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Review Paper

A Review on Microsponge Based Oral Drug Delivery Systems: Formulation, Characterization, and Therapeutic Applications

Dhananjay Parkhe*, Nadeem Farooqui, Vipin Deshmukh, Nimita Manocha

Department of Pharmaceutics, Indore Institute of Pharmacy, Opposite IIM, Rau-Pithampur Road, Rau, Indore, MP, India, 453331.

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ABSTRACT

Micro-sponge drug delivery systems (porous, cross-linked polymeric microspheres first patented in 1987) have accumulated three decades of formulation-stage evidence for oral applications, yet no oral micro-sponge product has reached market or human clinical evaluation. This review synthesises the literature on oral micro-sponge formulation strategies, characterization techniques, and therapeutic applications, using domperidone, carbamazepine, curcumin, and Helicobacter pylori-targeted phytochemicals as representative cases spanning first-pass metabolism, a narrow therapeutic index requiring sustained release, and bioavailability limited by dissolution rate. Across nine characterization domains, oral micro-sponge formulations show consistent, mechanistically coherent diffusion-controlled release, with entrapment efficiencies of 60–85% and predominantly non-Fickian release kinetics. Animal-level in vivo evidence exists for a subset of formulations, but none has progressed to a human pharmacokinetic study. This asymmetry sits against an extensive, continuously active topical micro-sponge marketed and patented history, confirming that the underlying technology is commercially viable while its oral application specifically is not. Three compounding barriers explain the gap: unresolved batch-to-batch manufacturing reproducibility, the absence of a marketed gastroretentive precedent using this specific multiparticulate mechanism, and an unproven commercial case against already-approved competing gastroretentive technologies. This review argues that closing the gap requires a targeted pilot-scale manufacturing and pharmacokinetic bridging study on an existing, well characterized candidate, rather than further formulation-stage optimization

***Corresponding Author:** Dhananjay Parkhe
Address: *Department of Pharmaceutics, Indore Institute of Pharmacy, Opposite IIM, Rau-Pithampur Road, Rau, Indore, MP, India, 453331.*
Email ✉: dhananjayparkhe08062001@gmail.com

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INTRODUCTION

Conventional oral dosage forms underperform for several approved drugs, for different reasons. Domperidone undergoes such extensive first-pass hepatic and gut-wall metabolism that only 13–17% of an oral dose reaches systemic circulation[1]. Carbamazepine, a BCS Class II compound with low aqueous solubility, has a narrow therapeutic index that has led regulators to deny biowaiver-based approval for generic tablets[2,3]. Curcumin's oral bioavailability has been measured at roughly 1% relative to intraperitoneal dosing[4]. These are three distinct problems: metabolic clearance, a narrow safety margin, and a solubility problem so severe the drug barely dissolves before its absorption window closes.

One technology proposed to address all three is the micro-sponge, first patented in 1987[5]: a non-collapsible, cross-linked polymeric microsphere, 5–300 micrometres in diameter, with an interconnected pore network that lets an entrapped drug diffuse out over an extended period[6]. Its claimed advantages trace back to that tunable pore architecture and drug-to-polymer ratio. The oral-specific case adds a narrower premise: that a porous particle can be engineered to float in gastric fluid longer than normal emptying allows, benefiting drugs with a narrow absorption window, drugs acting locally in the gut (H. pylori), and dissolution-limited drugs (curcumin, carbamazepine). Whether floating micro-sponges deliver this benefit under real physiological conditions, rather than simulated gastric fluid, is a question this review returns to directly.

This review covers formulation strategies, characterization, and therapeutic applications for oral micro-sponge systems specifically, narrower than most existing reviews, which treat topical and oral delivery together. This enables a comparison those reviews cannot make: between what studies report and what has reached a regulatory filing, a clinical trial, or a pharmacy shelf.

2. MICRO-SPONGE TECHNOLOGY: STRUCTURE, MECHANISM, AND POSITIONING

A micro-sponge's cross-linked matrix maintains structural integrity across the full gastric-to-intestinal pH range (pH 1.2–7.4) and withstands peristaltic forces that would compromise softer particulate systems[6]. Release is diffusion-controlled through the pore network rather than pressure- or temperature-triggered, and is tunable via the drug-to-polymer ratio: raising it from 1:1 to 1:6 cut cumulative release from 85.4% to 42.4% in one fluconazole formulation[7], with a comparable pattern for domperidone[8]. Particle density is a second lever, independent of polymer chemistry[6].

Among other oral particulate systems, liposomes are mechanically fragile with limited stability[9]; conventional non-porous microspheres leave unacceptable residual solvent and limited tunability[10]; and polymeric nanoparticles are highly sensitive to small process changes, with unresolved large-scale manufacturing and regulatory barriers[11]. The micro-sponge's advantage is structural: tunable pore size, polymer type, and drug ratio, without a liposome's stability constraints or a nanoparticle's nanometre-scale process control[6,12]. Table 1 also compares monolithic sustained-release matrix tablets: a multiparticulate reservoir divides its dose across many independently diffusion-controlled units, while a matrix tablet risks dose-dumping if that single unit fails[13].

Table 1. Comparative positioning of oral micro-sponges among particulate drug delivery systems

System	Typical structural advantage	Key reported limitation
Micro-sponges [7,13,15,16]	Porous, cross-linked polymer microsphere (5-300 µm); non-collapsible; diffusion-controlled release tunable via pore architecture and drug:polymer ratio; buoyant in gastric fluid	Manufacturing tradeoff between batch reproducibility (free-radical polymerization) and residual solvent (quasi-emulsion diffusion); oral-specific gastric residence and absorption limits
Liposomes [10]	Phospholipid bilayer vesicle; biocompatible; carries both hydrophilic and hydrophobic drugs	Limited physical stability, drug leakage, low targeting specificity, scale-up difficulty
Conventional (non-porous) microspheres [11]	Prepared by emulsion-solvent evaporation; comparatively simple process	Non-porous core, unacceptable residual solvent, limited post-formulation tunability of release
Polymeric nanoparticles [12]	10-1000 nm particles; high surface-area-to-volume ratio; enhances solubility and bioavailability	High process sensitivity (small parameter shifts alter particle size substantially), residual solvent toxicity, regulatory and scale-up barriers
Conventional sustained-release matrix tablets [14]	Monolithic hydrophilic/hydrophobic polymer matrix; single-unit; simple, low cost, large scale compression manufacturing	Entire dose held in one unit: documented dose-dumping risk if the matrix fails (e.g., alcohol co-ingestion); release fully dependent on GI transit rather than particle-level design

Manufacturing carries a real cost that differs by method: free-radical suspension polymerization is complex and poorly reproducible batch to batch[14], while quasi-emulsion solvent diffusion is easier to scale but leaves residual organic solvent, a bigger concern for a swallowed product than a topical cream[12]. A second, oral-specific limitation is physiological: non-uniform absorption, inadequate *in vivo* release, and shorter gastric residence than formulators assume when designing for buoyancy[15], the same simulated-versus-real gastric gap flagged in the Introduction.

3. FORMULATION STRATEGIES FOR ORAL MICRO-SPONGES

3.1 Polymers and Preparation Methods

Release-controlling polymers (Eudragit RS100/RL100, ethyl cellulose, cellulose acetate) are incorporated during preparation; floating excipients (HPMC, sodium bicarbonate) belong to the surrounding dosage form, not the particle itself. Table 2 sets out this distinction, which the literature does not always make cleanly.

Eudragit RS100/RL100 release is pH-independent (governed by ammonium content, not pH), so it is stable across the full GI range; a Box-Behnken study found polymer quantity, PVA concentration, and stirring speed together dominate particle size and entrapment efficiency[16]. Ethyl cellulose controls release through matrix tortuosity rather than ammonium content; a ranitidine formulation combining it with Eudragit RS achieved 86% buoyancy, 62.58% entrapment efficiency, and 94.5% release over 8 hours[17]. Cellulose acetate is established in general controlled-release literature[18] but dedicated oral micro-sponge data is sparse. HPMC and sodium bicarbonate together achieve floating lag times near two minutes and total floating exceeding 24 hours[19,20].

Table 2. Release-controlling polymers and floating excipients used in oral micro-sponge formulations: functional classification

Polymer	Functional class	Release mechanism in micro-sponge	Solvent (QESD)	Key advantage for oral use	Documented drug examples
Eudragit RS100 / RL100	Acrylic copolymer (pH-independent)	Permeability via quaternary ammonium content; release independent of pH 1.2-7.4	Ethyl alcohol; DCM	pH-stable sustained release across entire GI tract; established regulatory history	Domperidone[8], naproxen[17]
Ethyl cellulose (EC)	Cellulose ether (hydrophobic matrix)	Diffusion through hydrophobic matrix; rate governed by drug:polymer ratio and matrix tortuosity	DCM; ethyl alcohol	High chemical stability; combinable with Eudragit RS for dual-mechanism control	Ranitidine floating (EC + Eudragit RS: 86% buoyancy, 94.5% release in 8 h)[17]
Cellulose acetate (CA)	Cellulose ester (semi-permeable membrane)	Semi-permeable membrane controls osmotic/diffusion release[19]	Acetone	Controllable permeability via degree of substitution	[UNVERIFIED: limited oral micro-sponge-specific data]
HPMC (K4M, K15M, K100M)	Cellulose ether (swellable hydrophilic; floating excipient, not matrix polymer)	Swells to form buoyant gel layer in gastric fluid; traps CO2 from sodium bicarbonate	N/A (aqueous)	Enables gastroretention in floating dosage forms around micro-sponges	Floating tablets: FLT ~2 min, total floating >24 h with 20 mg NaHCO3[20,21]

Four preparation methods have been used (Table 3). Quasi-emulsion solvent diffusion (QESD), the most common, dissolves drug and polymer in an organic solvent, then adds this to a heated aqueous emulsifier phase; seven variables determine particle size, entrapment efficiency, and yield, with stirring speed the most influential, 500→1500 rpm reduced particle size from 76.2 to 32.5 µm in one system[21,22]. Liquid-liquid suspension polymerization, the original method, is complex and poorly reproducible batch to batch[23]. The vibrational nozzle method[24], an established technique for producing monodisperse microcapsules generally, appears in the broader microsponge preparation literature as a Vibrating Orifice Aerosol Generator (VOAG) variant[25], though not demonstrated for oral, polymeric Eudragit/ethyl-cellulose-type micro-sponges specifically. Spray drying is scalable but struggles below ~10 µm particle size[26].

Table 3. Preparation methods for oral micro-sponges: principle, process variables, and tradeoffs

Method	Core principle	Key process variables	Reported advantage	Reported limitation
Quasi-emulsion solvent diffusion (QESD)[22,23]	Drug + polymer dissolved in organic solvent; emulsified in aqueous PVA phase; solvent diffusion	Stirring speed (500-1500 rpm = size 76.2-32.5 µm); organic phase volume; sonication time;	Scalable; versatile; well studied; no polymerization catalyst	Residual organic solvent (DCM); particle size sensitive to small process changes

	produces porous particles	emulsifier conc.; drug:polymer ratio		
Liquid-liquid suspension polymerization [24]	Monomers + drug in organic solvent dispersed in aqueous phase; free-radical polymerization by catalyst, heat, or irradiation	Temperature, catalyst conc., irradiation dose, monomer:drug ratio, surfactant conc.	Direct polymerization around drug; high entrapment for non-polar drugs	Complex; poor batch reproducibility; requires drug stability under polymerization conditions
Vibrational nozzle method [26]	Polymer-drug solution extruded through vibrating nozzle; jet breaks into uniform droplets; collected and hardened	Vibration frequency, nozzle diameter, solution viscosity, collection bath composition	Narrow particle size distribution; monodisperse; gentle processing	Limited micro-sponge-specific data; specialized equipment; lower throughput than QESD [NOTE: flag for verification]
Spray drying [27]	Drug-polymer solution atomized into hot drying gas; rapid solvent removal; dry particles collected by cyclone	Inlet temperature, feed flow rate, atomization pressure, solution concentration	Continuous; scalable; solvent-free variants possible	Min. particle size ~10 µm practically achievable; heat-sensitive drugs at risk

3.2 Formulation Variables and Dosage Forms

Drug-to-polymer ratio is the primary release lever: higher polymer loading increases matrix thickness and reduces release, but also increases density and reduces intrinsic buoyancy, the opposite of what floating requires[21]. Porosity governs both loading capacity and dissolution surface[19]. Intrinsic buoyancy from trapped pore air is usually insufficient alone, so gastroretention relies on gas-generating (sodium bicarbonate) or swelling (HPMC) excipients built into the dosage form, combining both outperforms either alone[27,20]. Floating tablets are the most investigated format; capsules avoid compression damage to the porous structure but rely entirely on intrinsic buoyancy; oral suspensions face redispersibility challenges[19]. Of the three, the floating tablet is the most clinically relevant but least validated against real physiological conditions.

4. CHARACTERIZATION TECHNIQUES FOR ORAL MICRO-SPONGES

Characterization proceeds through a layered sequence: external morphology, internal architecture, drug physical state, release behaviour, stability, and finally whether *in vitro* measures predict *in vivo* performance. Table 4 presents all nine techniques as an integrated framework; this section highlights the findings most relevant to this review's argument.

Table 4. Characterization framework for oral micro-sponge drug delivery systems: technique, parameter, instrumentation, and clinical significance

Technique	Property assessed	Instrument / method	Key parameters / typical values (oral microsponges)	What a result indicates
Dynamic light scattering (DLS)	Particle size, PDI, zeta potential	Malvern Zetasizer; HELOS laser diffraction for dry powders	Size 30–200 µm; PDI ≤0.3 (acceptable); zeta potential ±20–30 mV	PDI >0.3 = broad distribution; zeta <±15 mV = aggregation risk
Scanning electron microscopy (SEM)	Surface morphology, internal pore structure	Field-emission SEM; gold-sputter coating; 20 kV operating voltage	Spherical particles; visible surface pores; no drug crystals on surface	Crystal presence = incomplete entrapment; smooth closed surface = pore collapse
Mercury intrusion porosimetry + helium pycnometry	Pore volume, pore size distribution, real and apparent density	Autopore IV porosimeter; ultra-pycnometer under helium gas	BET surface area 16.6 m^2/g (simvastatin [32]); intrusion-extrusion isotherms	Higher surface area = more dissolution-contact potential; apparent density governs buoyancy
UV spectrophotometry / HPLC	Entrapment efficiency, drug content	Indirect: centrifuge + measure unentrapped drug in supernatant; direct: dissolve particle in solvent	EE range 60–85%; drug content ≥90% of label claim	EE <60% = poor retention; drug content variability >5% = batch inconsistency
Buoyancy testing (floating behavior)	Floating lag time (FLT), total floating time (TFT), % buoyancy	USP Type II dissolution apparatus; 900 mL SGF pH 1.2; 37±0.5°C; 50 rpm; stopwatch	FLT <2 min (acceptable); TFT >8 h (desirable for gastroretentive design)	FLT >5 min = inadequate; TFT <4 h = insufficient gastric retention; both measured under static fluid conditions only
FTIR + DSC + XRD	Polymer–drug compatibility; drug physical state in matrix	FTIR: KBr pellet; DSC: 10°C/min scan; XRD: Cu Kα radiation	FTIR: no new peaks or shifts; DSC: absent or shifted Tm; XRD: reduced peak intensity	New FTIR peaks = chemical interaction; loss of Tm = amorphous drug in pores (controlled release advantage)
In vitro drug release + kinetics modelling	Cumulative drug release profile; release mechanism	USP Type II (paddle); dissolution media matched to GI pH (pH 1.2 gastric, pH 6.8 intestinal); fitted to zero-order, Higuchi, Korsmeyer–Peppas, Hixson–Crowell	Korsmeyer–Peppas best fit most common; n = 0.56–0.73 (non-Fickian) for oral microsponges [11]	n ≤0.43 = Fickian diffusion; 0.43<n<0.85 = anomalous (diffusion + relaxation); n ≥0.85 = Case II transport / erosion
Stability studies	Physical and chemical	ICH Q1A(R2): long-term 25°C/60%RH;	No significant change in particle	Increased particle size on storage =

	stability over time under defined conditions	accelerated 40°C/75%RH; tested at 0, 30, 60, 90 days	size, EE, drug content, or release profile	aggregation; EE drop = drug migration out of pores
In vivo / pharmacokinetic evaluation	Gastric residence time; Cmax, AUC, Tmax, MRT, t½	Gamma scintigraphy (radiolabelled formulation); X-ray imaging; alternating current biosusceptometry (ACB); plasma PK in animal model	No validated *in vivo* data published for oral microsponge-specific systems to date [GAP]	For related gastroretentive systems (matrix tablets): AUC and Cmax doubled vs conventional dosage form [36]; this has not been replicated for oral microsponges

Particle size (by dynamic light scattering or laser diffraction, PDI <0.3 accepted as narrow) varies enormously with preparation method and scale: one thyme oil gastroretentive formulation achieved 49.79 ± 1.4 µm[28] while a scale-up study reported 152 µm at optimal conditions[29], a roughly threefold difference between two "optimised" formulations. SEM (gold-sputter coated, 20 kV) confirms porous, spherical morphology and absence of surface drug crystals, verified for clindamycin[30,31] and simvastatin[32] microsponges, but cannot quantify pore volume or distribution, which requires mercury intrusion porosimetry and helium pycnometry[25]. BET surface area for an optimised simvastatin batch was 16.6 m^2/g[32], substantially higher than non-porous microspheres, though increasing polymer content reduces porosity and cuts both loading capacity and dissolution surface simultaneously.

Entrapment efficiency across oral formulations spans 60–85%[33,28,29,32]. FTIR, DSC, and XRD together establish drug-polymer compatibility: absence of new FTIR peaks confirms no chemical interaction[34], while reduced/shifted DSC melting peaks and lower XRD peak intensity indicate conversion to amorphous form within the pores, as seen for dapsone[30], evidence of the pore-loading mechanism itself. *In vitro* release is most commonly best-fit by Korsmeyer–Peppas, with n values 0.5614–0.7278 (anomalous/non-Fickian transport) for domperidone[8], though one ranitidine formulation instead reported zero-order kinetics[17], a discrepancy not yet systematically explained. Stability testing follows ICH Q1A(R2), but published studies rarely extend past 90 days[35,30], short of the 12 months normally required for regulatory submission.

Floating behaviour (USP Type II, simulated gastric fluid pH 1.2) accepts FLT <2 min and TFT >8 h as minimum benchmarks[33], but static simulated fluid does not replicate real gastric physiology, pH shifts after meals, motility generates forces the paddle apparatus cannot simulate, so *in vitro* floating success does not guarantee human gastric retention. This is the same gap that defines this section's central finding: no oral micro-sponge-specific system has reached a validated human pharmacokinetic study or clinical trial. Animal-level evidence does exist for a subset: apigenin[36] and thyme oil[28] H. pylori microsponges confirmed gastric floating in live rats by ultrasonography, and carbamazepine microsponges achieved a 2.6-times AUC increase in albino rabbits[37], genuine *in vivo* results, not merely *in vitro* proxies, but none progressed beyond a single animal species. The closest more complete comparator is a silymarin gastroretentive matrix tablet, not a microsponge, which doubled Cmax and AUC with scintigraphy-confirmed 12-hour gastric residence[38], evidence for

gastroretentive delivery generally but not transferable to micro-sponges given the different size scale and buoyancy mechanism. Why this human/clinical gap persists is addressed directly in Section 6.

5. THERAPEUTIC APPLICATIONS, MARKETED PRODUCTS, AND PATENT LANDSCAPE

This section compares bench-stage evidence for domperidone, carbamazepine, curcumin, and H. pylori phytochemicals against the marketed and patented reality of the technology as a whole. The answer diverges sharply by route: extensive marketed and patented history exists for topical products, while oral applications remain confined to preclinical literature.

5.1 Named Drug Examples

Domperidone's gastroretentive microsponge formulation prolongs gastric residence for a drug whose therapeutic target (gastroparesis) is local rather than systemic[8], but does not address the first-pass metabolism problem itself; retention increases local exposure without bypassing hepatic clearance. Carbamazepine has the strongest evidence trail: Abdalla et al.'s ethyl cellulose/PVA microsponges achieved a 2.6-times AUC increase in albino rabbits[37], the single most complete *in vivo* result in this literature. Curcumin's dedicated micro-sponge formulation (Bhatia and Saini) achieved 93.2% entrapment efficiency and released 93.2% of drug over 8 hours with zero-order kinetics, versus 11.7% for pure curcumin[39], correcting an earlier assumption in this review that no such study existed, though it remains *in vitro* only.

5.2 Helicobacter pylori and Narrow Absorption Window Drugs

Three phytochemicals, luteolin[33], apigenin[36], and thyme oil[28], have each been formulated as Eudragit-based gastroretentive microsponges with confirmed antibacterial activity and *in vivo* gastric floating in rats, the closest this literature comes to combining gastroretentive design with a therapeutically relevant endpoint. Conspicuously absent is any microsponge formulation of the antibiotics actually used in first-line H. pylori therapy (amoxicillin, clarithromycin, metronidazole); this body of work's clinical relevance depends on phytochemicals eventually being validated as therapy in their own right. Gastroretentive delivery is also proposed more broadly for narrow-absorption-window drugs (metformin, captopril, riboflavin, levodopa)[40], but none has a dedicated micro-sponge formulation; the rationale functions as a stated design justification rather than matched empirical evidence.

5.3 Marketed Products and Patents: The Topical-Only Reality

Against this preclinical evidence, the commercial history tells a different story, this review's central payoff finding. Every marketed micro-sponge product is topical: Retin-A Micro (tretinoin, 1997)[5,41], Carac (fluorouracil)[42], EpiQuin Micro, and Lactrex 12%[43]. Table 5 sets this record against the oral evidence above; no oral micro-sponge product has reached market or late-stage regulatory status anywhere in the record reviewed.

Table 5. Marketed micro-sponge products compared with oral micro-sponge drug candidates reviewed in this paper

Product / Candidate	Route	Indication / Target	Regulatory / Development Status
Retin-A Micro (tretinoin 0.1%)	Topical	Acne vulgaris	FDA-approved; marketed since 1997[6,42]
Carac (fluorouracil 0.5%)	Topical	Actinic keratosis	FDA-approved; marketed[43]
EpiQuin Micro	Topical	Hyperpigmentation	Marketed[44]
Lactrex 12%	Topical	Moisturizer / OTC	Marketed[44]
Domperidone microsponge	Oral	Gastroparesis (antiemetic)	Preclinical only: *in vitro*[9]
Carbamazepine microsponge	Oral	Epilepsy (sustained release)	Preclinical only: animal PK (rabbit)[38]
Curcumin microsponge	Oral	Bioavailability enhancement	Preclinical only: *in vitro*[40]
Luteolin / apigenin / thyme oil microsponges	Oral	H. pylori eradication	Preclinical: animal floating data; no human PK[34,37,29]

The foundational patent (US 4,690,825, Won, 1987) was assigned to Advanced Polymer Systems[5] and later licensed for cosmetic, OTC, and prescription use, with follow-on patents (e.g., US 6,670,335 B2 for the fluorouracil formulation later marketed as Carac) built on the same process scope[23,44]. None claims an oral or gastroretentive application; the patent landscape, like the marketed-product record, is built entirely around topical use.

6. MANUFACTURING, REGULATORY, AND COMMERCIAL BARRIERS

Manufacturing, regulatory, and economic barriers compound each other rather than acting alone, which is why this section treats them as one connected argument rather than isolated observations.

6.1 Manufacturing and Scale-Up Challenges

Free-radical suspension polymerization is complex and poorly reproducible batch to batch[14]; quasi-emulsion solvent diffusion is easier to scale but leaves residual solvent, a bigger concern for an oral product[12]. This process sensitivity is demonstrable (stirring speed alone shifted particle size from 76.2 to 32.5 µm in one system)[22] and is precisely the risk category that regulatory data identifies as the dominant failure mode for complex oral delivery systems: stability and manufacturing challenges, not clinical failure, drove roughly a quarter of recent 505(b)(2) reformulation efforts[45]. No published study has taken an oral micro-sponge through a pilot-scale or GMP-representative run[29], so CMC documentation for a first-in-class product would have to be built largely from laboratory-scale data.

6.2 Regulatory Pathway

A pathway for oral gastroretentive delivery does exist, Glumetza (metformin, Depomed's Acuform technology) was FDA-approved in 2005[46] and the Accordion Pill is a marketed gastroretentive product[47], with further examples across effervescent, swelling, and expandable-capsule mechanisms[48]. What none share with oral micro-sponges, however, is the underlying mechanism: every marketed gastroretentive product uses a single-unit swelling, expanding, or effervescent design, not a multiparticulate reservoir of

diffusion-controlled porous microspheres. A sponsor would not need to establish that gastroretentive delivery is approvable, but would still be first to establish that this specific mechanism performs predictably in humans, without a prior approved product of the same class to reference.

6.3 Economic Case

Full new-chemical-entity development averages an estimated $2.6 billion; even the cheaper 505(b)(2) pathway requires an estimated $15–100 million[45], much of it now absorbed by exactly the manufacturing risk oral micro-sponges have not resolved. The technology's current owners have little incentive to pursue oral development when the topical franchise already generates three decades of lower-risk revenue, and a new entrant would compete against already-approved gastroretentive technologies without comparative human evidence that micro-sponges outperform them. The absence of clinical translation is therefore the predictable result of formulation-stage promise never paired with a commercial case strong enough to fund the work required to test it.

7. RECENT ADVANCES AND FUTURE PERSPECTIVES

Recent progress is concentrated on manufacturing rather than the oral-translation gap. Cyclodextrin-based ‘nanosponges’ are a structurally different, nanometre-scale platform despite the overlapping name[49] and should not be read as evidence for the oral gastroretentive systems discussed here. AI/ML-driven formulation optimization[50] and 3D printing (levetiracetam/Spritam is the first FDA-approved 3D-printed drug)[51] are both advancing rapidly elsewhere in pharmaceutical science but have not yet been applied to oral micro-sponges specifically.

Three priorities follow directly from the barriers identified. First, a pilot- or GMP-representative manufacturing run with stability data against full ICH Q1A(R2) timeframes. Second, extending the existing carbamazepine result[37] toward full pharmacokinetic parameters and, if successful, a first-in-human bridging study, the most defensible next step given it already carries this literature's strongest *in vivo* evidence. Third, combining the micro-sponge core with established floating excipients rather than relying on intrinsic buoyancy. None of these requires a new formulation concept; each pushes the existing technology one stage further along the translation pathway.

CONCLUSION

Oral micro-sponge delivery systems present a mechanistically coherent, thoroughly characterized formulation-stage case for solving three genuinely different problems: extensive first-pass metabolism, a narrow therapeutic index compounded by poor solubility, and dissolution-limited bioavailability. This formulation-stage achievement, however, has not translated into oral clinical or commercial reality: zero marketed oral products exist against an extensive topical marketed history; zero human pharmacokinetic or clinical data exist against a small but genuine body of animal-level evidence; and the patent landscape remains built entirely around topical claims. The reasons are specific and compounding, unresolved manufacturing reproducibility, no mechanism-specific regulatory precedent, and a commercial case never made against already-approved competing technologies, rather than a simple need for more research.

The next contribution this field needs is not another polymer-ratio optimization study, of which the literature already contains many, but the first pilot-scale, regulatory-facing pharmacokinetic bridging study built on the

strongest existing evidence, most plausibly the carbamazepine microsponge system. Until that study is undertaken, oral micro-sponge delivery will remain a promising formulation technology rather than a delivered one.

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