and the gap that a standardised ginger floating microsphere would fill is identified.**

***Index Terms*—Zingiber officinale; floating microspheres; gastroretentive drug delivery; 6-gingerol; standardisation; Quality by Design; Box–Behnken design**

I. INTRODUCTION

Few botanicals have been studied as intensively as ginger, and fewer still have accumulated comparable clinical evidence. The rhizome of Zingiber officinale Roscoe is simultaneously a culinary staple, a traditional medicine across several systems, and the subject of a substantial body of randomised controlled trials and meta-analyses. Its pungent principles — the gingerols, and the shogaols formed from them by dehydration on drying and heating — are responsible for most of the documented pharmacology, which spans antiemetic, anti-inflammatory, antioxidant, antidiabetic and gastroprotective activity [1,2].

The clinical evidence is unusually concrete for a herbal medicine. A systematic review of meta-analyses found ginger supplementation associated with significant reductions in circulating C-reactive protein, high-sensitivity CRP and tumour necrosis factor-α, with doses of 1–3 g daily commonly used for anti-inflammatory, antioxidant and antidiabetic purposes and 500–1500 mg daily in divided doses for nausea and vomiting in pregnancy [3]. A meta-analysis of five randomised trials in 363 surgical patients found that a fixed dose of at least 1 g of ginger was more effective than placebo at preventing

postoperative nausea and vomiting, with summary relative risks of 0.69 and 0.61 for nausea-and-vomiting and vomiting respectively, and only abdominal discomfort reported as a side effect [4]. In a 576-patient multicentre trial, 0.5–1.0 g daily of ginger significantly reduced the severity of acute chemotherapy-induced nausea [5], and a meta-analysis of 508 subjects found approximately 1 g daily for at least four days associated with a five-fold likelihood of improvement in nausea and vomiting of early pregnancy [6].

Set against that, the pharmacokinetics are sobering. The pungent principles are poorly bioavailable, rapidly and almost completely conjugated, and short-lived in plasma. The gap between a well-evidenced therapeutic effect and a barely measurable systemic exposure is the central puzzle of ginger pharmacology, and it has a formulation answer.

That answer begins with an observation about where ginger acts. Its antiemetic effect is at least partly local, mediated through effects on gastrointestinal motility rather than through central receptors alone, and its gastroprotective activity — inhibition of the gastric proton pump and of Helicobacter pylori — is by definition exerted at the gastric mucosa [7]. For indications of this kind, what matters is not how much drug reaches the systemic circulation but how long an adequate concentration is maintained in the stomach. A dosage form that floats on gastric contents and resists emptying delivers exactly that, and simultaneously extends presentation to the upper small intestine for whatever systemic absorption does occur.

This review therefore examines gastroretentive delivery of standardised ginger extract, with particular attention to multiple-unit floating microspheres. It sets out the phytochemistry and standardisation requirements that distinguish a botanical extract from a single chemical entity, assembles the pharmacokinetic evidence, compares gastroretentive strategies, analyses the formulation variables that control buoyancy and release in microsphere systems, and identifies what remains to be done.

II. GINGER: CHEMISTRY, STANDARDISATION AND GASTRIC PHARMACOLOGY

2.1 The pungent principles

The pharmacologically important constituents of ginger are a homologous series of phenylalkylketones. The gingerols — principally 6-, 8- and 10-gingerol — are β-hydroxy ketones bearing a vanillyl head group and an alkyl side chain of varying length. They are thermally labile: on drying, heating or prolonged storage they undergo dehydration to the corresponding shogaols, which are the α,β-unsaturated analogues and are typically more pungent and, in several assays, more potent [1].

This interconversion is not a laboratory curiosity. It means that the composition of a ginger preparation depends on how the rhizome was processed, and that two extracts bearing the same botanical name can have materially different gingerol-to-shogaol ratios. Comparative work on 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol has shown that the homologues differ in antioxidant and anti-inflammatory potency [41], so the ratio is a pharmacological variable and not merely an analytical one. Interconversion also continues in vivo: a comprehensive rat study demonstrated bidirectional conversion between 6-gingerol and 6-shogaol after intravenous administration, with the clearance associated with conversion of 6-gingerol to 6-shogaol significantly larger than the reverse, and further biotransformation of 6-gingerol to zingerone [12].

For the formulator, the practical consequence is that heat exposure during manufacture is a process parameter with chemical consequences. A preparation route involving elevated temperature or prolonged solvent removal will shift the gingerol–shogaol balance, and the marker content of the finished product cannot be assumed equal to that of the input extract.

2.2 Standardisation: the precondition for everything else

A standardised extract is the minimum requirement for a reproducible botanical dosage form, and it is where a gastroretentive ginger formulation must begin rather than end. Raw-material quality control follows the established framework for medicinal plant materials — identity, foreign matter, ash values,

loss on drying, extractive values, heavy metals and microbial limits [9] — but the pharmaceutically decisive step is quantification of the pungent markers.

Chromatographic methods for this are well developed. A green reversed-phase HPTLC-densitometric method has been validated for simultaneous determination of 6-shogaol and 6-gingerol across a range of ginger extracts and commercial formulations, providing a practical quality-control tool that does not rely on large volumes of hazardous solvent [8]. HPLC and LC-MS/MS methods offer greater sensitivity where plasma or tissue analysis is required [11].

Three analytical commitments follow for any serious formulation study. The input extract must be characterised for 6-gingerol and 6-shogaol content before formulation. The finished dosage form must be assayed for the same markers, so that encapsulation efficiency and drug loading are expressed in terms of defined constituents rather than of total extract mass. And release and stability data must track the markers individually, because a formulation that preserves total phenolic content while converting gingerol to shogaol has changed its pharmacology even though its total assay is unchanged.

2.3 Activity at the gastric mucosa

The gastroprotective pharmacology of ginger is the part most directly relevant to a gastroretentive dosage form, because it is exerted locally.

A mechanistic study of ginger rhizome extract established gastroprotection operating through inhibition of H^+,K^+-ATPase — the gastric proton pump — and of Helicobacter pylori growth, together with an antioxidative component, and attributed a substantial part of these effects to gallic acid and cinnamic acid alongside the pungent principles [7]. Each of these three mechanisms is concentration-dependent at the mucosal surface and each is therefore improved by prolonged gastric residence rather than by rapid systemic absorption.

Ginger also acts on gastrointestinal motility directly: inhibitory effects on rat ileal motility have been demonstrated in vitro [42], which is consistent with a local component to the antiemetic action that meta-analyses have repeatedly confirmed clinically [4,6,43].

The implication is important enough to state plainly. For a drug whose target is the gastric mucosa, systemic bioavailability is the wrong endpoint, and a formulation optimised to maximise plasma exposure may be optimising against the wrong objective. Gastric residence time is the variable of interest.

III. THE PHARMACOKINETIC CASE FOR GASTRORETENTION

Table 1 assembles the available pharmacokinetic data for the ginger pungent principles. Figure 1 plots the human values.

The defining human study dosed 27 healthy volunteers with a ginger extract standardised to 5% gingerols in capsule form, at six dose levels from 100 mg to 2.0 g, with sampling from 15 minutes to 72 hours. No participant had detectable free 6-gingerol, 8-gingerol, 10-gingerol or 6-shogaol in plasma; all four were detected only as glucuronide conjugates, with 6-gingerol sulfate appearing above the 1.0 g dose. At the 2.0 g dose the estimated C_{max} values were 0.85 ± 0.43, 0.23 ± 0.16, 0.53 ± 0.40 and 0.15 ± 0.12 μg mL^{-1} and the areas under the curve 65.6 ± 44.4, 18.1 ± 20.3, 50.1 ± 49.3 and 10.9 ± 13.0 μg·h mL^{-1} for 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol respectively. Times to peak clustered around 65–75 minutes and elimination half-lives were under two hours [10].

Two features of that dataset deserve emphasis. The first is complete pre-systemic conjugation: nothing circulates free. The second is the magnitude of the standard deviations, which in several cases approach or exceed the means — the same inter-individual variability that frustrates dose-response work with botanical preparations generally.

A later study using LC-MS/MS refined the picture. After a 2.0 g oral dose of ginger extract, free 10-gingerol and 6-shogaol were detectable at low concentrations — 9.5 ± 2.2 and 13.6 ± 6.9 ng mL^{-1} at 1 h — while free 6-gingerol and 8-gingerol remained undetectable from 0.25 to 24 h. Glucuronide metabolites peaked at 0.47 ± 0.31, 0.17 ± 0.14, 0.37 ± 0.19 and 0.73 ± 0.54 μg mL^{-1} at 1 h. Half-lives of all analytes and metabolites were 1–3 h, and no accumulation occurred on repeated daily dosing [11].

The last point matters: a short half-life with no accumulation means that a conventional immediate-

release product produces a brief daily spike rather than sustained exposure.

Animal data quantify the absorption barrier directly. In rats dosed with pure compounds rather than extract, the parent molecules showed rapid but partial absorption and extensive organ distribution with substantial biotransformation, limiting oral bioavailability of each compound to below 2%; conjugated glucuronides were eliminated partly through renal excretion with minimal faecal excretion [12]. Earlier intravenous work in rats found 6-gingerol cleared from plasma with a terminal half-life of approximately 8.5 minutes, rising to 11.0 minutes in carbon tetrachloride-intoxicated animals, with more than 90% serum protein binding and no contribution from renal excretion — establishing hepatic elimination as the dominant route [13]. Plasma pharmacokinetics and tissue distribution of 6-gingerol in rats have been described in further detail [14,15].

The formulation brief that emerges has three parts. Sustain delivery, because the half-life is short and a conventional product gives a spike. Extend presentation to the upper gastrointestinal tract, because absorption is partial and the window is proximal. And above all keep the extract in the stomach, because that is where the gastroprotective and a part of the antiemetic activity is exerted and where residence time, not plasma concentration, is the operative variable.

Table 1. Reported pharmacokinetics of the ginger pungent principles in humans and rats. Values are as published; human doses refer to standardised extract, rat values in the final rows to pure compounds.

Study / species	Dose and design	Key findings	Ref.
Healthy human volunteers (n = 27)	Ginger extract standardised to 5% gingerols, 100 mg to 2.0 g, single oral dose, sampling 15 min to 72 h	No free 6-, 8-, 10-gingerol or 6-shogaol detectable; all present as glucuronide conjugates, 6-gingerol sulfate above 1.0 g. At 2.0 g: C_{max} 0.85 ± 0.43, 0.23 ± 0.16, 0.53 ± 0.40, 0.15 ± 0.12 μg mL^{-1} and AUC 65.6 ± 44.4, 18.1 ± 20.3, 50.1 ± 49.3, 10.9 ± 13.0 μg·h mL^{-1}. t_{max} 65–75 min; t½ < 2 h	[10]
Healthy humans, LC-MS/MS	2.0 g ginger extract orally; plasma and colon tissue	Free 10-gingerol and 6-shogaol detectable at 9.5 ± 2.2 and 13.6 ± 6.9 ng mL^{-1} at 1 h; free 6- and 8-gingerol undetectable 0.25–24 h. Glucuronides peaked at 0.47, 0.17, 0.37 and 0.73 μg mL^{-1}. Half-lives 1–3 h; no accumulation on repeated dosing	[11]
Rats, pure compounds	Single i.v. (3 mg kg^{-1}) or oral (30 mg kg^{-1}) [6]-gingerol, [6]-shogaol or zingerone	Rapid but partial absorption with extensive organ distribution and substantial biotransformation; oral bioavailability below 2% for each compound. Bidirectional 6-gingerol ↔ 6-shogaol interconversion, with larger clearance in the gingerol → shogaol direction; glucuronides excreted mainly renally	[12]
Rats, intravenous bolus	[6]-Gingerol i.v. in control, nephrectomised and CCl_4-intoxicated animals	Two-compartment disposition; terminal t½ 8.5 min, rising to 11.0 min with hepatic intoxication; > 90% serum protein binding; renal excretion did not contribute to plasma disappearance	[13]
Rats, oral	[6]-Gingerol, plasma pharmacokinetics and tissue distribution	Rapid distribution with extensive conjugation; supporting data on tissue levels and excretion routes	[14,15]

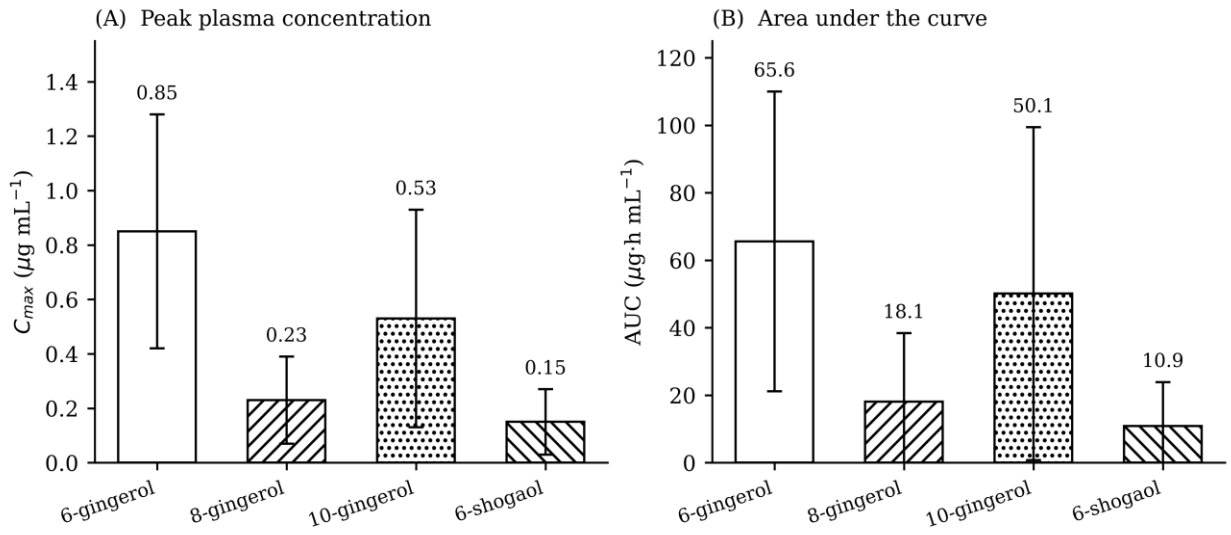


Fig. 1. Human pharmacokinetics of ginger pungent principles after a single 2.0 g oral dose of a ginger extract standardised to 5% gingerols in 27 healthy volunteers [10]. (A) Peak plasma concentrations and (B) areas under the concentration–time curve for 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol, determined after hydrolysis of conjugates. Error bars are the reported standard errors; their magnitude relative to the means is itself a finding, and no free (unconjugated) analyte was detectable in any participant.

IV. GASTRORETENTIVE DRUG DELIVERY: PHYSIOLOGY AND STRATEGIES

Gastric emptying is the obstacle. In the fasted state the stomach is swept by the migrating myoelectric complex, a cyclical sequence of contractions recurring roughly every 1.5–2 hours whose third phase — the so-called housekeeper wave — clears undigested material into the duodenum. Any dosage form that happens to be present when that wave arrives is emptied, which is why the gastric residence time of a conventional unit is short and, more problematically, highly variable [16,17].

Feeding changes the picture. After a mixed meal the motility pattern shifts to the digestive pattern, the onset of the migrating myoelectric complex is delayed, and gastric emptying slows; high-calorie meals containing protein, fat and fibre prolong retention further. Dosage-form density is the other principal lever: a unit less dense than gastric contents floats, whereas a denser unit sinks to the antrum, and gastric content density is conventionally taken as approximately 1.004 g cm^{-3}, so a density below about 1.0 g cm^{-3} is required for reliable buoyancy [18,19,20]. Size, shape, age, sex and posture all modulate residence time, with slower emptying reported in women and in the elderly.

Several strategies exploit these facts, and Table 2 compares them. Floating systems lower bulk density, either by generating carbon dioxide in situ from a carbonate–acid couple (effervescent systems) or by incorporating entrapped air or a hollow core (non-effervescent systems). Swelling and expandable systems enlarge beyond the pyloric aperture after hydration. Mucoadhesive systems bind to gastric mucin, though mucus turnover limits their durability. High-density systems sink into the antral folds. Raft-forming systems generate a cohesive alginate gel layer floating on gastric contents and are particularly well suited to local treatment of mucosal injury [16,17,18].

The single most consequential design choice, however, is between single-unit and multiple-unit systems. A single unit empties in an all-or-nothing fashion: it is either retained or it is not, and the outcome for an individual dose is close to binary. Multiple-unit systems distribute uniformly in the gastric contents, empty gradually rather than at once, give more reproducible absorption, reduce the risk of local irritation from a concentrated dose, and provide a larger margin of safety against the failure of any individual unit [23]. A scintigraphic study in seven healthy volunteers illustrated the difference directly: freeze-dried calcium alginate multiple-unit floating

dosage forms showed prolonged gastric residence in the fed state, whereas non-floating beads of identical material had short residence times with a mean onset of emptying of 1 h [21].

For a botanical extract this argument is decisive. Extract loading per unit is necessarily limited by the bulk of the extract itself, the therapeutic doses involved are in the hundreds of milligrams to grams, and the local indications benefit from distribution of the dose across the mucosal surface rather than its concentration at one point. Multiple-unit floating microspheres are the architecture that satisfies all three constraints.

Table 2. Gastroretentive strategies compared, with the considerations that bear on delivery of a standardised botanical extract.

Approach	Principle	Strengths	Limitations for a botanical extract
Effervescent floating	CO_2 generated in situ from a carbonate–acid couple lowers bulk density	Reliable buoyancy; simple to formulate	Requires gas-generating chemistry in contact with the extract; floating lag time while gas evolves; acid-dependent
Non-effervescent floating (hollow microspheres)	Entrapped air or a hollow polymer core gives density below that of gastric fluid	No gas generation; multiple-unit; immediate buoyancy achievable; high surface distribution	Encapsulation efficiency depends on extract polarity; wall thickness trades off against buoyancy
Swelling / expandable systems	Hydration expands the unit beyond the pyloric aperture	Retention independent of gastric fluid density; effective in the fed state	Single-unit, so emptying is all-or-nothing; large doses of extract give bulky units
Mucoadhesive systems	Polymer binds to gastric mucin	Direct and prolonged mucosal contact, attractive for local action	Mucus turnover limits durability; adhesion is variable in the acidic, agitated gastric environment
High-density systems	Density above gastric contents causes sedimentation into the antral folds	Independent of the fed/fasted state	Requires dense inert excipient, limiting extract payload per unit
Raft-forming systems	Alginate forms a cohesive floating gel layer on gastric contents	Excellent for local mucosal therapy; liquid dosing suits high extract loads	Liquid format complicates dose uniformity and stability of a multicomponent extract

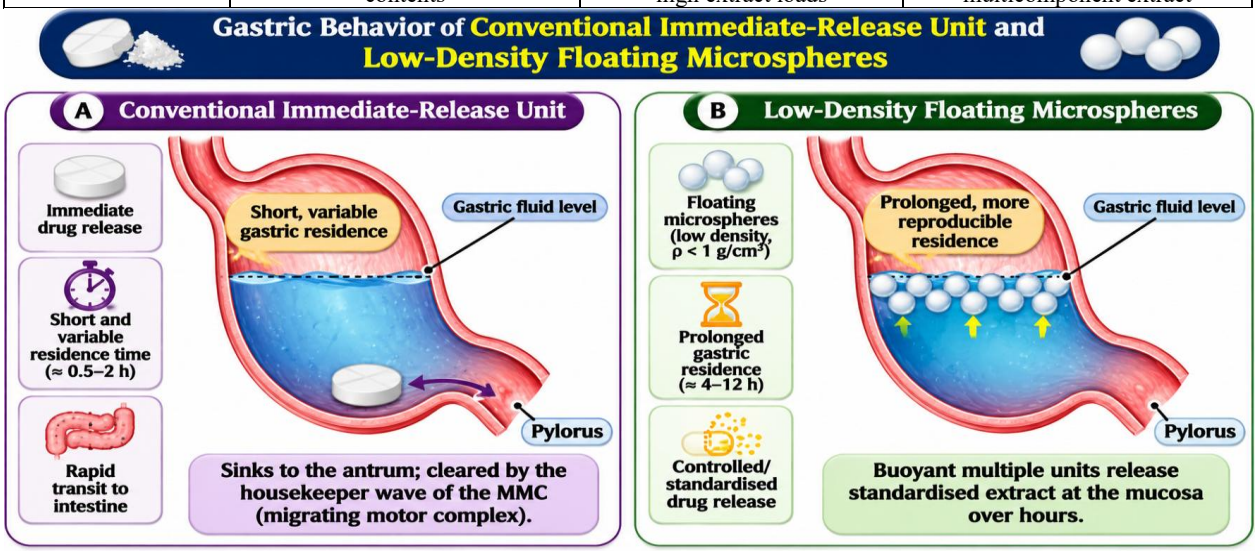


Fig. 2. The gastroretentive rationale, shown schematically. A conventional immediate-release unit sinks toward the antrum and is cleared by the migrating myoelectric complex, giving short and variable gastric residence. Low-density floating microspheres distribute across the gastric contents, remain buoyant above the fluid level, and release standardised extract at the mucosa over an extended period, serving both the local gastroprotective indication and the proximal absorption window. Not to scale.

V. FLOATING MICROSPHERES: PREPARATION AND CRITICAL VARIABLES

Floating microspheres — also called hollow microspheres or microballoons — are free-flowing spherical particles, conventionally 1–1000 µm in diameter, with an internal hollow core or entrapped air that lowers their density below that of gastric fluid. They are non-effervescent gastroretentive systems, which is an advantage for an acid-labile or pH-sensitive payload because no gas-generating reaction is required [23].

The architecture was established by Kawashima and colleagues, who prepared hollow microspheres for use as a floating controlled-release system in the stomach using an emulsion solvent diffusion technique [22]. The method remains the workhorse. Polymer and extract are dissolved in a volatile organic solvent pair, typically dichloromethane with methanol or ethanol with diethyl ether, and the solution is emulsified into an aqueous phase containing a stabiliser such as polyvinyl alcohol. The more water-miscible solvent diffuses rapidly into the aqueous phase while the volatile solvent evaporates, and the cavity left behind as the polymer precipitates forms the hollow core that confers buoyancy.

Polymer selection governs both buoyancy and release. Ethylcellulose is the most widely used matrix former, valued for its film-forming behaviour, chemical inertness and pH-independent insolubility; it has been reviewed as a multidirectional pharmaceutical excipient and as the basis of a wide range of drug-delivery architectures, with reported encapsulation efficiencies across ethylcellulose micro- and nanoparticle systems spanning a very wide range depending on method and polymer level [33,34]. Eudragit grades offer pH-dependent alternatives, and hydroxypropyl methylcellulose grades are commonly incorporated as release modifiers, with the viscosity grade determining whether buoyancy or release retardation dominates.

Table 3 sets out the formulation and process variables and the critical quality attributes each affects. Several relationships are consistent across the literature. Increasing the polymer-to-extract ratio increases particle size, wall thickness and encapsulation efficiency and retards release, but excessive wall thickness reduces the internal void fraction and can compromise buoyancy. The ratio of the two solvents controls the rate of diffusion relative to evaporation and therefore the size and integrity of the internal cavity, making it the dominant determinant of floating behaviour. Stirring speed inversely determines particle size through droplet break-up. Stabiliser concentration controls coalescence and hence size distribution.

Precedents across model drugs are numerous and consistent. Floating microspheres have been developed and evaluated for metformin hydrochloride [24], verapamil hydrochloride [25], itraconazole with statistical optimisation [26], pregabalin by a w/o/o multiple emulsion method [45], ciprofloxacin [46] and, recently, furosemide [44]. Gastroretentive floating tablets have likewise been developed using biological macromolecules [27] and optimised under a Quality by Design framework with a Box–Behnken design for famotidine [28].

A caution specific to botanical payloads deserves mention. A plant extract is a multicomponent mixture whose constituents differ in polarity and in solubility in the organic phase. Partition of individual markers between the polymer solution and the aqueous continuous phase during emulsification need not be uniform, so encapsulation efficiency measured for 6-gingerol is not necessarily that of 6-shogaol. Marker-specific assay of the finished microspheres is therefore not optional.

5.1 Mechanisms of release from a hollow polymer shell

Release from a floating microsphere is not a single process, and distinguishing the components matters for interpretation of dissolution data. Extract located at or near the particle surface dissolves immediately on contact with gastric fluid, producing the burst commonly seen in the first fifteen to thirty minutes. Extract dispersed within the polymer wall must diffuse through a tortuous, partially hydrated matrix, which is the phase normally described by a Higuchi square-root-of-time relationship. Where the polymer swells or erodes, a third, relaxation-controlled component is superimposed.

The Korsmeyer–Peppas power-law exponent is the standard diagnostic. For spherical particles, a release exponent near 0.43 indicates Fickian diffusion, values between 0.43 and 0.85 indicate anomalous transport combining diffusion and polymer

relaxation, and values approaching 0.85 indicate case-II relaxation-controlled transport. Because ethylcellulose is insoluble and non-swelling across the gastric pH range, ethylcellulose microspheres generally give exponents in the Fickian or low anomalous range, whereas incorporation of a hydrophilic release modifier shifts the exponent upward as a hydrated gel layer begins to contribute.

Two cautions apply to botanical payloads. First, an extract contains constituents of differing polarity and molecular size, so the release exponent fitted to total extract is an average over species that may be released at different rates; marker-resolved profiles can diverge visibly from the composite curve. Second, a burst phase is not necessarily undesirable here. For a locally acting gastroprotective formulation, an initial pulse that rapidly establishes a mucosal concentration, followed by sustained replenishment, may be preferable to a strictly zero-order profile. The target release profile should therefore be specified from the indication rather than assumed.

5.2 From liquid dispersion to a dosage unit

A microsphere suspension is not a product. The dried particles must be filled into hard gelatin or hypromellose capsules, which imposes requirements that are easy to overlook at laboratory scale: adequate flow for reproducible fill weight, a particle size distribution narrow enough to prevent segregation during filling, and sufficient mechanical strength to survive handling without fracturing and losing the hollow core on which buoyancy depends.

Micromeritic characterisation — bulk and tapped density, Carr's compressibility index, Hausner ratio and angle of repose — is therefore part of the formulation work rather than an afterthought, and a batch with excellent in vitro buoyancy but poor flow is not a viable candidate. Capsule shell compatibility also deserves attention, since residual organic solvent from the emulsification step can interact with gelatin over time; residual solvent should be controlled to the relevant ICH limits and verified in the finished unit.

Finally, the capsule shell itself must not defeat the design. A shell that fails to rupture promptly in gastric fluid delays dispersion of the microspheres and extends the effective floating lag time of the product beyond that measured for the particles alone — a discrepancy between particle-level and product-level buoyancy data that is worth measuring explicitly rather than assuming away.

Table 3. Formulation and process variables for floating microspheres prepared by emulsion solvent evaporation or diffusion, and the critical quality attributes each governs.

Variable	Direction of effect	Critical quality attributes affected
Polymer : extract ratio	Higher ratio increases wall thickness and particle size, raises encapsulation efficiency and retards release, but reduces the internal void fraction	Encapsulation efficiency; particle size; release rate; buoyancy
Polymer identity and grade	Ethylcellulose gives pH-independent retardation; Eudragit grades give pH-dependent behaviour; HPMC grades act as release modifiers with viscosity-dependent effect	Release mechanism and rate; buoyancy; stability
Solvent ratio (diffusing : volatile)	Governs the relative rates of solvent diffusion and evaporation, and therefore the size and integrity of the internal cavity	Buoyancy; floating lag time; particle morphology
Stirring speed	Higher shear reduces emulsion droplet size and hence particle size; excessive shear can rupture nascent particles	Particle size and distribution; yield; encapsulation efficiency
Stabiliser (e.g. PVA) concentration	Higher concentration reduces coalescence and narrows the size distribution; excess retards solvent removal	Particle size distribution; yield; surface morphology
Aqueous phase volume and	Determine solvent removal rate; higher temperature accelerates evaporation but risks gingerol → shogaol	Cavity formation; marker ratio in the product; yield

Variable	Direction of effect	Critical quality attributes affected
temperature	conversion	
Extract load	Higher load raises payload per unit but can exceed polymer solvent capacity, giving surface deposition and burst release	Drug loading; burst release; surface morphology
Drying conditions	Elevated temperature or prolonged drying shifts the gingerol–shogaol balance	Marker ratio; stability; pharmacological profile

VI. GINGER-SPECIFIC GASTRORETENTIVE PRECEDENTS

Three reported systems bear directly on the proposition, and all three are encouraging without closing the gap.

Starch/chitosan expandable films have been developed as a gastroretentive carrier for a ginger extract-loaded solid dispersion, combining unfolding-type gastric retention with dissolution enhancement of the poorly soluble pungent principles [29]. The same group developed raft-forming liquid formulations loaded with a ginger extract solid dispersion for the treatment of gastric ulceration, which is the clearest expression in the literature of the local-action rationale: a raft floating on gastric contents delivers extract to the mucosa over an extended period [30]. Earlier, synbiotic floating beads combining a probiotic with ginger extract were evaluated in an experimental paradigm of gastric ulcer and presented as a novel therapeutic option [31].

What these have in common is that each is a single-unit or liquid system, and none is a multiple-unit microparticulate formulation optimised under a formal design of experiments with marker-based standardisation of both input extract and finished product. That combination — standardised extract, multiple-unit floating microspheres, statistical optimisation, marker-specific release and stability — does not appear to have been reported, and it is the obvious next step rather than a speculative one.

VII. QUALITY BY DESIGN AND STATISTICAL OPTIMISATION

Floating microspheres present the classic multi-factor, multi-response optimisation problem. The polymer-to-extract ratio, the solvent ratio and the stirring speed each influence particle size, encapsulation efficiency, buoyancy and release rate, and they do so with interactions: raising the polymer level improves encapsulation but thickens the wall and can sink the particle. Sequential one-factor-at-a-time experimentation cannot resolve such a system efficiently and will generally miss the optimum.

The Quality by Design framework described in ICH Q8(R2) replaces that approach with a quality target product profile, explicit identification of critical quality attributes and critical process parameters, and the establishment of a design space within which performance is demonstrably robust [35,36]. For a ginger floating microsphere the critical quality attributes follow from the preceding sections: percentage buoyancy and total floating time, to be maximised; encapsulation efficiency expressed against the standardised markers, to be maximised; particle size, to be controlled within a range appropriate to gastric distribution; and the extent of marker release at a defined time point, to be targeted rather than simply maximised.

The Box–Behnken design is well suited to the task. Introduced as a family of three-level designs for quantitative variables [37], it estimates a full quadratic response surface without the extreme corner combinations of a full factorial — a real advantage here, because extreme polymer or solvent ratios may fail to form discrete microspheres at all. Its merits as an alternative to other response-surface designs have been reviewed [38], and it has been applied successfully to gastroretentive systems, including Quality by Design optimisation of a famotidine floating tablet [28] and statistical optimisation of itraconazole gastroretentive microspheres [26].

Analysis should proceed through analysis of variance on the fitted polynomials, inspection of contour and three-dimensional response-surface plots, numerical optimisation against a composite desirability

function, and confirmation: preparation of the predicted optimum and comparison of observed with predicted responses. A design space without a confirmation batch is a model rather than a result.

VIII. HOW SUCH A SYSTEM SHOULD BE EVALUATED

A credible evaluation package has six components.

Extract standardisation and analytics. Pharmacognostic quality control of the raw material against established criteria [9], followed by validated quantification of 6-gingerol and 6-shogaol by HPTLC-densitometry or HPLC [8]. Analytical methods should be validated to ICH Q2(R1) for linearity, accuracy, precision, specificity, detection and quantitation limits and robustness [39]. Drug–excipient compatibility is assessed by FTIR and thermal analysis.

Particle characterisation. Percentage yield, particle size and size distribution, surface morphology and evidence of the internal cavity by scanning electron microscopy, micromeritic properties including bulk and tapped density, Carr's index and angle of repose, and — the parameter that actually determines buoyancy — measured particle density, which should be reported rather than inferred from floating behaviour.

Buoyancy. In vitro floating lag time and total floating time in simulated gastric fluid at pH 1.2 and 37 °C, with the percentage of particles remaining buoyant quantified at intervals over at least 12 hours rather than recorded as a single endpoint [20].

Release. Dissolution in simulated gastric fluid with marker-specific assay, data fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models to characterise the release mechanism. Reporting release of total extract alone is insufficient for the reasons given above.

Biological evaluation. For the local indications, a gastric ulcer model with the conventional extract as comparator is the relevant test, following the precedent of the ginger floating bead and raft-forming work [30,31]. Where systemic exposure is the objective, a pharmacokinetic study in rats comparing the floating microspheres with an equivalent dose of unformulated extract is required; in vivo confirmation of gastric retention by radiographic or scintigraphic means would substantially strengthen any such study [21].

Stability. Accelerated testing to ICH Q1A(R2) at 40 ± 2 °C and 75 ± 5% relative humidity over at least three months [40], monitoring not only total marker content but specifically the gingerol-to-shogaol ratio, since thermally driven interconversion during storage would alter the pharmacological profile while leaving a total-phenolic assay unchanged.

IX. GAPS AND OUTLOOK

Several gaps are worth naming directly.

The multiple-unit gap. Reported ginger gastroretentive systems are expandable films, rafts and beads [29,30,31]. No standardised-extract floating microsphere optimised by response-surface methodology appears to have been reported, despite the architecture being well established for synthetic drugs [22,24,25,26].

The endpoint gap. Most botanical formulation papers report systemic pharmacokinetics as the measure of success. For ginger, whose best-evidenced activities include local gastroprotection and anti-Helicobacter effects [7], gastric residence and mucosal concentration are at least as relevant, and very few studies measure them.

The marker gap. Encapsulation efficiency and release are frequently reported for total extract. Given documented differences in potency between 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol [41] and the thermal lability that links them [1], marker-resolved data are necessary rather than merely desirable.

The in vivo retention gap. In vitro floating time is a surrogate. Scintigraphic or radiographic confirmation of gastric residence, of the kind performed for alginate floating systems [21], is rare in the microsphere literature and would materially strengthen the evidence base.

The translation gap. Clinical trials of ginger have used conventional powder or extract capsules at doses of 0.5–3 g daily [3,4,5,6]. No gastroretentive ginger preparation has been tested clinically. A formulation that reduced dose or dosing frequency while maintaining or improving the antiemetic or gastroprotective effect would be a real contribution, and the dose range involved makes a multiple-unit

capsule-filled microsphere product a practical proposition rather than a theoretical one.

X. CONCLUSION

Ginger presents an unusual configuration: strong clinical evidence, well-characterised phytochemistry, and pharmacokinetics that on their face should not support the observed effects. Human data show that the pungent principles circulate essentially entirely as glucuronide and sulfate conjugates with half-lives under two hours, and rat data with pure compounds put oral bioavailability below 2%. The resolution of the paradox is that much of the relevant activity is local — inhibition of the gastric proton pump, suppression of Helicobacter pylori, modulation of gastrointestinal motility — and local activity is governed by residence time rather than by plasma concentration.

Gastroretentive delivery addresses the systemic and the local problem with one intervention, and among gastroretentive architectures multiple-unit floating microspheres are the best match to a botanical extract: they distribute across the gastric contents, empty gradually rather than all at once, avoid the gas-generating chemistry of effervescent systems, and accommodate the substantial extract loads that herbal doses require. The preparation route is established, the polymer chemistry is mature, and the critical variables are known.

What is missing is the specific combination: a ginger extract standardised to defined gingerol and shogaol content, formulated as multiple-unit floating microspheres, optimised through a Box–Behnken design against buoyancy, encapsulation and release, and evaluated with marker-resolved analytics, in vivo confirmation of gastric retention, and a biological endpoint matched to the local mechanism. Each component exists; none has been assembled. On the evidence reviewed here, assembling them is a well-motivated piece of work rather than a speculative one.

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