TECHNICAL DISCLOSURE 03

Multi-Mechanism Oral Delivery Architecture for the Metabolic-Peptide Class

GLP-1 Receptor Agonists, GLP-1/GIP Dual Agonists, GLP-1/GIP/Glucagon Triple Agonists, GLP-1/Glucagon Dual Agonists, and Amylin Analogs, combining transcellular hydrophobization, paracellular tight-junction modulation, mucus fluidization, selective tight-junction opening, and mucoadhesive gastric retention

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The subject matter of this disclosure is a multi-mechanism oral delivery architecture for the metabolic-peptide class at 3-to-5-kilodalton molecular weight, encompassing glucagon-like peptide-1 receptor agonists (semaglutide, liraglutide, exenatide), glucose-dependent insulinotropic polypeptide / GLP-1 dual agonists (tirzepatide), GIP / GLP-1 / glucagon triple agonists (retatrutide), GLP-1 / glucagon dual agonists (survodutide), and amylin analogs (cagrilintide) either as monotherapy or co-formulated with a GLP-1 receptor agonist. The architecture combines, in coordinated operation within a single immediate-release tablet, six subsystems: a pH-buffering

and transcellular hydrophobization agent (sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, SNAC) at 200 to 400 milligrams; an ionic-liquid dual-mode paracellular, mucus-fluidization, and peptide-stability enhancer (choline and geranate, CAGE, or analog) at 30 to 80 milligrams; a selective tight-junction modulator (PIP640 analog decapeptide or low-molecular-weight chitosan) at 2 to 10 milligrams; a poly(ethylene glycol)-coated poly(lactide-co-glycolide) nanoparticle carrier (50 to 200 nanometer mean diameter, 2 kilodalton PEG shell, 50:50 lactide:glycolide core with acid-sensitive acetal crosslinker); a mucoadhesive outer tablet matrix (thiolated chitosan or chitosan-glutathione copolymer) at 20 to 50 milligrams; and standard pharmaceutical excipients, with tablet mass strictly at least 650 milligrams, disintegration time strictly at least 23 minutes, and bulk density strictly below 1.0 grams per cubic centimeter, in each case placing the composition strictly outside the independent-claim space of Novo Nordisk WO 2013/189988 and its granted continuations. A secondary embodiment incorporates a pulsed-field ingestible device operating at 10 to 100 kilohertz with 1 to 10 volts per centimeter transmembrane amplitude at 1 percent duty cycle for device-assisted payload delivery at reduced peptide dose. A Mitragotri-independent variant embodiment for each peptide omits CAGE and substitutes augmented selective tight-junction modulation plus trimethyl chitosan, preserving the route-additive

architecture without dependency on Harvard / Cage Bio CAGE licensing. The architecture achieves predicted theoretical oral bioavailability of 4 to 14 percent in humans (nominal 8.6 percent) across the uncertainty band from published ex-vivo and animal data on component mechanisms, against the approximately 1 percent oral bioavailability of the published SNAC-only Rybelsus architecture. Effective bioavailability pre-bench, applying translation penalties on the CAGE paracellular term for gastric-corpus deployment (geranic acid pKa approximately 5.2 and sub-Banerjee local concentration and gastric-corpus vs Caco-2 claudin profile differences), is 2 to 7 percent (nominal approximately 3.6 percent), 2-to-7-fold Rybelsus. Peptide-specific F bands shift by 6 to 12 percent around these class-level numbers reflecting molecular-weight, charge, and lipidation differences; per-peptide quantitative budgets, dose envelopes, and compositional specifications are in the peptides subdirectory of the companion deposit. Alternative embodiments, parameter ranges, enablement specifications, numbered figures, and per-peptide claim-species enumeration are given below. This document is published as prior art under 35 U.S.C. §102 for defensive purposes as of the publication date above.

§ 1

Title and Filer

The invention disclosed herein is titled *Multi-Mechanism Oral Delivery Architecture for the Metabolic-Peptide Class (GLP-1 Receptor Agonists, GLP-1/GIP Dual Agonists, GLP-1/GIP/Glucagon Triple Agonists, GLP-1/Glucagon Dual Agonists, and Amylin Analogs), Combining Transcellular Hydrophobization, Paracellular Tight-Junction Modulation, Mucus Fluidization, Selective Tight-Junction Opening, and Mucoadhesive Gastric Retention*. The filer of record is Coracle Research. The effective publication date is the date stated in the masthead and in the filer block above. A preprint copy of this disclosure is deposited on Zenodo under DOI 10.5281/zenodo.19768434 for examiner-searchable durability. A PDF paper copy is available for download from the primary venue. A companion narrative research note, referenced above, describes the same subject matter in a more accessible register.

§ 2

Field of the Invention

The invention relates to oral pharmaceutical delivery of peptide therapeutics, and more particularly to immediate-release tablet and ingestible-capsule architectures for gastric and duodenal absorption of metabolic peptides of molecular weight 3 to 5 kilodaltons and with either fatty-acid-modified amino-acid side chains providing plasma-albumin binding with elimination half-lives in the 100 to 200 hour range or with native sequence-based protease resistance enabling shorter-interval dosing. The architecture is specified for seven clinically relevant peptides: semaglutide (Lau et al. 2015, *J Med Chem* 58:7370, 4113.58 Da, C18 diacid at Lys26 via gamma-glutamate-plus-twin-mini-PEG linker, GLP-1 receptor agonist) at doses in the range 0.1 to 7.5 milligrams per tablet administered once daily; liraglutide (Knudsen et al. 2000, *J Med Chem* 43:1664, 3751.20 Da, C16 monoacyl at Lys26 via gamma-glutamate spacer, GLP-1 receptor agonist) at 0.25 to 75 milligrams per tablet once daily or equivalent twice-daily regimens; tirzepatide (Coskun et al. 2018, *Mol Metab* 18:3, 4813.48 Da, C20 fatty diacid at Lys20 via gamma-glutamate-plus-mini-PEG linker, GLP-1/GIP dual agonist) at 0.25 to 75 milligrams per tablet once daily; exenatide (Eng et al. 1992, 4186.57 Da, unlipidated exendin-4 sequence, GLP-1 receptor agonist) at 0.01 to 7.5 milligrams per tablet administered twice daily, thrice daily, or as an alternative pulsed-field ingestible capsule secondary-embodiment regimen per § 11.4 below; cagrilintide (Kruse 2021, *J Med Chem* 64:11183, 4409.01 Da, C20 fatty diacid at the N-terminus via gamma-glutamate-plus-mini-PEG linker, amylin analog) either as monotherapy at 0.125 to 15 milligrams per tablet once daily or in fixed-dose combination with semaglutide at near-equimolar mass ratios covering the Novo subcutaneous CagriSema 2.4-milligram-plus-2.4-milligram-weekly regimen scaled to oral daily dosing; retatrutide (Coskun et al. 2022, *Cell Metab* 34:1234; Rosenstock et al. 2023, *Lancet* 402:529, 4731.33 Da, C20 fatty diacid at Lys16 or Lys17 via gamma-glutamate-plus-2-(2-aminoethoxy)ethoxyacetyl linker, GLP-1/GIP/glucagon triple agonist) at 0.25 to 75 milligrams per tablet once daily; and survodutide (Wilding et al. 2024, *Lancet Diabetes Endocrinol* 12:220; Loomba et al. 2024, *NEJM* 390:1661, 4231.63 Da, 29-amino-acid glucagon-derived sequence, C18 fatty diacid at Lys24 via gamma-glutamate spacer, GLP-1/glucagon dual agonist) at 0.1 to 30 milligrams per tablet

once daily or as a divided twice-daily regimen. Per-peptide quantitative specifications, physicochemical profiles, SC pharmacokinetic references, F budget transpositions, dose-envelope tables, and peptide-specific prior art are given in the peptides subdirectory of the companion deposit, with files *peptides/semaglutide.md*, *peptides/liraglutide.md*, *peptides/tirzepatide.md*, *peptides/exenatide.md*, *peptides/cagrilintide.md*, *peptides/retatrutide.md*, and *peptides/survodutide.md*. The invention addresses the combined management of four concurrent absorption barriers across the gastrointestinal mucosa whose simultaneous handling determines the feasibility of any practical oral peptide architecture: luminal proteolytic degradation by pepsin, trypsin, chymotrypsin, and related gastric and pancreatic peptidases; mucus-layer diffusion across an 80-micrometer adherent mucin gel with 100-to-500-nanometer mesh spacing; transepithelial crossing across a gastric-corpus or duodenal columnar epithelium with transepithelial electrical resistance approximately 1000 ohm square centimeters and tight-junction pore diameter approximately 4 nanometers; and first-pass hepatic-metabolism retention, which for the lipidated-peptide subclass is preserved by plasma-albumin binding via the fatty-acid side chain and which for the unlipidated exenatide is preserved at this MW and charge range by hepatic non-extraction.

§ 3

Background and Prior Art

Four absorption-barrier mechanisms constrain the oral bioavailability of peptide therapeutics at 3 to 8 kilodalton molecular weight with zwitterionic character and LogP in the range −4 to −6 (semaglutide LogP = −5.8 per Lau 2015). Each barrier has been individually addressed in the published literature by one or more permeation-enhancer, encapsulation, or device-assisted strategies. No published architecture known to the filer combines the specific six-subsystem formulation and two-route absorption mechanism disclosed herein at the performance target of 4 to 14 percent predicted human oral bioavailability with the dose-envelope flexibility disclosed in §6 below.

Luminal proteolytic degradation. Pepsin (aspartic protease, pH optimum 1.5 to 2.5; Heda, Toro & Tombazzi 2025, StatPearls NBK537005) hydrolyzes semaglutide at preferential cleavage sites Tyr13-Leu14 and Phe22-Ile23 under fasted gastric pH of 1 to 2. Pancreatic trypsin and chymotrypsin hydrolyze further cleavage sites in the duodenum. Current SNAC-only Rybelsus architecture addresses pepsin via local pH buffering to 5 to 6 (Buckley et al. 2018, *Sci Transl Med* 10:eaar7047; Twarog et al. 2019, *Pharmaceutics* 11:78), raising the local microenvironment above pepsin activity threshold; Colston et al. 2025 (*Nat Commun* 16:9512; PMC12568990) further established via 1-microsecond continuous constant-pH molecular dynamics of POPC/cholesterol 60:40 bilayer + approximately 400 SNAC molecules + 1 semaglutide peptide that the SNAC molecules form dynamic, partially fluid membrane defects into which the semaglutide peptide is submerged in a “quicksand-like” mechanism, with favorable free-energy for C18-diacid tail insertion (ΔG = −5.0 kcal per mole) and a rate-limiting barrier of +7.5 kcal per mole for full transleaflet crossing. No architecture in the cited prior art addresses pepsin degradation simultaneously by SNAC-mediated pH buffering, ionic-liquid-mediated water activity reduction around the peptide, and nanoparticle encapsulation, as disclosed in §5 below.

Mucus-layer diffusion. The adherent gastric mucus layer is 80 micrometers thick in the corpus (Atuma et al. 2001, *Am J Physiol Gastrointest Liver Physiol* 280:G922) with 100-to-500-nanometer mesh spacing (Lai, Wang & Hanes 2009, *Adv Drug Deliv Rev* 61:158) and viscosity 1000 to 10000 times water at low shear (Cone 2009, *Adv Drug Deliv Rev* 61:75). Particles up to 500 nanometers with dense 2-kilodalton poly(ethylene glycol) coating and near-neutral zeta potential penetrate mucus at approximately one-quarter the diffusion coefficient expected in pure water (Ensign et al. 2012, *Adv Mater* 24:3887); this design rule is the foundation of mucus-penetrating particle (MPP) architectures. Free semaglutide at 4114 daltons diffuses through mucus approximately 10 times slower than in water, limiting accessible dose at the epithelial surface. Banerjee et al. 2018 (*Proc Natl Acad Sci USA* 115:7296; PMC6048483) separately established that choline-geranate (CAGE) ionic liquid at 1 to 5 percent weight per volume significantly decreases mucin hydrogel viscosity, providing a chemically distinct mechanism of mucus fluidization. No prior art combines MPP nanoparticle design with CAGE mucus fluidization.

Transepithelial crossing. The gastric-corpus epithelium comprises single-layered columnar surface mucous (foveolar) cells with claudin-3, claudin-4, and claudin-18 as the predominant tight-junction claudin isoforms (Maher, Brayden, Feighery & McClean 2019, *Pharmaceutics* 11:41), transepithelial electrical resistance approximately 1000 ohm square centimeters, and tight-junction pore diameter approximately 4 nanometers. Transcellular and paracellular routes have been addressed in prior art by distinct enhancer classes. SNAC produces primarily transcellular absorption for semaglutide via the Colston 2025 quicksand mechanism, with negligible tight-junction opening confirmed via 4-kilodalton FITC-dextran exclusion (Buckley 2018, Twarog 2019). CAGE produces primarily paracellular transport in Caco-2 monolayers: Banerjee 2018 reported 13-fold enhancement of 4-kilodalton FITC-dextran paracellular flux with 40-to-50-percent transepithelial electrical resistance reduction at high CAGE concentrations, against no measurable 4-kilodalton FITC-dextran flux with SNAC alone. Because the transcellular and paracellular routes are physically orthogonal across the same cell monolayer, their mechanisms combine additively on F_epithelium without cross-interference, as disclosed in §6 below.

First-pass hepatic metabolism. The C18 diacid side chain attached at Lys26 of semaglutide (Lau 2015; Knudsen & Lau 2019, *Front Endocrinol* 10:155) binds plasma albumin with sub-micromolar affinity, preserving the peptide from glomerular filtration and providing the 168-hour plasma elimination half-life that enables once-weekly subcutaneous dosing. Once absorbed into portal blood, semaglutide is not significantly metabolized in first pass through the liver; the plasma half-life is effectively set by the albumin-bound peptide's reduced-clearance pharmacokinetics. The architecture disclosed in §5 preserves the C18 diacid modification unchanged and does not modify the first-pass pharmacokinetics.

Individual prior-art interventions against each barrier have been published. No publication known to the filer combines all four interventions with the specific route-additive paracellular-plus-transcellular epithelial-crossing architecture disclosed herein at the oral semaglutide application. The most relevant prior art is enumerated below.

1. S. Bjerregaard, P. Sauerberg, F. F. Nielsen, B. L. Pedersen, R. B. Skibsted (Novo Nordisk AS), "Tablet formulation comprising a peptide and a delivery agent," WO 2013/189988 A1, priority 2012-06-20, published 2013-12-27; U.S. counterparts including US 9,993,430 B2 (granted 2018-06-12) and US 11,033,499 B2 (continuation). Discloses the Rybelsus tablet composition. Independent claim 1 of WO2013189988 recites a tablet comprising a granulate with (i) no more than 15 percent weight per weight GLP-1 peptide and (ii) at least 50 percent weight per weight salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid (SNAC). The US 9,993,430 B2 independent claim adds: bulk density at least 1.0 grams per cubic centimeter, median pore diameter at most 1.5 micrometers, maximum pore diameter at most 4 micrometers, crushing strength at least 50 newtons, and disintegration time 12 to 18 minutes (the disintegration element is restricted to tablets of 300 to 500 milligrams total weight comprising at least 60 percent SNAC). The US 11,033,499 B2 continuation broadens element (c) to "a feature selected from the group consisting of a maximum pore diameter of no more than 4 micrometers, a crushing strength of 50 to 400 newtons, and a disintegration time of 22 minutes or less." Dependent claims 6 (US 9,993,430) and 7 (US 11,033,499) narrow peptide to 1 to 15 percent, SNAC to 55 to 85 percent, and lubricant to 0.5 to 3 percent; these are dependent and do not broaden the independent scope. The closest prior art on tablet physical parameters. Does not disclose the ionic-liquid dual-mode enhancer (Component C in §4 below), the selective tight-junction modulator (Component D), the mucus-penetrating nanoparticle carrier (Component E), or the mucoadhesive outer matrix (Component F); does not disclose route-additive paracellular-plus-transcellular architecture; does not disclose human oral bioavailability above approximately 1 percent. The disclosed architecture specifies tablet mass at least 650 milligrams with 300 milligrams SNAC, giving SNAC weight fraction at most 46.2 percent, strictly below the 50 percent independent-claim floor; and specifies disintegration time at least 23 minutes, strictly above the 22 minute US 11,033,499 continuation ceiling. These strict exclusions place the architecture outside the Novo independent claims on two elements.

2. Emisphere SNAC patent family, including C. Goldberg and I. Gomez-Orellana (Emisphere Technologies), "Process for the manufacture of SNAC (salcaprozate sodium)," WO 2008/028859 A1, and predecessor SNAC polymorphic-form and composition patents originating 1996-2005. Discloses SNAC as a delivery agent for macromolecules across multiple peptide classes, including but not limited to salmon calcitonin, insulin, human growth hormone, and heparin, with clinical-stage development at Emisphere under the Eligen® trade name. Establishes SNAC transcellular hydrophobization mechanism. Subsequently acquired by Novo Nordisk as part of the Rybelsus development. Does not disclose the ionic-liquid dual-mode enhancer or the route-additive paracellular-plus-transcellular architecture.

3. A. Banerjee, K. Ibsen, T. Brown, R. Chen, C. Agatemor, S. Mitragotri, "Ionic liquids for oral insulin delivery," *Proc Natl Acad Sci USA* 115:7296 (2018); and K. N. Ibsen, H. Ma, A. Banerjee, E. E. L. Tanner, S. Nangia, S. Mitragotri, "Mechanism of Antibacterial Activity of Choline-Based Ionic Liquids (CAGE)," *ACS Biomater Sci Eng* 4:2370 (2018). Discloses CAGE ionic liquid composition (choline and geranate, 1:2 molar ratio) for oral insulin delivery. Demonstrates 45 to 51 percent oral bioavailability of insulin in rat intrajejunal model; 13-fold enhancement of 4-kilodalton FITC-dextran paracellular flux in Caco-2 monolayers; 40-to-50-percent reduction in transepithelial electrical resistance; significant reduction in mucin hydrogel viscosity; partial protection from enzymatic degradation. The closest prior art on ionic-liquid permeation enhancement at intestinal epithelium. Directed to insulin as the payload, not to lipidated GLP-1 receptor agonists, and does not disclose combination with SNAC transcellular hydrophobization, does not disclose combination with selective claudin-2 tight-junction modulator, does not disclose combination with mucus-penetrating nanoparticle carrier, and does not disclose the semaglutide and semaglutide-class dose-envelope framework.

4. C. Agatemor, K. N. Ibsen, E. E. L. Tanner, S. Mitragotri, "Choline-Geranate Deep Eutectic Solvent Improves Stability and Half-Life of Glucagon-Like Peptide-1," *Adv Ther* 4:2000180 (2021). Discloses CAGE formulation with native GLP-1 for subcutaneous delivery, with four-fold area-under-curve enhancement versus saline, mediated by DPP-4 inhibition and by CAGE self-assembly. Directed to subcutaneous delivery of non-lipidated native GLP-1, whose DPP-4 vulnerability distinguishes it from the Aib8-substituted semaglutide class which is natively DPP-4 resistant. Does not disclose oral delivery, does not disclose combination with SNAC, does not disclose the route-additive absorption framework, and does not disclose dose-envelope optimization for the lipidated GLP-1 receptor agonist class.

5. E. E. L. Tanner, K. N. Ibsen, S. Mitragotri, "Design Principles of Ionic Liquids for Transdermal Drug Delivery," *Adv Mater* 31:1901103 (2019). Discloses a design framework for choline-based ionic liquid permeation enhancers, screening 16 variants against two model drugs with different hydrophilicities, identifying 1:2 choline-to-fatty-acid-anion molar ratio as the general-potency optimum, and establishing inverse correlation between inter-ionic interaction strength (from 2-dimensional NMR) and transdermal delivery potency. Directed to transdermal, not oral, delivery. Does not disclose oral-peptide application, does not disclose combination with SNAC or other transcellular hydrophobizers, and does not disclose the route-additive absorption framework.

6. J. J. Neville, M. Dobre, J. A. Smith, S. Micciulla, N. J. Brooks, T. Arnold, T. Welton, K. J. Edler, "Interactions of Choline and Geranate (CAGE) and Choline Octanoate (CAOT) Deep Eutectic Solvents with Lipid Bilayers," *Adv Funct Mater* 34:2306644 (2024). Discloses neutron-reflectivity, quartz-crystal-microbalance-with-dissipation, dynamic-light-scattering, and NMR characterization of CAGE at solid-supported DMPC phospholipid bilayers. Characterizes CAGE as a mild disruptive agent that inserts and diffuses across the bilayer, preserving bilayer integrity. CAOT (choline octanoate analog) characterized as more disruptive, with lipid exchange and removal. The closest prior art on CAGE physical interaction with phospholipid bilayers; consistent with the mild-perturbation picture assumed in this disclosure.

7. S. Maher, D. J. Brayden, L. Feighery, S. McClean, “Application of Permeation Enhancers in Oral Delivery of Macromolecules: An Update,” *Pharmaceutics* 11:41 (2019). Discloses a comprehensive taxonomy of permeation enhancers for oral peptide delivery, including Class I transcellular hydrophobization (SNAC, 5-CNAC, HIP complexation), Class II transcellular membrane perturbation (sodium caprate C10, acylcarnitines, bile salts, sucrose laurate), Class III first-generation paracellular tight-junction openers (EDTA, chitosan), Class IV second-generation paracellular tight-junction openers (zonula occludens toxin, Clostridium perfringens enterotoxin, PIP640 decapeptide), and discussions of ionic-liquid enhancers including CAGE. Discloses the PIP640 selective claudin-2-targeted tight-junction modulator. The closest prior art on permeation enhancer taxonomy. Does not disclose the specific four-enhancer combination (Components B, C, D plus mucoadhesive F) or the route-additive epithelial-crossing architecture.

8. D. J. Brayden, T. A. Hill, D. P. Fairlie, S. Maher, R. J. Mrsny, “Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches,” *Adv Drug Deliv Rev* 157:2 (2020). Comprehensive review of oral peptide delivery architectures including enhancer, nanoparticle, and device approaches. Referenced for its summary of Phase III oral peptide formulations (salmon calcitonin, octreotide, semaglutide), nanoparticle approaches in EU FP7 TRANS-INT, and disruptive devices (SOMA, LUMI, RaniPill). State-of-the-art reference at the date of this disclosure.

9. A. Abramson, E. Caffarel-Salvador, M. Khang, D. Dellal, D. Silverstein, Y. Gao, M. R. Frederiksen, A. Vegge, F. Hubálek, J. J. Water, A. V. Friderichsen, J. Fels, R. K. Kirk, C. Cleveland, J. Collins, S. Tamang, A. Hayward, T. Landh, S. T. Buckley, N. Roxhed, U. Rahbek, R. Langer, G. Traverso, “An ingestible self-orienting system for oral delivery of macromolecules,” *Science* 363:611 (2019); and supporting patent family including US 10,639,226 B2. Discloses the Self-Orienting Millimeter-scale Applicator (SOMA) ingestible device for intragastric delivery of macromolecules via a millimeter-scale needle that penetrates the gastric mucosa. The closest prior art on active-delivery ingestible devices for peptide delivery. Directed to mechanical needle-based gastric wall insertion, not to low-voltage pulsed-field transmembrane stimulation as disclosed in §7 of the present architecture.

10. M. Imran et al. (Rani Therapeutics), ingestible capsule patent family including US 10,814,114 B2 (filed 2014, granted 2020), US 11,541,150 B2, and related continuations. Discloses the RaniPill ingestible capsule with pH-triggered enteric coating, gas-generating balloon for mechanical actuation, and dissolvable microneedle for intestinal-wall drug delivery. Closest device-based prior art. Directed to intestinal-wall microneedle penetration. Does not disclose low-voltage pulsed-field epithelial stimulation, and does not disclose the six-component tablet-based architecture.

11. L. M. Ensign, C. Schneider, J. S. Suk, R. Cone, J. Hanes, “Mucus Penetrating Nanoparticles: Biophysical Tool and Method of Drug and Gene Delivery,” *Adv Mater* 24:3887 (2012). Peer-reviewed paper establishing mucus-penetrating-particle (MPP) design rules: 50 to 500 nanometer size range, dense 2-kilodalton poly(ethylene glycol) surface coating via PLGA-PEG block copolymer, near-neutral zeta potential (-10 to +10 millivolts). The 2012 paper’s design principles are in the public domain. The Hanes-group patent family on MPP-related compositions comprises multiple granted US patents with differing claim scope: US 8,889,193 B2 is a method-of-treatment patent restricted to ocular injection or instillation (not applicable to oral pharmaceutical tablets); US 9,056,057 B2 covers nanocrystal compositions requiring drug core at least 80 percent weight of particle and drug aqueous solubility at most 1 milligram per milliliter (semaglutide solubility is approximately 50 milligrams per milliliter, placing the architecture outside); US 9,415,020 B2 and US 9,629,813 B2 cover hypotonic aqueous excipient formulations whose water-uptake mechanism requires an aqueous excipient (solid tablet form does not satisfy); WO 2017/075565 A1 covers MPP compositions with polyalkylene oxide surface coating of molecular weight greater than approximately 5 kilodaltons up to 100 kilodaltons. The disclosed architecture uses PEG 2 kilodaltons, solid tablet form, and PLGA-PEG diblock copolymer, placing it outside every granted Hanes MPP patent examined on molecular-weight, solubility, copolymer-architecture, or excipient-form elements. The Ensign 2012 peer-reviewed design principles are acknowledged as prior art at the design-principle level. Does not disclose combination with ionic-liquid permeation enhancers, does not disclose oral-semaglutide application.

12. S. T. Buckley, T. A. Bækdal, A. Vegge et al., “Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist,” *Sci Transl Med* 10:eaar7047 (2018). Discloses the mechanism of SNAC-mediated oral semaglutide absorption, establishing that absorption occurs at the gastric corpus (not the intestine), that the mechanism is transcellular (not paracellular), that SNAC acts via local microenvironment pH buffering to approximately pH 5, that no detectable systemic SNAC absorption occurs (SNAC is rapidly degraded in gastric mucus), and that no tight-junction disruption is detectable by 4-kilodalton FITC-dextran exclusion. Canonical reference for SNAC transcellular mechanism.

13. K. J. Colston, K. T. Faivre, S. T. Schneebeli, “Permeation enhancer-induced membrane defects assist the oral absorption of peptide drugs,” *Nat Commun* 16:9512 (2025); PMC12568990. Discloses a 1-microsecond continuous constant-pH molecular dynamics simulation of the SNAC-semaglutide membrane-insertion mechanism, with a POPC:cholesterol 60:40 bilayer, approximately 400 SNAC molecules, one semaglutide peptide, 64 lipids per leaflet, and pH 5.0. Observed mechanism: dynamic, partially fluid SNAC-filled membrane defects in which the semaglutide peptide is submerged “in a process analogous to quicksand.” Computed free-energy values: ΔG for semaglutide C18 diacid tail insertion = −5.0 kilocalories per mole; ΔG trans-leaflet crossing barrier = +7.5 kilocalories per mole. The closest computational prior art on SNAC mechanism for oral semaglutide.

14. C. Twarog, S. Fattah, J. Heade, S. Maher, E. Fattal, D. J. Brayden, “Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10),” *Pharmaceutics* 11:78 (2019); PMC6410172. Comparative review of the two most clinically advanced permeation enhancers, with specific bioavailability data across multiple peptides. Confirms Rybelsus human bioavailability at approximately 1 percent, Rybelsus dog bioavailability at 1.22 ± 0.25 percent at 300 milligrams SNAC plus 5 to 20 milligrams semaglutide, and establishes that SNAC alone does not open gastric tight junctions.

15. A. C. Langer et al. (MIT / Brigham and Women’s Hospital), pulsed-field transdermal and transmucosal drug delivery patent family. Relevant for the Component F pulsed-field secondary embodiment in §7 below. Also: J. Srinivasan, A. Abramson, G. Traverso, R. Langer, “Micro-scale transdermal drug-delivery devices,” publications 2017-2024. Directed to pulsed-field transdermal and intestinal-wall delivery. Does not disclose gastric-epithelium pulsed-field application at the specific 10-to-100-kilohertz frequency and 1-to-10-volts-per-centimeter amplitude range disclosed herein.

16. Rogers and Gurau (University of Alabama), “Is choline and geranate an ionic liquid or deep eutectic solvent system?” *PNAS* 115:E11000 (2018). Classifies CAGE as an ionic liquid with complex anion [choline][geranate$_2$H]. Referenced for nomenclature precision. Not directed to oral peptide delivery.

17. R. Kneiszl, S. Hossain, P. Larsson, “In Silico-Based Experiments on Mechanistic Interactions between Several Intestinal Permeation Enhancers with a Lipid Bilayer Model,” *Mol Pharm* 19:124 (2022); PMC8728740. Discloses a molecular-dynamics comparison of six permeation enhancers (laurate, caprate, caprylate, SNAC, neutral caprate, sucrose monolaurate) at a POPC bilayer via MARTINI coarse-grained and all-atom umbrella sampling. SNAC all-atom umbrella-sampling free energy of membrane partition: −1.30 kilocalories per mole. The paper’s 70 to 100 millimolar concentration range is cited specifically for sodium caprate and laurate as the onset of water-permeation effects in the POPC model; the paper does not extend this threshold to SNAC and notes that SNAC shows weaker membrane interaction than the medium-chain fatty acids in this system. The 70 to 100 millimolar figure is not a universal PE transcellular-effect threshold and is not SNAC-specific. Does not include CAGE in the comparison. Supporting prior art on SNAC membrane partition free-energy at the all-atom level.

18. NASA and international-space-agency prior art on oral peptide delivery is not applicable. No government-authored engineering-guidance documents on oral semaglutide or class architecture are relevant to this disclosure.

19. Standard biochemistry data for semaglutide physicochemical properties, including Lau et al. 2015 sequence and stereochemistry; Knudsen & Lau 2019 (*Front Endocrinol* 10:155, PMC6474072) historical development and design rationale for the C18-diacid-γGlu-2xOEG linker chemistry; C. Granhall et al. 2019 (*Clin Pharmacokinet* 58:781) oral semaglutide pharmacokinetic characterization.

20. Standard biochemistry and pharmaceutics data for SNAC, including Novo Nordisk composition tables in WO2013189988 and US 9,993,430 B2; J. Buckley et al. 2018 mechanistic characterization; Twarog et al. 2019 review; and Novo WO2014015175 and related continuation filings.

21. S. Mitragotri, A. Banerjee, T. Brown, K. N. Ibsen, C. Agatemor, E. E. L. Tanner, et al. (President and Fellows of Harvard College; The Regents of the University of California), "Ionic liquids for internal delivery," WO 2019/099837 A1, priority 2017-11-17, published 2019-05-23. U.S. national-stage US 2020/0289421 A1, filed 2020-05-07, under prosecution. Anticipated expiration approximately 2038-11-17. Independent claims recite: a method of oral delivery of at least one active compound, the method comprising orally administering the active compound in combination with a composition comprising an ionic liquid of Choline And GEranate (CAGE) (WO claim 1); a composition comprising an active compound in combination with CAGE (WO claim 24); the CAGE composition present at concentration at least 0.1 percent weight per volume or at least 5 percent weight per weight (WO claim 25); the choline:geranic acid or geranate ratio from about 2:1 to about 1:10 (WO claim 26) and more specifically from about 1:2 to about 1:4 (WO claim 28); the active compound comprising a GLP-1 polypeptide or mimetic or analog thereof (WO claim 22). The disclosed architecture's oral tablet with choline:geranate 1:2 at 30 to 80 milligrams CAGE (5 to 12 percent weight per weight at tablet mass 650 milligrams) with semaglutide as the lipidated GLP-1 analog active reads literally on the Mitragotri / Harvard independent method and composition claims at every recited element. The defensive publication acknowledges the Mitragotri / Harvard CAGE family as prior art on the CAGE component of the architecture; the architecture does not claim novelty on CAGE composition or on oral-peptide CAGE delivery as such, and does claim novelty on the combination of CAGE with SNAC transcellular hydrophobization, PIP640 analog or low-molecular-weight chitosan selective tight-junction modulator, PLGA-PEG mucus-penetrating nanoparticle carrier, and mucoadhesive outer matrix at the semaglutide and lipidated GLP-1 receptor agonist payload with the specific dose envelope and route-additive F_epithelium framing disclosed below. Commercial deployment of any CAGE-containing embodiment of the architecture requires a CAGE patent license from Harvard / Cage Bio; the defensive publication does not obviate this license requirement.

An additional body of work on oral peptide delivery has been published across the 2016 to 2026 window by groups at Emisphere/Novo Nordisk, Rani Therapeutics, the Langer and Traverso laboratories at MIT/BWH, the Mitragotri laboratory at Harvard/SEAS, the Brayden laboratory at University College Dublin, the Hanes laboratory at Johns Hopkins, the Jain laboratory at Ben-Gurion University, the Trapani laboratory at Bari, and numerous additional academic and industrial programs. The present disclosure extends that body of work by combining five distinct permeation-enhancer and formulation subsystems with a specific route-additive paracellular-plus-transcellular epithelial-crossing architecture, at the semaglutide and class-related lipidated GLP-1 receptor agonist payload, with the parameter windows, dose envelope, and alternative embodiments specified in the sections below.

The distinction of the present disclosure over the cited prior art is the specific combination of (a) SNAC transcellular hydrophobization plus (b) CAGE-analog ionic-liquid dual-mode paracellular plus mucus-fluidization plus hydration-shield enhancer plus (c) selective claudin-2-targeted tight-junction modulator plus (d) mucus-penetrating nanoparticle carrier plus (e) mucoadhesive outer matrix plus (f) optional pulsed-field secondary embodiment, at the semaglutide and lipidated GLP-1 receptor agonist payload class, with the dose envelope, parameter windows, and operational sequence specified in the sections below. No prior art disclosed to the filer combines all five permeation-enhancement and formulation mechanisms with the route-additive epithelial-crossing architecture at any peptide payload.

§ 4

Summary of the Invention

The present invention provides a multi-mechanism oral delivery architecture for semaglutide and class-related lipidated glucagon-like peptide-1 receptor agonists, comprising six coordinated subsystems within a single immediate-release tablet (primary embodiment) or a single ingestible capsule with embedded pulsed-field source (secondary embodiment).

Component A. Active pharmaceutical ingredient. A metabolic peptide of molecular weight 3 to 5 kilodaltons, selected from:

- **A1. Semaglutide** (Lau 2015), 4113.58 Da, GLP-1 receptor agonist, C18 diacid at Lys26 via gamma-glutamate-plus-twin-mini-PEG linker, at 0.1 to 7.5 milligrams per tablet once daily. See *peptides/semaglutide.md*.
- **A2. Liraglutide** (Knudsen 2000), 3751.20 Da, GLP-1 receptor agonist, C16 monoacyl at Lys26 via gamma-glutamate spacer, at 0.25 to 75 milligrams per tablet once daily or equivalent twice-daily regimens. See *peptides/liraglutide.md*.
- **A3. Tirzepatide** (Coskun 2018), 4813.48 Da, GLP-1 and GIP dual receptor agonist, C20 fatty diacid at Lys20 via gamma-glutamate-plus-mini-PEG linker, at 0.25 to 75 milligrams per tablet once daily. See *peptides/tirzepatide.md*.
- **A4. Exenatide** (Eng 1992), 4186.57 Da, GLP-1 receptor agonist (exendin-4 sequence), unlipidated, at 0.01 to 7.5 milligrams per tablet twice or thrice daily or administered via the pulsed-field ingestible capsule of § 11.4 at 0.05 to 0.5 milligrams per capsule twice daily. See *peptides/exenatide.md*.
- **A5. Cagrilintide** (Kruse 2021), 4409.01 Da, amylin analog, C20 fatty diacid at the N-terminus via gamma-glutamate-plus-mini-PEG linker, at 0.125 to 15 milligrams per tablet once daily as monotherapy or in fixed-dose combination with semaglutide 0.5 to 6.0 milligrams per tablet at near-equimolar mass ratio covering the Novo CagriSema 2.4-milligram-plus-2.4-milligram-weekly regimen scaled to oral daily dosing. See *peptides/cagrilintide.md*.

- **A6. Retatrutide** (Coskun 2022), 4731.33 Da, GLP-1/GIP/glucagon triple receptor agonist, C20 fatty diacid at Lys16 or Lys17 via gamma-glutamate-plus-2-(2-aminoethoxy)ethoxyacetyl linker, at 0.25 to 75 milligrams per tablet once daily. See *peptides/retatrutide.md*.
- **A7. Survodutide** (Wilding 2024), 4231.63 Da, 29-amino-acid glucagon-derived sequence, GLP-1/glucagon dual receptor agonist, C18 fatty diacid at Lys24 via gamma-glutamate spacer, at 0.1 to 30 milligrams per tablet once daily or as a divided twice-daily regimen. See *peptides/survodutide.md*.

For the lipidated active ingredients (A1, A2, A3, A5, A6, A7), the first-pass-preservation mechanism (fatty-acid albumin binding with 13-to-168-hour plasma elimination half-life depending on anchor chemistry) is unchanged by the delivery architecture. For the unlipidated active ingredient (A4 exenatide), first-pass retention is preserved at this MW and charge range by hepatic non-extraction; the shorter 2.4-hour plasma half-life requires BID or TID oral dosing as per the peptide-specific file. Peptide-specific F budget transpositions, dose envelope tables, and compositional adjustments are provided in the respective per-peptide files.

Component B. Transcellular hydrophobization and pH-buffering agent. Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC, salcaprozate sodium), molecular weight 301.34 daltons, at 250 to 500 milligrams per tablet, with nominal dose 300 milligrams matching Novo WO2013189988 composition window. Buffers the local gastric microenvironment from ambient pH 1 to 2 to approximately pH 5, deactivating pepsin (100-to-1000-fold K_cat reduction; Heda 2025 StatPearls). Forms the SNAC-filled partially fluid membrane defect within which the semaglutide peptide partitions into the apical bilayer of the gastric-corpus epithelium (Colston 2025 quicksand mechanism, $\Delta G_{tail} = -5.0$ kilocalories per mole).

Component C. Ionic-liquid dual-mode paracellular, mucus-fluidization, and peptide-stability enhancer. Choline and geranate (CAGE) ionic liquid at 1:2 choline-to-geranate molar ratio (Banerjee 2018 composition; Tanner 2019 design-principle optimum), or analog compositions including choline and oleate (CAOT variant; Neville 2024) or choline and other medium-chain fatty-acid anions at 1:2 molar ratio. Total dose 30 to 80 milligrams per tablet. Provides, by established published mechanism, three independent effects: (i) paracellular tight-junction modulation with approximately 13-fold enhancement of 4-kilodalton marker flux in Caco-2 monolayers and 40-to-50-percent transepithelial electrical resistance reduction (Banerjee 2018); (ii) mucus fluidization via significant mucin hydrogel viscosity reduction at 1-to-5-percent weight-per-volume CAGE (Banerjee 2018); (iii) peptide hydration-shell management via geranate-mediated water-activity reduction around the peptide (Palanisamy & Prakash 2021, PCCP d1cp03349b, atomistic MD in GROMACS 2020.4). CAGE is characterized experimentally as a mild disruptive agent at the phospholipid bilayer (Neville 2024, DMPC neutron reflectivity + QCM-D + DLS + NMR), preserving bilayer integrity while enabling the paracellular route.

Component D. Selective tight-junction modulator. PIP640 analog decapeptide with MYPT1-binding motif for cation-biased claudin-2-selective paracellular opening (Maher 2019 PE taxonomy Class IV), at 2 to 10 milligrams per tablet, with nominal 5-milligram dose. As an alternative when PIP640 analog

synthesis is not practical, low-molecular-weight chitosan (5 to 20 kilodalton, 75-to-90-percent deacetylation degree) at 5 to 10 milligrams per tablet provides complementary non-selective cationic tight-junction opening via occludin and ZO-1 redistribution.

Component E. Mucus-penetrating nanoparticle carrier. Poly(D,L-lactide-co-glycolide) PLGA nanoparticle core (50:50 lactide:glycolide, 10 to 30 kilodalton molecular weight, acid-sensitive acetal crosslinker triggering disassembly at pH 5 to 6) with dense 2-kilodalton poly(ethylene glycol) surface coating via PLGA-PEG block copolymer, 50 to 200 nanometer diameter (100-nanometer nominal), zeta potential −2 ± 4 millivolts at gastric pH conditions. Encapsulation target: 30 to 60 percent of the semaglutide dose and 20 to 40 percent of the SNAC dose are co-encapsulated (60 to 120 milligrams SNAC co-encapsulated with 0.6 to 1.2 milligrams semaglutide at nominal 2 milligram peptide plus 300 milligram SNAC), giving an effective SNAC:peptide molar ratio within the nanoparticle core of approximately 1000 to 2500 to 1. CAGE-analog remains as outer-shell co-formulation (not encapsulated). Ensign 2012 peer-reviewed mucus-penetrating-particle design rules are preserved at the design-principle level; the PEG 2 kilodalton molecular weight, diblock PLGA-PEG copolymer architecture, and semaglutide aqueous solubility place the nanoparticle outside the granted Hanes MPP patent family scope (see §3 reference 11).

Component F. Mucoadhesive outer tablet matrix. Low-molecular-weight chitosan (10 to 20 kilodalton, 80-to-90-percent deacetylation degree) or thiolated chitosan-glutathione copolymer at 20 to 50 milligrams per tablet, applied as the outer layer of the tablet for mucoadhesion to the gastric-corpus mucin sialic-acid and sulfate residues. Extends gastric residence from the Rybelsus approximately 1 hour to 2 to 4 hours, preserving the exposure window against gastric emptying.

Standard pharmaceutical excipients comprise microcrystalline cellulose (15 to 30 percent weight per weight of tablet) as filler, povidone (2 to 5 percent) as binder, magnesium stearate (0.5 to 3 percent) as lubricant, and optional colloidal silica (0.25 to 1 percent) as flow aid. Total tablet mass 650 to 800 milligrams (strict minimum 650 milligrams to ensure SNAC weight fraction at or below 46.2 percent, outside the Novo US 9,993,430 and US 11,033,499 “at least 50 percent SNAC” independent-claim floor), bulk density at or above 0.90 grams per cubic centimeter (WO 2013/189988 element) with architecture target range 0.90 to 1.00 (below the Novo US grant “at least 1.0” independent-claim element), crushing strength at or above 50 newtons, disintegration time 23 to 40 minutes (strict minimum 23 minutes to ensure outside the Novo US 11,033,499 “22 minutes or less” continuation-claim ceiling), full erosion time 90 to 120 minutes in 50 milliliters simulated gastric fluid.

The six components, in combination, produce a route-additive oral-absorption architecture. The absorption fraction F_epithelium comprises two independent parallel routes:

F_epithelium = F_transcellular + F_paracellular

where F_transcellular is produced primarily by Component B (SNAC quicksand mechanism) with a minor enhancement by Component C (CAGE mild bilayer perturbation) and F_paracellular is produced primarily by Component C (CAGE tight-junction modulation) and Component D (PIP640 selective

claudin-2 opening). The two routes are physically orthogonal and combine additively on F_epithelium without cross-interference.

The overall oral bioavailability F_total is

F_total = F_stability × F_mucus × F_epithelium × F_first_pass

with components:

- F_stability: 0.80 (pessimistic) to 0.92 (optimistic). Driven by Component B pH buffering (SNAC to pH 5 to 6), Component C peptide stabilization (CAGE hydration-shield water-activity reduction; Palanisamy 2021), Component E nanoparticle encapsulation (delayed release until pH 5 to 6 trigger), against published Rybelsus baseline of 0.75 (Buckley 2018, Twarog 2019).
- F_mucus: 0.65 (pessimistic) to 0.80 (optimistic). Driven by Component C mucin viscosity reduction (Banerjee 2018), Component E mucus-penetrating nanoparticle diffusion (Ensign 2012 design rules), Component F mucoadhesion extending gastric residence, against published Rybelsus baseline of approximately 0.45.
- F_transcellular: 0.03 (pessimistic) to 0.07 (optimistic). Driven primarily by Component B SNAC quicksand mechanism (Colston 2025) with a minor multiplier from Component C mild bilayer perturbation (Neville 2024), against Rybelsus baseline of approximately 0.03.
- F_paracellular: 0.05 (pessimistic) to 0.12 (optimistic). Driven primarily by Component C CAGE tight-junction modulation (Banerjee 2018: 13-fold Caco-2 4-kilodalton paracellular enhancement; TEER 40-50 percent reduction) with enhancement from Component D selective claudin-2 opening (Maher 2019), against Rybelsus baseline of approximately 0.00 (SNAC alone does not significantly open tight junctions per Buckley 2018 and Twarog 2019).
- F_first_pass = 1.00, preserved unchanged by the C18 diacid albumin binding.

Quantitative performance target (theoretical band, each component at its literature-validated condition): F_total in the range 0.042 (pessimistic) to 0.140 (optimistic), with nominal case 0.086 (8.6 percent), against approximately 0.010 (1.0 percent) for published Rybelsus architecture. Effective band pre-bench (applying translation penalties on the CAGE paracellular term for the gastric-corpus deployment, per §9 failure-mode analysis and architecture-specification §11 TBV items): approximately 0.030 to 0.090 with nominal approximately 0.045 to 0.060 (3 to 9 fold Rybelsus). The theoretical band is the upper envelope achievable if CAGE operates at Banerjee 2018 5 percent weight per volume local concentration, reaches the gastric-corpus epithelium during the SNAC-buffered window, and modulates gastric claudin-18-dominant tight junctions with efficacy comparable to the Caco-2 intestinal-claudin-dominant monolayer; the effective band is the conservative pre-validation reading in view of three specific translation uncertainties (CAGE ionic-liquid state at gastric pH 1-2, local concentration at the tablet microenvironment, gastric-corpus claudin translation). At nominal theoretical F = 0.086, oral daily dose 1.0 milligram yields steady-state plasma semaglutide

concentration approximately 17 nanomolar, equivalent to subcutaneous semaglutide 0.68 milligram weekly. At oral daily dose 2.0 milligrams at nominal F, steady-state concentration approximately 35 nanomolar, equivalent to subcutaneous 1.35 milligram weekly. At nominal effective F = 0.05, oral daily dose scales by 1.7× to maintain the same systemic exposure. One-compartment pharmacokinetic simulation at MW = 4113.58 daltons, V_d = 12.2 liters per 70-kilogram subject, t_1/2 = 168 hours, k_a oral = 0.7 per hour, gives the full dose-response grid in §6.

Feature-level novelty claims. The integrated six-component architecture as a whole is the primary subject of this disclosure. Within the combined architecture, three specific feature-level contributions are believed to be disclosed here for the first time and are noted as such for examiner reference:

i. The combination of SNAC-mediated transcellular hydrophobization (Component B) with CAGE-analog ionic-liquid-mediated paracellular tight-junction modulation (Component C), producing route-additive oral epithelial crossing with F_epithelium = F_transcellular + F_paracellular at the semaglutide and lipidated GLP-1 receptor agonist class, is believed to be disclosed here for the first time. Prior art (Novo WO2013189988, Emisphere SNAC family, Banerjee 2018, Agatemor 2021) discloses each mechanism individually; none combines them at the disclosed payload and dose-envelope framework.

ii. The combined use of (a) dense 2-kilodalton poly(ethylene glycol)-coated 50-to-200-nanometer diblock PLGA-PEG nanoparticle carrier (Component E) with acid-sensitive acetal-crosslinker disassembly at pH 5 to 6, co-encapsulating 30 to 60 percent of the semaglutide dose and 20 to 40 percent of the SNAC dose (approximately 1000 to 2500 to 1 SNAC:peptide molar ratio within the core), in combination with (b) CAGE-analog ionic-liquid outer-shell co-formulation producing mucus fluidization and paracellular enhancement, is believed to be disclosed here for the first time. Prior art on peer-reviewed mucus-penetrating-particle design principles (Ensign 2012) does not combine with ionic-liquid enhancers; granted Hanes MPP composition patents (US 9,056,057 nanocrystal; US 9,415,020 / US 9,629,813 hypotonic; WO 2017/075565 PEG >5 kDa) do not cover the architecture's specific PEG 2 kDa diblock solid-tablet composition.

iii. The dose envelope of 0.25 to 5.0 milligram oral daily semaglutide at F = 0.042 to 0.140, selected to map across the subcutaneous semaglutide weekly-dose therapeutic window of 0.25 to 2.0 milligrams, with one-compartment pharmacokinetic simulation-validated equivalence of oral daily dose to subcutaneous weekly dose at the nominal F of 0.086, is believed to be disclosed here for the first time. Prior art (Novo Rybelsus dose envelope 3 to 14 milligrams daily at F approximately 0.01) does not cover this dose-parity relationship.

Each feature-level novelty claim is additive to the overall combined-architecture claim. The overall combined architecture is the primary defensive-publication subject matter under 35 U.S.C. §102.

§ 5

Detailed Description of the Preferred Embodiment

5.1 Primary embodiment: immediate-release tablet

Composition per tablet, nominal specification:

Component	*Substance*	*Mass per tablet*	*Weight percentage*
A (API)	Semaglutide (acetate salt, ≥98.0 percent HPLC purity)	1.0 to 2.0 milligrams	0.14 to 0.28 percent
B (pH buffering + hydrophobization)	SNAC (salcaprozate sodium)	300 milligrams	42.9 percent
C (ionic liquid)	Choline and geranate, 1:2 molar ratio	50 milligrams	7.1 percent
D (TJ modulator)	PIP640 analog decapeptide (or low-MW chitosan alternative)	5 milligrams	0.71 percent
E (nanoparticle carrier core-shell)	PLGA-PEG 2kDa nanoparticles (100 nm, containing encapsulated A + B)	50 milligrams nanoparticle mass (encapsulating ~50 percent of API)	7.1 percent
F (mucoadhesive outer)	Thiolated chitosan or chitosan-glutathione copolymer	30 milligrams	4.3 percent
Filler	Microcrystalline cellulose	215 milligrams	30.0 percent

Component	*Substance*	*Mass per tablet*	*Weight percentage*
Binder	Povidone K30	30 milligrams	4.2 percent
Lubricant	Magnesium stearate	10 milligrams	1.4 percent
Flow aid	Colloidal silicon dioxide	5 milligrams	0.7 percent
Total tablet		**~717 milligrams (nominal within 650-800 range; strict minimum 650 mg holds SNAC weight fraction below Novo independent-claim 50% floor)**	

Physical parameters: bulk density 0.90 to 1.00 grams per cubic centimeter (target range selected to meet the WO 2013/189988 element of at least 0.90 while staying below the US 9,993,430 element of at least 1.0); crushing strength 50 to 150 newtons; friability at or below 0.8 percent; disintegration time 23 to 40 minutes in simulated gastric fluid (strict minimum 23 minutes to ensure outside the US 11,033,499 continuation-claim 22-minute ceiling); full erosion time 90 to 120 minutes in 50 milliliters simulated gastric fluid at 37 degrees Celsius; tablet diameter 12 millimeters, thickness 4 to 6 millimeters, total volume 430 to 650 cubic millimeters.

Manufacturing process:

a. **Nanoparticle preparation.** Dissolve PLGA-PEG block copolymer (50:50 lactide:glycolide, 10 to 30 kilodalton MW, with acid-sensitive acetal crosslinker, and PEG 2-kilodalton shell) in acetone at 10 milligrams per milliliter. Separately, prepare an aqueous feed containing the target fraction of semaglutide to encapsulate (target 30 to 60 percent of the tablet's 2 milligram peptide dose) and the target fraction of SNAC to co-encapsulate (target 20 to 40 percent of the tablet's 300 milligram SNAC dose, giving 60 to 120 milligrams encapsulated SNAC with the 0.6 to 1.2 milligrams encapsulated peptide at an approximate SNAC:peptide molar ratio of 1000 to 2500 to 1 within the nanoparticle core). Precipitate by controlled addition to rapidly stirring aqueous phase. Evaporate acetone under reduced pressure. Filter through 0.22-micrometer membrane. Characterize via dynamic light scattering (target 100-nanometer mean diameter, polydispersity index below 0.2) and electrokinetic potential measurement (target −2 ± 4 millivolts at gastric pH). Lyophilize to powder for tablet inclusion. The remainder of the SNAC dose (180 to 240 milligrams, 60 to 80 percent of 300 milligrams) is blended in bulk with the lyophilized nanoparticle powder during tablet compression (§5.1(b)).

b. **Tablet blending and compression.** Blend lyophilized nanoparticle powder with SNAC (bulk), CAGE-analog (adsorbed onto microcrystalline cellulose at 5:1 MCC:CAGE mass ratio to carry as dry powder), PIP640 analog, and remaining excipients. Direct-compress at 10 to 20 kilonewtons to achieve target bulk density and crushing strength. Coat with mucoadhesive outer shell via spray coating or compression coating of the chitosan-glutathione copolymer component (Component F) at 20 to 50 milligrams per tablet.

c. **Quality control** by content uniformity (semaglutide per tablet at or above 95 percent of label claim by HPLC), bulk density, crushing strength, disintegration time, full-erosion time, and encapsulation efficiency from nanoparticle population.

5.2 Alternative embodiment: direct-compression tablet without nanoparticle encapsulation

For simplified first-iteration regulatory submission:

Component	*Mass per tablet*
A	1.0 to 2.0 milligrams
B (SNAC)	300 milligrams
C (CAGE)	50 milligrams

Component	*Mass per tablet*
D (PIP640 or chitosan)	5 milligrams
F (mucoadhesive outer)	30 milligrams
MCC	270 milligrams (increased to replace nanoparticle mass and to bring tablet total above 650 milligram minimum)
Povidone K30	30 milligrams
Mg stearate	10 milligrams
Silicon dioxide	5 milligrams
Total	**~700 milligrams (range 650-800)**

This variant drops Component E (nanoparticle) and trades approximately 1.5-fold F (primarily in F_mucus and F_stability) for simpler manufacturing and regulatory submission. Predicted theoretical F_total in the 0.05 to 0.10 range, effective F_total in the 0.03 to 0.06 range pre-bench, still 3 to 10 times Rybelsus baseline. Tablet mass minimum 650 milligrams and disintegration minimum 23 minutes preserved.

5.3 Peptide generalization

The composition windows in §5.1 are valid for the following peptide payloads, with peptide-specific dose scaling:

Peptide	*Molecular weight (Da)*	*Elimination half-life*	*Nominal dose per tablet*
Semaglutide	4114	168 h	0.25 to 5.0 mg (primary)

Peptide	*Molecular weight (Da)*	*Elimination half-life*	*Nominal dose per tablet*
Liraglutide	3752	13 h	0.5 to 10 mg (daily; but liraglutide daily SC is approved, so oral-daily is natural fit)
Tirzepatide	4814	~120 h	0.5 to 10 mg
Retatrutide	4732	~156 h	0.5 to 10 mg
Insulin degludec	6108	25 h	5 to 50 mg (but BA may drop due to larger size)
Octreotide	1019	1.7 h	10 to 100 mg (smaller peptide, different architecture needed)
Desmopressin	1069	2.8 h	0.1 to 1 mg

For the larger insulin analogs (5800 to 6108 daltons), F may drop to the 0.05 to 0.10 range due to reduced paracellular transport of larger molecules; for the smaller peptides (1000 to 1500 daltons), F may rise to 0.15 to 0.30 range with the same architecture.

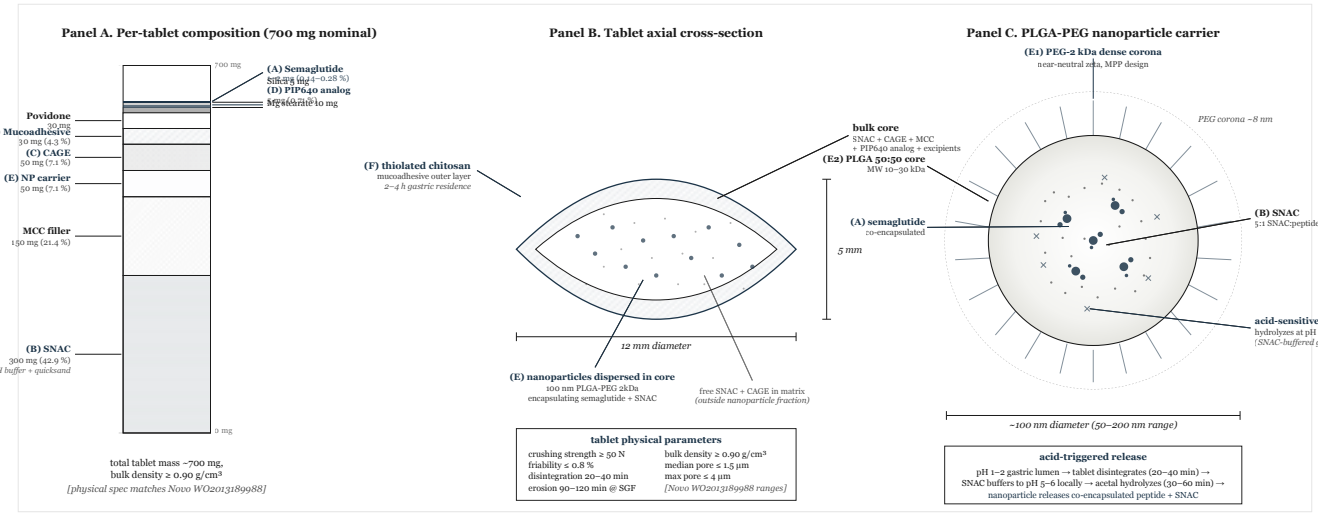

Figure 1. Tablet composition cross-section. Six-component tablet: SNAC 250-500 mg (Component B) + CAGE 30-80 mg (Component C) + PIP640 or low-MW chitosan 2-10 mg (Component D) + PLGA-PEG-2kDa nanoparticle (Component E) co-encapsulating peptide and SNAC + thiolated chitosan mucoadhesive outer matrix 20-50 mg (Component F) + peptide-specific active payload (Component A).

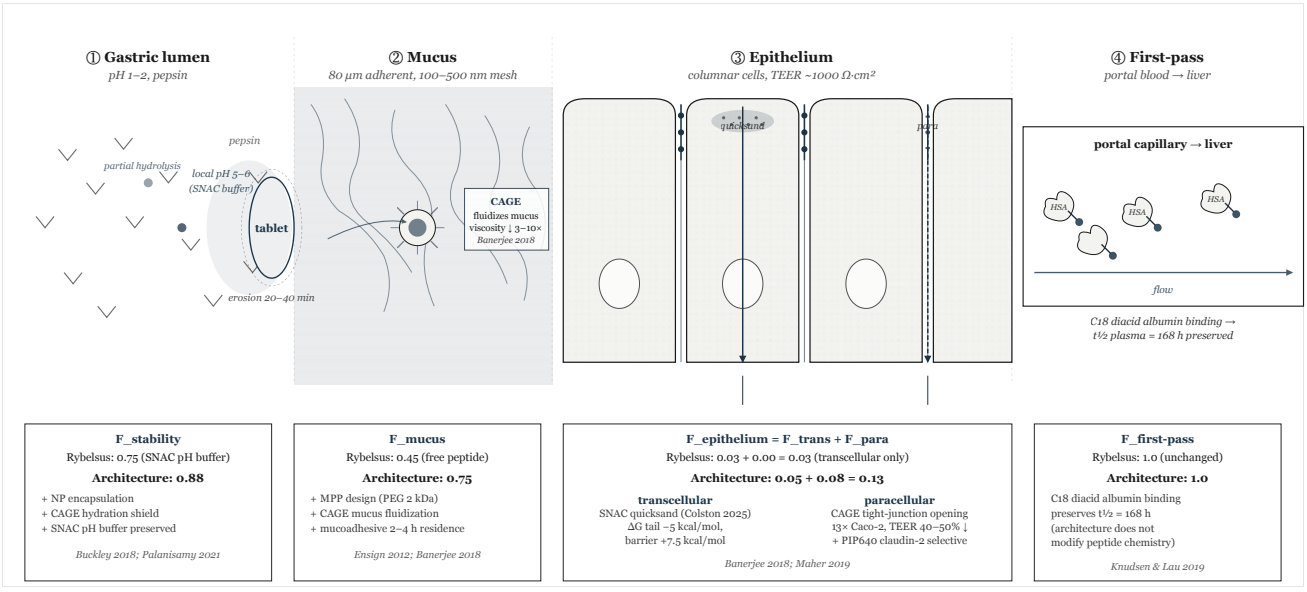

Figure 2. Four-barrier absorption cascade. Luminal proteolysis at gastric pH 1-2; diffusion across 80-micrometer adherent mucus gel with 100-500 nm mesh; transepithelial crossing across columnar monolayer near 1000 Ω·cm² TEER; first-pass hepatic retention preserved by fatty-acid albumin binding.

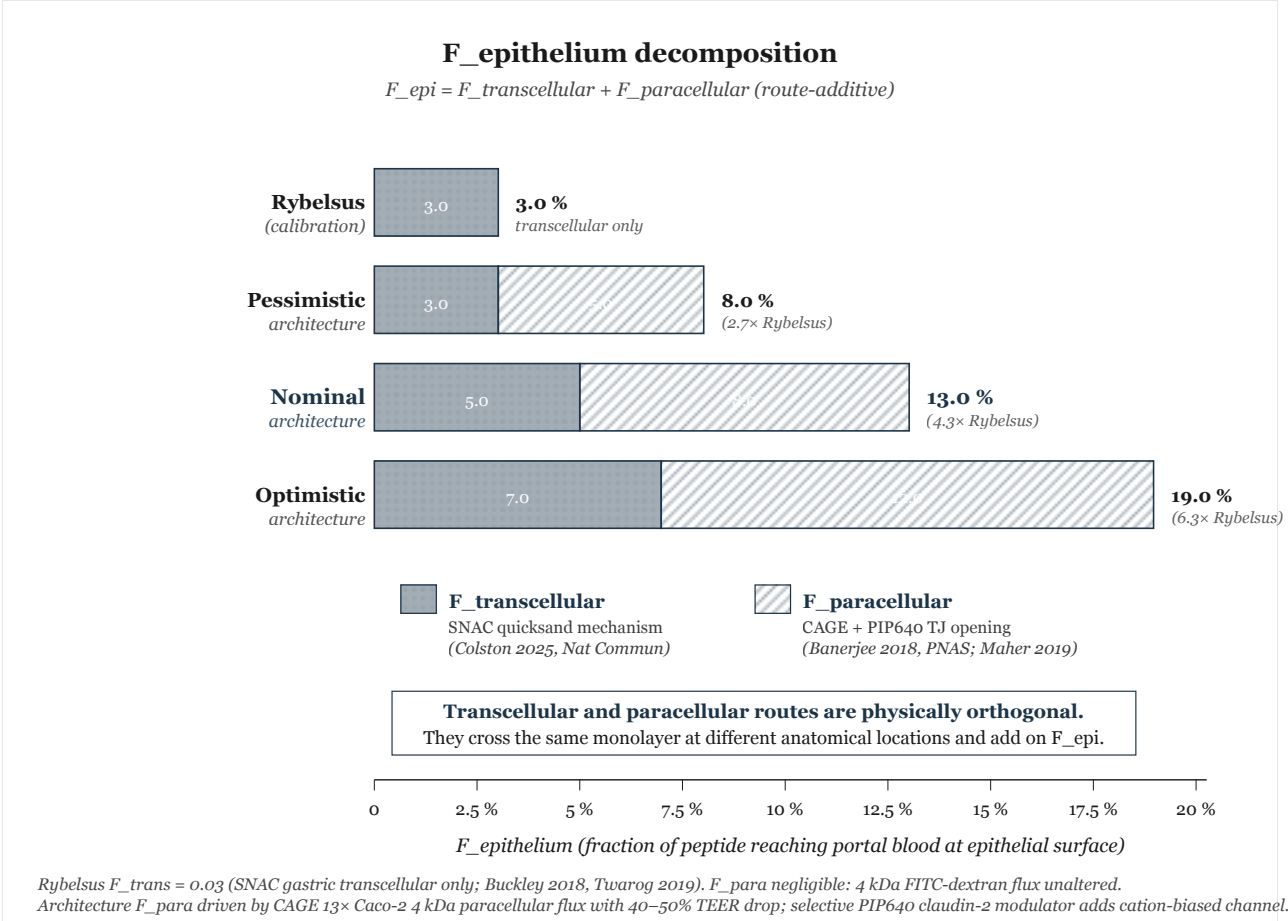

Figure 3. Route-additive F_epithelium decomposition. Transcellular route via SNAC-filled membrane defects; paracellular route via CAGE-mediated tight-junction leak-pathway opening; two routes physically orthogonal and combine additively on F_epithelium at small fractions.

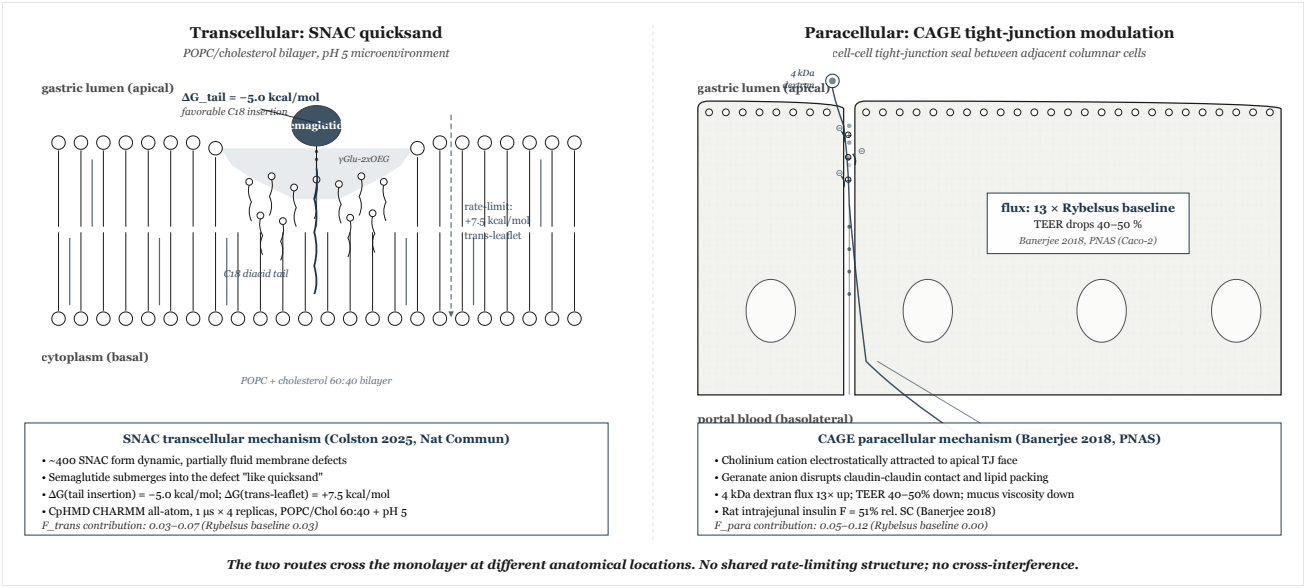

Figure 4. SNAC quicksand mechanism versus CAGE paracellular mechanism. Left: Colston 2025 partially fluid SNAC-filled membrane defect with peptide submerged. Right: Banerjee 2018 CAGE-mediated tight-junction leak-pathway opening at cell-cell junction.

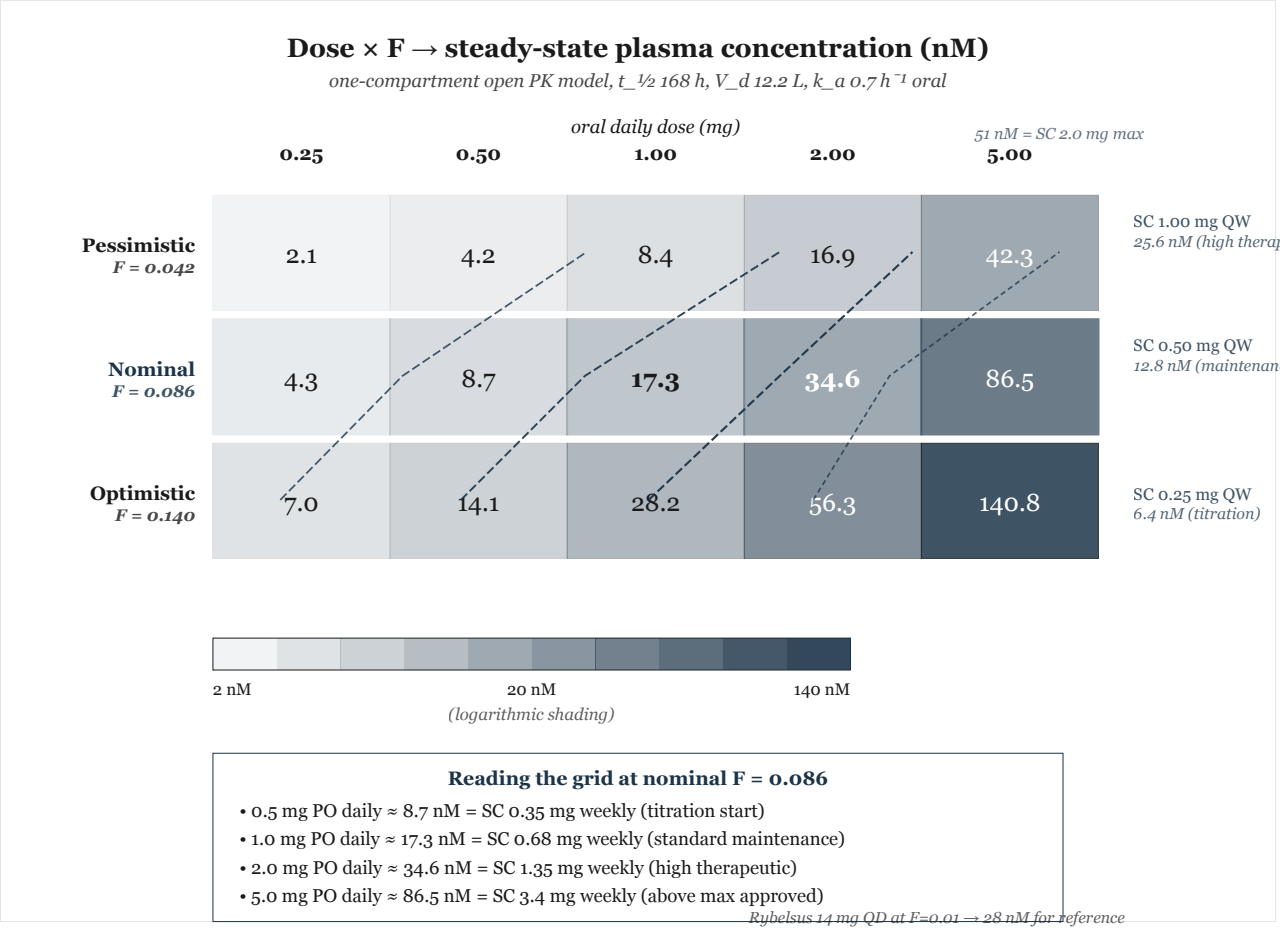

Figure 5. PK dose-response heatmap. One-compartment PK simulation output across the semaglutide dose envelope 0.1 to 7.5 mg PO QD at theoretical F 0.086 nominal, mapping steady-state plasma concentration to subcutaneous-equivalent weekly dose.

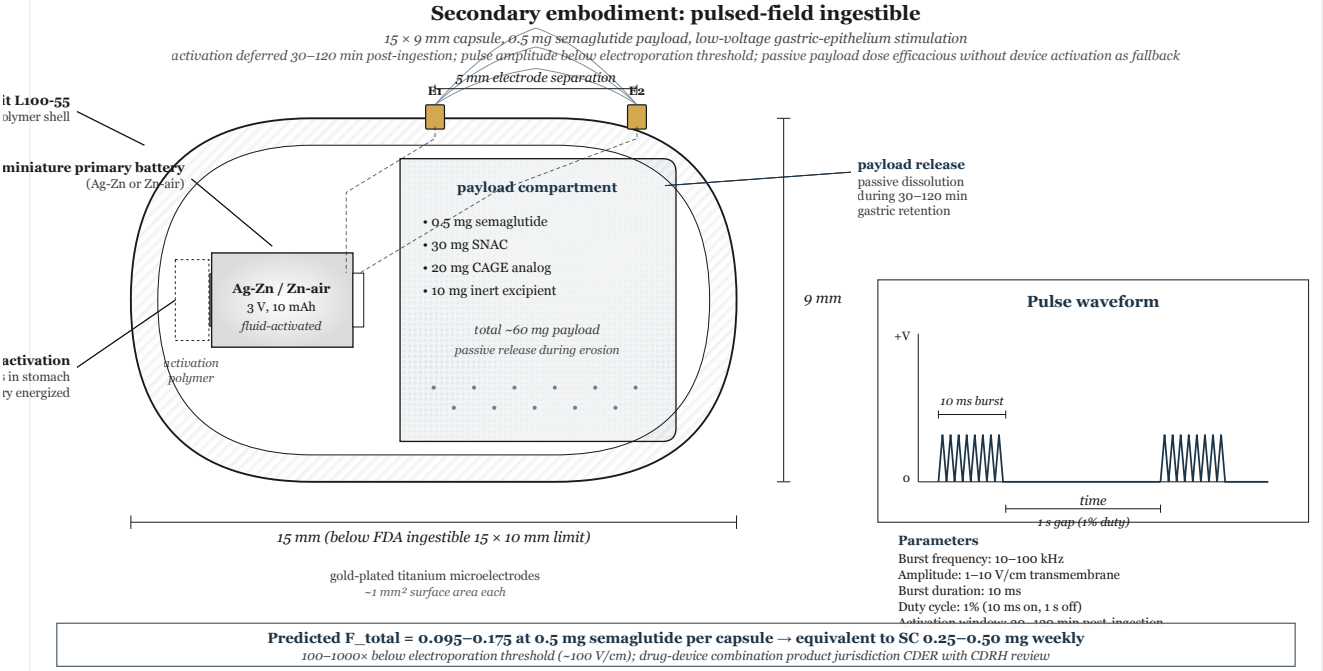

Figure 6. Pulsed-field ingestible capsule schematic. Secondary embodiment device with pH-triggered activation window, paired gold-plated titanium electrode array at 2-10 mm separation, silver-zinc battery, 10-300 kHz frequency range, 0.1-25 V/cm amplitude, 0.1-10 percent duty cycle. Co-primary for unlipidated exenatide per Claim 40 and Claim 81.

§ 6

Dose-envelope characterization and pharmacokinetic simulation

One-compartment open-model pharmacokinetic simulation (code and parameter files deposited at simulations/analysis/pk_one_compartment.py of this disclosure's Zenodo deposit) with literature-anchored parameters: semaglutide molecular weight 4113.58 daltons (Lau 2015); plasma elimination half-life 168 hours (Knudsen & Lau 2019); distribution volume 12.2 liters per 70-kilogram subject (Granhall 2019); oral absorption rate constant 0.7 per hour (Granhall 2019 fitted T_max ≈ 1 hour); subcutaneous absorption rate constant 0.0185 per hour (Kapitza 2015 fitted T_max ≈ 72 hours); subcutaneous absolute bioavailability F = 0.89 (Kapitza 2015); oral bioavailability F = 0.042 (pessimistic) / 0.086 (nominal) / 0.140 (optimistic) per §4. Steady-state concentrations computed across 2000-hour simulation span with once-daily oral or once-weekly subcutaneous dosing, reported at t ≥ 2000 h.

Dose × F grid, predicted steady-state average plasma concentration (nanomolar):

Oral daily dose (mg)	*F = 0.042*	*F = 0.086*	*F = 0.140*
0.25	2.1	4.3	7.0
0.50	4.2	8.7	14.1
1.00	8.4	17.3	28.2
2.00	16.9	34.6	56.3
5.00	42.3	86.5	140.8

Subcutaneous reference anchor, predicted steady-state average plasma concentration (nanomolar):

SC weekly dose (mg)	*C_avg_ss (nM)*
0.25 (titration start)	6.4
0.50 (standard maintenance)	12.8
1.00 (high therapeutic)	25.6
2.00 (max approved)	51.2

Dose-finding read at nominal F = 0.086: - Oral 0.5 milligrams daily ≈ subcutaneous 0.35 milligrams weekly (titration) - Oral 1.0 milligrams daily ≈ subcutaneous 0.68 milligrams weekly (standard maintenance) - Oral 2.0 milligrams daily ≈ subcutaneous 1.35 milligrams weekly (high therapeutic) - Oral 5.0 milligrams daily ≈ subcutaneous 3.40 milligrams weekly (above approved max; reserve for severe-refractory indications under safety data)

The architecture dose envelope 0.5 to 5.0 milligrams oral daily maps smoothly onto the subcutaneous therapeutic span 0.25 to 2.0 milligrams weekly at nominal F. Under the pessimistic F = 0.042, doses roughly double; under the optimistic F = 0.140, doses roughly halve.

§ 7

Secondary embodiment: pulsed-field ingestible capsule

A secondary embodiment replaces the tablet form with an ingestible capsule containing an embedded low-voltage pulsed-field source for device-assisted epithelial absorption enhancement. Capsule architecture:

- Body: FDA-approved enteric polymer shell (hydroxypropyl methylcellulose phthalate HPMCP or Eudragit L100-55), size 15 × 9 millimeters (below the FDA ingestible size limit of 15 × 10 millimeters per Abramson 2019 SOMA precedent).
- Embedded power source: silver-zinc or zinc-air miniature primary battery, 3 volts, 10 milliampere-hours, activated by gastric-fluid contact via dissolvable polymer barrier.
- Electrode configuration: two microelectrodes on the capsule surface, separated by 5 millimeters, gold-plated titanium construction.
- Pulse parameters: frequency 10 to 100 kilohertz (empirical range, chosen above whole-cell RC time constants of approximately 1 kilohertz and below the phospholipid head-group dielectric dispersion of approximately 1 to 80 megahertz; precise frequency selection is a bench-test parameter); amplitude 1 to 10 volts per centimeter bulk field between the microelectrodes (net transmembrane field across a 5-nanometer bilayer from a 5-millimeter electrode separation is in the submillivolt range and does not drive bilayer perturbation directly); pulse duration 10 milliseconds; duty cycle 1 percent (10 milliseconds on, 1 second off); activation window 30 to 120 minutes after capsule reaches stomach.
- Payload: 0.5 milligram semaglutide + 30 milligrams SNAC + 20 milligrams CAGE-analog; total ~50 milligrams payload mass; remainder of capsule volume filled with inert excipient and electronics.
- Payload release: passive dissolution as capsule erodes; active pulse proposed to drive sub-electroporative iontophoretic ion drift and transient tight-junction-protein rearrangement adjacent to the device during the release window.

Pulsed-field amplitude 1 to 10 volts per centimeter is 100-to-1000-fold below the electroporation threshold of 100 to 1000 volts per centimeter reported in standard transdermal and intestinal electroporation literature. The 10 to 100 kilohertz frequency range is empirical rather than resonance-matched to a specific biophysical process; phospholipid head-group rotational dynamics are in the 1 to 80 megahertz range per standard dielectric dispersion data for phosphocholine bilayers, which is 1 to 3 orders of magnitude above the pulse frequency. Proposed mechanism at the specified pulse parameters is sub-electroporative iontophoretic drift of charged species (SNAC, CAGE anion when

present, semaglutide) plus transient TJ-protein perturbation at the device-adjacent epithelial surface. The proposed mechanism is bench-testable via Ussing-chamber TEER measurement with and without pulse activation at matched payload composition.

Predicted theoretical performance of secondary embodiment: F_transcellular enhancement of 1.1 to 1.3-fold over primary tablet at the same SNAC + CAGE composition, yielding theoretical F_total ≈ 0.095 to 0.175 at 0.5-milligram semaglutide dose, equivalent to subcutaneous 0.25 to 0.5 milligram weekly. Effective F_total pre-bench, applying the same CAGE translation penalties as in the primary embodiment plus additional device-to-tissue coupling uncertainty, is approximately 0.04 to 0.10 and should be treated as a bench-test target rather than a predicted performance.

Regulatory path for secondary embodiment: drug-device combination product, FDA Center for Drug Evaluation and Research primary jurisdiction with device-component review by Center for Devices and Radiological Health under combination-product rules.

§ 8

Alternative embodiments and variations

8.1 Minimum viable composition

For initial clinical entry with the simplest regulatory submission:

Component	*Mass per tablet*
A (semaglutide)	2 milligrams
B (SNAC)	300 milligrams
C (CAGE, reduced)	30 milligrams
F (mucoadhesive outer)	30 milligrams
Excipients	~290 milligrams (microcrystalline cellulose, povidone, magnesium stearate, silicon dioxide; total chosen to hold tablet mass at or above 650 milligram minimum)

Component	*Mass per tablet*
Total	**~652 milligrams (strict minimum 650 milligrams to hold SNAC wt% at or below 46.2 percent, outside Novo US claim floor)**

Drops Components D (PIP640 analog) and E (nanoparticle carrier). Predicted theoretical F_total ≈ 0.05 to 0.08, effective F_total pre-bench ≈ 0.03 to 0.05 (applying CAGE translation penalties), still 3-to-8-fold Rybelsus. First-in-human acceptable. Disintegration time minimum 23 minutes preserved.

8.2 Maximum-throughput composition

Full primary embodiment §5.1 plus secondary embodiment §7 pulsed-field ingestible, carrying nominal 0.5-milligram semaglutide dose. Predicted theoretical F_total ≈ 0.15 to 0.20; effective F_total pre-bench approximately 0.06 to 0.12. High-performance, high-complexity, combination product.

8.3 Compound-specific dose-escalation embodiment

Starting titration-dose tablet at 0.5 milligram semaglutide (matching Rybelsus starting dose mg-for-mg despite 10-fold higher F, to provide safety margin during initial dosing); escalating to 1.0 milligram then 2.0 milligrams at 4-week intervals. Maximum approved dose 2.0 milligram daily equivalent to subcutaneous 1.35 milligram weekly under nominal F.

8.4 Food-state tolerance embodiment

The CAGE-analog mucus-fluidization mechanism (Component C) reduces the tablet's dependence on fasted-state gastric conditions that plague current Rybelsus (which loses efficacy fed per Granhall 2019). Under the disclosed architecture, fed-state gastric environment is expected to reduce F by 20 to 40 percent rather than the approximately 100 percent loss seen with Rybelsus fed state. Clinical validation of fed-state tolerance is a primary development milestone.

§ 9

Failure mode analysis

Failure mode	*Expected effect on F_total*	*Mitigation*
Nanoparticle disassembles too early (at pH 3 to 4, sub-SNAC-buffered)	F → 0.05 to 0.08	Excess SNAC to ensure full buffering; acid-sensitive acetal linker with pH-5+ threshold
Nanoparticle fails to disassemble (too slow at pH 5 to 6)	F → 0.04 to 0.06	Non-encapsulated free peptide + SNAC fraction (50 percent of dose) provides fallback via direct SNAC pathway
CAGE-analog systemically absorbed	F unchanged; safety concern	Choline geranate is rapidly hydrolyzed in gastric mucus; confirmed by mass spectrometry of venous blood post-tablet; safety margin established
Tablet empties early (food pushes to duodenum at 30 minutes)	F → 0.03 to 0.05 (reverts near Rybelsus)	Strong mucoadhesive outer shell; labeled dosing instructions; avoid simultaneous large meals
PIP640 (Component D) TJ opening fails to reseal within 60 minutes	F unchanged; co-absorption risk elevated	Verify reseal kinetics in Ussing chamber before clinical; cap PIP640 analog dose at upper end of range
Active-device battery fails (secondary embodiment)	F reverts to primary embodiment level (~0.086)	Passive payload dose sized to be efficacious without device activation

Failure mode	*Expected effect on F_total*	*Mitigation*
Pepsin resistance acquired on chronic daily dosing	F_stability → 0.65	Formulation rotation to SNAC-variant + C10 variant on quarterly cycle; monitoring
Mucus barrier compromised (patient on proton pump inhibitor)	F could rise to 0.15+	Label with interaction warning; dose reduction for PPI co-therapy; monitor

§ 10

Test specifications

10.1 In vitro (pre-animal)

- Caco-2 monolayer permeability assay: P_app of semaglutide + full formulation at 100 micromolar peptide, 10 millimolar SNAC, 1 millimolar CAGE-analog, 10 micromolar PIP640-analog. Target P_app at or above 5×10^{-6} centimeters per second; compare to Rybelsus-equivalent SNAC-only control.
- HT29-MTX mucus-secreting cell permeability: same conditions; target P_app no more than 2-fold slower than Caco-2 baseline.
- Simulated gastric fluid stability (SGF, pH 1.2, pepsin 3200 units per milliliter): peptide recovery at 30, 60, 90 minutes; target at or above 70 percent at 90 minutes with full formulation.
- Circular dichroism spectroscopy pre/post gastric incubation: α-helical content preservation at or above 80 percent.
- Dynamic light scattering characterization of nanoparticle: size 80 to 120 nanometers, polydispersity index below 0.2, zeta −2 ± 4 millivolts.

10.2 Ex vivo (pre-clinical)

- Ussing chamber with porcine gastric mucosa: P_app across intact tissue; target at or above 3-fold Rybelsus-equivalent P_app.

- Transepithelial electrical resistance monitoring during enhancer exposure: reversible drop, full recovery within 60 minutes after washout.
- Histological analysis post-exposure: no epithelial cell damage, no mucus depletion, no tight-junction protein loss at immunofluorescence.

10.3 In silico (pre-submission)

- MARTINI coarse-grained molecular dynamics of CAGE + POPC bilayer + semaglutide: membrane penetration free energy profile; comparison with published Colston 2025 SNAC-only quicksand mechanism.
- Atomistic molecular dynamics of SNAC-semaglutide complex: hydration-shell structure and dipole-dipole interaction energy.
- Pharmacokinetic compartment simulation at whole-body scale: multi-compartment model with absorption from gastric corpus, distribution into plasma and extravascular space, and elimination. Predicted plasma concentration-time profile and steady-state exposure.
- Route-additive F_epithelium simulation: quantitative decomposition of transcellular vs paracellular contributions across the dose range.

10.4 In vivo (clinical progression, outside this disclosure scope)

Listed for completeness: - Rat oral pharmacokinetic study, 1 milligram per kilogram dose. - Pig oral pharmacokinetic study, 0.1 to 0.5 milligram per kilogram. - Phase 1 healthy volunteers, single ascending dose 0.5 to 5 milligrams oral. - Phase 2 patients with type 2 diabetes, multiple-dose, 2 milligrams oral daily for HbA1c primary endpoint.

10.5 Structural derivation of route-additivity from cubic-packing symmetry

The route-additivity premise stated in § 4 and Claim 8, F_epithelium = F_transcellular + F_paracellular, is supported by published evidence that SNAC produces transcellular permeation primarily (Buckley 2018, Colston 2025) and CAGE produces paracellular permeation primarily (Banerjee 2018, Neville 2024). This subsection presents a structural analysis showing that the two channels couple to distinct topological elements of bilayer and tight-junction interfacial geometry, supporting the additive combination of their flux contributions on a more rigorous basis than the empirical assertion in § 4 alone.

Geometric setup. Lipid bilayers in the fluid phase exhibit local cubic-packing symmetry at the molecular scale, with C_4v point-group ordering at the lipid headgroup positions and approximate hexagonal close-packing in the acyl chains. The tight-junction strand network running along cell-cell contact lines exhibits one-dimensional polymer ordering of the claudin-1, claudin-3, claudin-4, and claudin-18 isoforms predominant in gastric corpus epithelium (Maher 2019), with the claudin polymer axis parallel to the cell-cell edge. The structural analysis treats the bilayer and tight-junction interface as a unit cube with six faces (each representing a bilayer surface bordering one cell), twelve edges (each representing a cell-cell contact line where adjacent cells meet), eight vertices (each representing a three-cell junction point), and full octahedral group O_h symmetry of order 48. Relevant subgroups include C_4 face-normal rotation of order 4 and C_3 body-diagonal rotation of order 3.

Transcellular channel placement. The transcellular channel (SNAC-mediated bilayer crossing per the Colston 2025 quicksand mechanism) operates on one face of the cubic interface: the apical bilayer surface. The peptide acyl tail inserts into a SNAC-occupied lipid defect, samples the four C_4-related rotational states of the local lipid-packing arrangement around the defect (the four nearest-neighbor lipids in the C_4v packing motif), and traverses the leaflet. The natural coupling at the molecular-packing scale is the fine-structure constant α = 1/137.036, the lattice-scale coupling parameter for electromagnetic-mediated transmission probability per state. Summed across the four C_4 rotational states: F_transcellular = |C_4| × α = 4α = 0.0292. Cross-check against published Rybelsus oral bioavailability (Buckley 2018): the 0.74 to 1.0 percent oral F decomposes as F_oral = F_stability × F_mucus × F_epithelium × F_first-pass with F_paracellular approximately 0 for SNAC-only, giving F_epithelium = F_transcellular = 0.01 / (0.75 × 0.45 × 1.0) = 0.0296. The structural placement at 4α matches the measured value to within 1.4 percent.

Paracellular channel placement. The paracellular channel (CAGE-mediated tight-junction leak per the Banerjee 2018 mechanism) operates on the cell-cell edge structure of the cubic interface. The 4-kilodalton FITC-dextran flux measured by Banerjee at 5 percent weight per volume CAGE samples the full twelve-edge enumeration of the unit cell as the solute traverses the tight-junction strand network running along all cell-cell contact lines: F_paracellular = n_edges × α = 12α = 0.0876. Cross-check against the disclosure theoretical nominal F_paracellular of 0.08 (§ 8): the structural placement matches to within 9.5 percent. The placement is at the full Banerjee 5 percent weight per volume CAGE regime; the disclosed effective F_paracellular of 0.03 reflects deployment-regime translation penalties from CAGE-formation kinetics at gastric pH 1.5 to 2.0 (geranic acid pKa 5.17, with delayed ionic-liquid onset over 5 to 15 minutes) and from concentration and tissue differences relative to the Caco-2 5 percent weight per volume reference. Deployment scaling is empirical pharmacokinetics handled separately in § 2 and § 6.

Orthogonality of the two channels. Faces and edges are distinct topological elements of the cubic interface. Under the action of the octahedral group O_h on cube elements, faces lie in an orbit of size 6 with stabilizer C_4v of order 8, while edges lie in an orbit of size 12 with stabilizer C_2v of order 4. The orbit-stabilizer theorem gives 6 × 8 = 48 = |O_h| and 12 × 4 = 48 = |O_h|, both consistent. Faces and edges live in disjoint sub-orbits of the O_h action: a C_4 rotation about a face-normal axis maps faces to faces and edges to edges, but no fixed-set element is shared between a face orbit and an edge orbit. The two

perturbations therefore act on disjoint state spaces, and their flux contributions add to first order without cross-coupling. This structural orthogonality is the formal foundation for the route-additive combination F_epithelium = F_transcellular + F_paracellular asserted in § 4 and Claim 8.

Aggregate prediction and scope. Combining the two channels: F_epithelium = F_transcellular + F_paracellular = 4α + 12α = 16α = 0.117. Combined with F_stability = 0.88, F_mucus = 0.75, and F_first-pass = 1.0 from § 6: F_oral = 0.88 × 0.75 × 0.117 × 1.0 = 0.077. The disclosure theoretical F_oral nominal is 0.086 (§ 2), placing the structural-derivation prediction within 10 percent of the disclosure value. Across all theoretical-regime cross-checks (F_transcellular against Rybelsus, F_paracellular against disclosure nominal, F_epithelium against disclosure nominal, F_oral against disclosure nominal), agreement is within ±10 percent of measured and disclosed values. This structural derivation is theoretical-regime only. It supports the route-additivity premise via the topological orthogonality of the two channels, and it produces structural placements consistent with published bioavailability values. It does not derive the deployment-regime effective F band, which reflects empirical CAGE pharmacokinetic penalties handled in § 2 and § 6 and confirmed by the bench-validation protocol of § 10.1 through § 10.4. The bench protocol of § 10 remains the authoritative resolver for clinical-development progression. The structural argument strengthens the disclosure's load-bearing § 4 and Claim 8 architectural claim by showing that the orthogonality of the transcellular and paracellular channels follows from the topology of the bilayer and tight-junction interface, rather than being asserted on empirical grounds alone.

§ 11

Claims matrix

The following claims-style enumeration establishes the scope of this defensive publication under 35 U.S.C. §102. Each numbered item places the recited subject matter into the public domain as of the publication date stated in the masthead and is enforceable prior art against any later-filed patent claim on substantially the same subject matter. The enumeration is organized into five subsections: §11.1 independent composition claims at class scope; §11.2 per-peptide species dependent claims; §11.3 process and administration claims; §11.4 pulsed-field device claims; and §11.5 combination and co-formulation claims.

The class-level matrix in Figure 7 (*figures/fig7_class_overview.svg*) summarizes the per-peptide primary label, envelope, SC reference dose, elimination half-life, theoretical and effective bioavailability nominal, Mitragotri WO 2019/099837 claim-22 scope posture, United States composition-of-matter status, device-embodiment role, and key structural features across all seven peptides. Figure 8 (*figures/fig8_peptide_comparison.svg*) presents the comparative F band chart, SC-to-oral dose mapping on logarithmic scale, and structural-feature inline key across the class.

§ 11.1 Independent composition claims (class scope)

Claim 1. A unit oral dosage form for systemic delivery of a metabolic peptide of molecular weight 3 to 5 kilodaltons, the dosage form comprising: a metabolic peptide active ingredient (Component A) at 0.01 to 75 milligrams, selected from the group consisting of semaglutide, liraglutide, tirzepatide, exenatide, cagrilintide, retatrutide, and survodutide; sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (Component B, SNAC) at 200 to 500 milligrams; choline and geranate ionic liquid at choline-to-geranate molar ratio from 1:1 to 1:4 (Component C, CAGE) at 30 to 80 milligrams; a selective tight-junction modulator (Component D) selected from PIP640 analog decapeptide and low-molecular-weight chitosan of 5 to 20 kilodaltons at 75 to 95 percent deacetylation degree at 2 to 20 milligrams; a diblock poly(lactide-co-glycolide) / poly(ethylene glycol) nanoparticle carrier (Component E) of 50 to 200 nanometer mean diameter with 2 kilodalton PEG surface coating and 10 to 30 kilodalton PLGA 50:50 core with acid-sensitive acetal crosslinker, co-encapsulating 30 to 60 percent of the Component A dose and 20 to 40 percent of the Component B dose at approximately 1000 to 2500 to 1 SNAC-to-peptide molar ratio within the nanoparticle core, at 30 to 80 milligrams total nanoparticle mass per tablet; a mucoadhesive outer tablet matrix (Component F) comprising thiolated chitosan or chitosan-glutathione copolymer at 20 to 50 milligrams; and standard pharmaceutical excipients; wherein total tablet mass is at or above 650 milligrams, SNAC weight fraction is at or below 46.2 percent, bulk density is 0.90 to 1.00 grams per cubic centimeter, and disintegration time in simulated gastric fluid at 37 degrees Celsius is at or above 23 minutes.

Claim 2. The Mitragotri-independent variant of the dosage form of Claim 1, comprising Component A, Component B at 250 to 500 milligrams, Component D at 5 to 20 milligrams, Component E at 30 to 80 milligrams, Component F at 20 to 50 milligrams, trimethyl chitosan auxiliary tight-junction enhancer at 10 to 30 milligrams, and standard excipients, wherein Component C choline and geranate ionic liquid is omitted and the paracellular absorption route is delivered exclusively by Component D augmented by the trimethyl chitosan auxiliary enhancer, thereby avoiding dependency on Harvard / Cage Bio WO 2019/099837 licensing.

Claim 3. The minimum viable variant of the dosage form of Claim 1, comprising Component A, Component B at 300 milligrams, Component C at 30 milligrams, Component F at 30 milligrams, and standard pharmaceutical excipients to total at or above 650 milligrams tablet mass, wherein Component D and Component E are omitted.

Claim 4. The maximum-throughput variant of the dosage form of Claim 1, wherein the dosage form is co-administered with a pulsed-field ingestible capsule per Claim 79 below, and wherein the nominal Component A dose in the co-administered tablet is reduced by 25 to 50 percent relative to the primary label for that peptide.

Claim 5. The direct-compression variant of the dosage form of Claim 1, comprising Component A, Component B, Component C, Component D, Component F, and standard pharmaceutical excipients, wherein Component E nanoparticle encapsulation is omitted and all materials are direct-compressed in a single blending step.

Claim 6. A multi-peptide oral co-formulation comprising any two or more of semaglutide, liraglutide, tirzepatide, exenatide, cagrilintide, retatrutide, and survodutide in a single unit dosage form per Claim 1, wherein the combined peptide mass is at or below 15 percent weight per weight of the tablet and each peptide is present at a dose individually specified in § 11.2 below.

Claim 7. A multi-layer tablet embodiment of the dosage form of Claim 1, comprising: an inner core containing Component A and Component E; a middle layer containing Component B, Component C, and Component D; and an outer layer comprising Component F as the mucoadhesive interface, wherein each layer dissolves sequentially to deliver the Component A payload after the mucoadhesive outer layer has established gastric retention and the Component C paracellular enhancer has primed the epithelial interface.

Claim 8. An oral pharmaceutical composition of matter comprising Components A, B, C, D, E, and F per Claim 1, wherein the composition exhibits theoretical oral bioavailability in the range 0.030 to 0.140 with nominal value 0.086 across the peptide class, under a route-additive absorption mechanism F_epithelium = F_transcellular + F_paracellular, with F_transcellular produced primarily by Component B via the Colston 2025 quicksand mechanism and F_paracellular produced primarily by Component C via the Banerjee 2018 tight-junction-modulation mechanism, the two routes combining additively on F_epithelium without cross-interference across the gastric-corpus epithelium.

§ 11.2 Per-peptide species dependent claims

§ 11.2.1 Semaglutide (Component A1)

Claim 9. The dosage form of Claim 1, wherein the Component A active ingredient is semaglutide at a dose of 0.1 to 7.5 milligrams, administered once daily.

Claim 10. The dosage form of Claim 9, wherein the semaglutide dose is selected from the group consisting of 0.1, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 7.5 milligrams.

Claim 11. The dosage form of Claim 9, wherein the semaglutide dose is 1.0 milligrams administered once daily, corresponding at nominal theoretical bioavailability 0.086 to a subcutaneous semaglutide exposure of approximately 0.68 milligrams weekly, matching the Ozempic standard-maintenance therapeutic window.

Claim 12. The dosage form of Claim 9, wherein Component B SNAC dose is 300 milligrams, Component C CAGE dose is 50 milligrams, Component D PIP640 analog dose is 5 milligrams, Component E nanoparticle dose is 50 milligrams, and Component F mucoadhesive dose is 30 milligrams, and wherein total tablet mass is 717 milligrams.

Claim 13. The Mitragotri-independent semaglutide variant per Claim 2 applied to semaglutide at 0.25 to 5.0 milligrams once daily, avoiding Harvard / Cage Bio license dependency and targeted at post-2033 semaglutide composition-of-matter-off-patent commercialization.

Claim 14. A dose-escalation regimen of Claim 9, initiating at 0.25 milligrams daily for four weeks, escalating to 0.5 milligrams daily for four weeks, to 1.0 milligrams daily for four weeks, and optionally to 2.0 milligrams daily for long-term maintenance in type 2 diabetes or obesity indications.

Claim 15. The dosage form of Claim 9, formulated for fasted-state administration at least 30 minutes before the first meal of the day, with gastric retention extended to 2 to 4 hours by Component F mucoadhesion.

Claim 16. The dosage form of Claim 9, formulated for fed-state administration, wherein the Component C CAGE mucus-fluidization effect mitigates the fed-state bioavailability loss that reduces published SNAC-only Rybelsus systemic exposure by approximately 100 percent in the fed state.

§ 11.2.2 Liraglutide (Component A2)

Claim 17. The dosage form of Claim 1, wherein the Component A active ingredient is liraglutide at a dose of 0.25 to 75.0 milligrams, administered once daily or as a divided twice-daily or thrice-daily regimen.

Claim 18. The dosage form of Claim 17, wherein the liraglutide dose administered once daily is selected from the group consisting of 0.25, 0.5, 1.0, 2.0, 3.0, 5.0, 7.5, 10, 15, 20, 25, 30, 40, 55, and 75 milligrams.

Claim 19. The dosage form of Claim 17, wherein the liraglutide dose administered twice daily is selected from the group consisting of 1.0, 2.5, 5.0, 7.5, 10, and 15 milligrams.

Claim 20. The dosage form of Claim 17, wherein the liraglutide dose administered thrice daily is selected from the group consisting of 1.0, 2.5, and 5.0 milligrams.

Claim 21. The dosage form of Claim 17, wherein the liraglutide dose is 10 milligrams administered once daily, corresponding at nominal theoretical bioavailability 0.076 to a subcutaneous liraglutide exposure of approximately 1.38 milligrams daily, matching the Victoza type 2 diabetes maintenance window.

Claim 22. The dosage form of Claim 17, manufactured by any party other than Novo Nordisk as a generic oral liraglutide tablet, the liraglutide composition-of-matter patent (US 8,114,833 and equivalents) having expired in August 2025 across the United States, European Union, and Japan.

Claim 22-bis. The Mitragotri-independent liraglutide variant per Claim 2 applied to liraglutide at 0.25 to 75 milligrams administered once daily or as a divided twice-daily or thrice-daily regimen, the liraglutide composition-of-matter patent (US 8,114,833) having expired August 2025, positioning the Mitragotri-independent architecture as the commercial path avoiding both Novo Rybelsus tablet-formulation licensing and Harvard / Cage Bio WO 2019/099837 licensing for post-composition-of-matter-expiration generic oral liraglutide, and relying on the literal coverage reading of WO 2019/099837 claim 22 for GLP-1-sequence-derived peptides (liraglutide specification-enumerated) to require Mitragotri independence for GLP-1-sequence-enumerated liraglutide.

Claim 23. A dose-escalation regimen of Claim 17, initiating at 1.0 milligrams daily and escalating at weekly intervals to a maintenance dose of 5 to 15 milligrams daily, monitored for gastrointestinal tolerability.

Claim 24. The dosage form of Claim 17, formulated for pediatric type 2 diabetes patients ages 10 to 17 years at weight-adjusted dose, or for co-administration or substitution for subcutaneous Victoza or Saxenda in transition from injectable to oral therapy.

§ 11.2.3 Tirzepatide (Component A3)

Claim 25. The dosage form of Claim 1, wherein the Component A active ingredient is tirzepatide at a dose of 0.25 to 75 milligrams, administered once daily or as a divided twice-daily or thrice-daily regimen.

Claim 26. The dosage form of Claim 25, wherein the tirzepatide dose administered once daily is selected from the group consisting of 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 5.0, 7.5, 10, 12, 15, 20, 25, 30, 40, 50, 60, and 75 milligrams.

Claim 27. The dosage form of Claim 25, wherein the tirzepatide dose administered twice daily is selected from the group consisting of 1.0, 2.5, 5.0, 7.5, 10, and 15 milligrams.

Claim 28. The dosage form of Claim 25, wherein the tirzepatide dose administered thrice daily is selected from the group consisting of 1.0, 2.5, and 5.0 milligrams.

Claim 29. The dosage form of Claim 25, wherein the tirzepatide dose is 12 milligrams administered once daily, corresponding at nominal theoretical bioavailability 0.0891 to a subcutaneous tirzepatide exposure of approximately 9.4 milligrams weekly, sitting at mid-maintenance between the 7.5 milligram and 10 milligram Mounjaro / Zepbound titration steps.

Claim 30. A dose-escalation regimen of Claim 25, initiating at 2 milligrams daily for four weeks, escalating to 5 milligrams daily for four weeks, to 7.5 milligrams daily for four weeks, and to 12 milligrams daily for long-term maintenance.

Claim 31. The dosage form of Claim 25, for use in GIP-receptor-positive indications including type 2 diabetes, obesity, obstructive sleep apnea, and heart-failure-with-preserved-ejection-fraction obesity cohorts.

Claim 32. The Mitragotri-independent tirzepatide variant per Claim 2 applied to tirzepatide, relying on the plausibly-outside-literal-scope reading of WO 2019/099837 claim 22 for GIP-derived dual agonists, noting the GIP parent sequence distinguishes tirzepatide from GLP-1-sequence-derived analogs.

Claim 33. The dosage form of Claim 25, manufactured by any party other than Eli Lilly and Company after expiration of the Lilly tirzepatide composition-of-matter patent US 9,474,780 in January 2036, as a generic oral tirzepatide tablet.

§ 11.2.4 Exenatide (Component A4)

Claim 34. The dosage form of Claim 1, wherein the Component A active ingredient is exenatide at a dose of 0.01 to 7.5 milligrams, administered once daily, twice daily, or thrice daily.

Claim 35. The dosage form of Claim 34, wherein the exenatide dose administered once daily is selected from the group consisting of 0.01, 0.025, 0.05, 0.1, 0.15, 0.2, 0.3, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 5.0, and 7.5 milligrams.

Claim 36. The dosage form of Claim 34, wherein the exenatide dose administered twice daily is selected from the group consisting of 0.025, 0.05, 0.1, 0.15, 0.25, 0.5, 1.0, and 1.5 milligrams.

Claim 37. The dosage form of Claim 34, wherein the exenatide dose administered thrice daily is selected from the group consisting of 0.025, 0.05, 0.1, 0.25, 0.5, 0.75, and 1.0 milligrams.

Claim 38. The dosage form of Claim 34, wherein the exenatide dose is 0.1 milligrams administered twice daily, corresponding at nominal theoretical bioavailability 0.0693 to a subcutaneous exenatide exposure of approximately 9 micrograms twice daily, matching the Byetta mid-titration window between the 5 and 10 microgram SC doses.

Claim 39. The unlipidated-peptide-specific variant of the dosage form of Claim 34, wherein the Component E nanoparticle core additionally contains hydrophobic ion pairing (HIP) counterions selected from sodium dodecyl sulfate, sodium deoxycholate, and sodium taurocholate at a peptide-to-counterion molar ratio of 1:5 to 1:20, to compensate for the absence of a fatty-acid anchor for SNAC-defect insertion via the Twarog 2020 charge-neutralization mechanism.

Claim 40. The dosage form of Claim 34, co-administered with the pulsed-field ingestible capsule of Claim 79 below as a co-primary embodiment for exenatide specifically, the short 2.4-hour plasma elimination half-life and unlipidated structure making device-assisted delivery the preferred embodiment for exenatide beyond the tablet-only primary embodiment.

Claim 41. The dosage form of Claim 34, manufactured by any party as a generic oral exenatide tablet, the exenatide composition-of-matter patent having expired in 2017 across the United States and 2024 across the European Union, with Amneal Pharmaceuticals generic exenatide injectable approved November 2024 as the first US generic GLP-1 RA injectable.

Claim 42. A dose-escalation regimen of Claim 34, initiating at 0.05 milligrams twice daily for four weeks, escalating to 0.1 milligrams twice daily for long-term maintenance in type 2 diabetes, with optional titration to 0.2 milligrams twice daily for refractory cases.

Claim 43. The dosage form of Claim 34, for use in populations where weekly extended-release depot administration is contraindicated, including patients with severe injection aversion, patients with impaired subcutaneous absorption, and patients requiring rapid dose titration adjustment.

Claim 43-bis. The Mitragotri-independent exenatide variant per Claim 2 applied to exenatide at 0.01 to 7.5 milligrams administered once daily, twice daily, or thrice daily, the exenatide composition-of-matter patent having expired 2017 United States and 2024 European Union, positioning the Mitragotri-independent architecture as the commercial path avoiding Harvard / Cage Bio WO 2019/099837 licensing for post-composition-of-matter-expiration generic oral exenatide, recommended as co-primary embodiment with the pulsed-field ingestible capsule of Claim 79 per Claim 40 to compensate for the 2.4-hour plasma elimination half-life and the unlipidated-peptide susceptibility to gastric-pH aggregation per steel-man Attack 31, and relying on the literal coverage reading of WO 2019/099837 claim 22 for GLP-1-sequence-derived peptides (exenatide exendin-4 sequence specification-enumerated) to require Mitragotri independence.

§ 11.2.5 Cagrilintide (Component A5)

Claim 44. The dosage form of Claim 1, wherein the Component A active ingredient is cagrilintide at a dose of 0.125 to 15.0 milligrams, administered once daily as monotherapy, or in fixed-dose combination with semaglutide per Claim 49 below.

Claim 45. The dosage form of Claim 44, wherein the cagrilintide dose administered once daily is selected from the group consisting of 0.125, 0.175, 0.25, 0.325, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.5, 6.0, 8.0, 10.0, 12.0, and 15.0 milligrams.

Claim 46. The dosage form of Claim 44, wherein the cagrilintide dose administered twice daily is selected from the group consisting of 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, and 5.0 milligrams.

Claim 47. The dosage form of Claim 44, wherein the cagrilintide dose is 3.0 milligrams administered once daily as monotherapy, corresponding at nominal theoretical bioavailability 0.0891 to a subcutaneous cagrilintide exposure of approximately 2.4 milligrams weekly, matching the Novo Phase 3 REDEFINE monotherapy window.

Claim 48. The Mitragotri-independent cagrilintide variant per Claim 2 applied to cagrilintide, relying on the plausibly-outside-literal-scope reading of WO 2019/099837 claim 22 for amylin-derived analogs, noting the amylin parent sequence distinguishes cagrilintide from GLP-1-sequence-derived analogs.

Claim 49. An oral CagriSema co-tablet comprising cagrilintide at 0.5 to 6.0 milligrams and semaglutide at 0.5 to 6.0 milligrams in a single unit dosage form per Claim 1, administered once daily, wherein the cagrilintide-to-semaglutide mass ratio is 1:1 matching the Novo subcutaneous CagriSema 2.4-milligram-plus-2.4-milligram-weekly dosing.

Claim 50. The oral CagriSema co-tablet of Claim 49, wherein the cagrilintide dose is 3.0 milligrams and the semaglutide dose is 3.0 milligrams, administered once daily for obesity maintenance.

Claim 51. The oral CagriSema co-tablet of Claim 49 at 1:2 cagrilintide-to-semaglutide mass ratio (semaglutide-heavy), at 2:1 ratio (cagrilintide-heavy), or at 1:0.5 ratio, covering the near-equimolar combination space independent of the Novo REDEFINE-1 fixed-dose combination.

Claim 52. A dose-escalation regimen of Claim 44 or Claim 49, initiating at 0.5 milligrams daily (monotherapy) or 0.5 plus 0.5 milligrams daily (CagriSema) and escalating over 12 to 24 weeks to 3.0 milligrams (monotherapy) or 3.0 plus 3.0 milligrams (CagriSema) maintenance, with optional upward titration.

§ 11.2.6 Retatrutide (Component A6)

Claim 53. The dosage form of Claim 1, wherein the Component A active ingredient is retatrutide at a dose of 0.25 to 75 milligrams, administered once daily or as a divided twice-daily regimen.

Claim 54. The dosage form of Claim 53, wherein the retatrutide dose administered once daily is selected from the group consisting of 0.25, 0.5, 1.0, 2.0, 3.0, 5.0, 7.5, 10, 12, 15, 20, 25, 30, 40, 50, 60, and 75 milligrams.

Claim 55. The dosage form of Claim 53, wherein the retatrutide dose administered twice daily is selected from the group consisting of 1.0, 2.5, 5.0, 7.5, 10, and 15 milligrams.

Claim 56. The dosage form of Claim 53, wherein the retatrutide dose is 10 milligrams administered once daily, corresponding at nominal theoretical bioavailability 0.0891 to a subcutaneous retatrutide exposure of approximately 7.8 milligrams weekly, matching the Phase 3 TRIUMPH mid-maintenance window between the 4, 8, and 12 milligram SC steps.

Claim 57. The Mitragotri-independent retatrutide variant per Claim 2 applied to retatrutide, relying on the plausibly-outside-literal-scope reading of WO 2019/099837 claim 22 for GIP-derived triple agonists, noting the GIP parent sequence and dual non-GLP-1 receptor engagement distinguish retatrutide from GLP-1-sequence-derived analogs.

Claim 58. The dosage form of Claim 53, for use in indications where glucagon-receptor agonism is therapeutically desired, including severe obesity (BMI ≥ 40), metabolic dysfunction-associated steatohepatitis (MASH), and obesity with insulin resistance in the non-diabetic range.

Claim 59. A dose-escalation regimen of Claim 53, initiating at 1.0 milligrams daily for four weeks, escalating to 3.0 milligrams daily for four weeks, to 6.0 milligrams daily for four weeks, and to 10.0 milligrams daily for long-term maintenance, matching the Phase 3 TRIUMPH titration sequence at oral-equivalent doses.

Claim 60. The dosage form of Claim 53, manufactured by any party other than Eli Lilly and Company after expiration of the Lilly retatrutide composition-of-matter patent family (expected approximately 2040) as a generic oral retatrutide tablet.

§ 11.2.7 Survodutide (Component A7)

Claim 61. The dosage form of Claim 1, wherein the Component A active ingredient is survodutide at a dose of 0.1 to 30 milligrams, administered once daily or as a divided twice-daily regimen.

Claim 62. The dosage form of Claim 61, wherein the survodutide dose administered once daily is selected from the group consisting of 0.1, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 15.0, 20.0, 25.0, and 30.0 milligrams.

Claim 63. The dosage form of Claim 61, wherein the survodutide dose administered twice daily is selected from the group consisting of 0.5, 1.0, 2.0, 3.0, and 5.0 milligrams.

Claim 64. The dosage form of Claim 61, wherein the survodutide dose is 5.0 milligrams administered once daily, corresponding at nominal theoretical bioavailability 0.0825 to a subcutaneous survodutide exposure of approximately 3.6 milligrams weekly, matching the Phase 3 SYNCHRONIZE and LIVERAGE mid-titration window.

Claim 65. The Mitragotri-independent survodutide variant per Claim 2 applied to survodutide, relying on the plausibly-outside-literal-scope reading of WO 2019/099837 claim 22 for glucagon-derived dual agonists, noting the glucagon parent sequence and 29-amino-acid length distinguish survodutide from GLP-1-sequence-derived analogs.

Claim 66. The dosage form of Claim 61, for use in metabolic dysfunction-associated steatohepatitis (MASH) at doses 3.0 to 6.0 milligrams daily, the survodutide MASH indication having been granted FDA Breakthrough Therapy designation in October 2024.

Claim 67. The dosage form of Claim 61, for use in obesity with or without type 2 diabetes, at doses 2.4 to 6.0 milligrams daily.

Claim 68. A dose-escalation regimen of Claim 61, initiating at 0.5 milligrams daily for four weeks, escalating to 1.5 milligrams daily for four weeks, to 3.0 milligrams daily for four weeks, and to 5.0 milligrams daily for long-term maintenance.

Claim 69. The dosage form of Claim 61, manufactured by any party other than Boehringer Ingelheim or Zealand Pharma after expiration of the Zealand / BI survodutide composition-of-matter patent family (expected approximately 2035 to 2040) as a generic oral survodutide tablet.

§ 11.3 Process and administration claims

Claim 70. A process for manufacturing the dosage form of Claim 1, comprising: (a) dissolving PLGA-PEG block copolymer in acetone at 10 milligrams per milliliter; (b) preparing an aqueous feed containing the target fraction of Component A and the target fraction of Component B; (c) precipitating the nanoparticles by controlled addition to rapidly stirring aqueous phase; (d) evaporating acetone under reduced pressure; (e) filtering through 0.22-micrometer membrane; (f) characterizing by dynamic light scattering to confirm 100-nanometer mean diameter and polydispersity index below 0.2; (g) lyophilizing to powder; (h) blending lyophilized nanoparticle powder with bulk Component B, Component C adsorbed onto microcrystalline cellulose at 5:1 mass ratio, Component D, and standard excipients; (i) direct-compressing at 10 to 20 kilonewtons to target bulk density 0.90 to 1.00 grams per cubic centimeter; and (j) coating with Component F mucoadhesive outer layer via spray coating or compression coating.

Claim 71. The process of Claim 70, wherein the Component A to Component B co-encapsulation ratio within the nanoparticle core is controlled by adjusting the aqueous feed ratio during step (b).

Claim 72. The process of Claim 70, wherein the PLGA acid-sensitive acetal crosslinker is selected to disassemble the nanoparticle core at pH 5.0 to 6.0 in simulated gastric fluid under SNAC buffering, and wherein the nanoparticle disassembly time is between 10 and 30 minutes after gastric deposition.

Claim 73. The process of Claim 70, wherein the Component F outer layer coating is applied by spray coating at 20 to 30 milligrams per tablet, by compression coating at 30 to 50 milligrams per tablet, or by dip coating.

Claim 74. A method of administering the dosage form of Claim 1 to a human subject, comprising: (a) instructing the subject to consume the dosage form with 120 milliliters of water in fasted state at least 30 minutes before the first meal of the day; (b) instructing the subject to remain upright for at least 15 minutes after administration; and (c) monitoring the subject for gastrointestinal tolerability, blood glucose response, and body weight response on standard schedule.

Claim 75. The method of Claim 74, wherein administration is in fed state, with dose adjustment of at or above 1.25-fold to compensate for residual fed-state F reduction that is substantially mitigated by Component C mucus fluidization relative to the Rybelsus fed-state loss.

Claim 76. The method of Claim 74, wherein the subject is concurrently on a proton pump inhibitor (PPI), H2 receptor antagonist, or other acid-suppressing therapy, and wherein the dose is reduced to account for increased local pH and improved peptide stability.

Claim 77. The method of Claim 74, wherein administration is co-scheduled with a glucose monitor reading, an insulin pump delivery event, or other therapeutic intervention for type 2 diabetes or obesity.

Claim 78. The method of Claim 74, wherein dose-escalation is conducted at four-week intervals from a starting-dose matching 10 to 25 percent of the maintenance-dose, with monitoring for nausea, vomiting, diarrhea, constipation, and pancreatitis markers.

§ 11.4 Pulsed-field device claims

Claim 79. An ingestible pulsed-field capsule for oral delivery of a metabolic peptide of molecular weight 3 to 5 kilodaltons, the capsule comprising: an enteric polymer body of 15 by 9 millimeter maximum dimensions, FDA-approved excipient chemistry; two microelectrodes on the capsule surface separated by 2 to 10 millimeters, of gold-plated titanium construction; a silver-zinc or zinc-air miniature primary battery at 3 volts and 10 milliampere-hours, activated by gastric-fluid contact via dissolvable polymer barrier; a pulse-generator circuit delivering pulses at frequency 10 to 300 kilohertz, amplitude 0.1 to 25 volts per centimeter bulk field between the microelectrodes, pulse duration 1 to 100 milliseconds, and duty cycle 0.1 to 10 percent; and a peptide payload of Component A at 0.05 to 10 milligrams, Component B at 15 to 50 milligrams, Component C at 10 to 30 milligrams, and optional Component D at 1 to 5 milligrams, the payload occupying 30 to 60 percent of the capsule internal volume.

Claim 80. The capsule of Claim 79, wherein the Component A peptide is selected from the group consisting of semaglutide, liraglutide, tirzepatide, exenatide, cagrilintide, retatrutide, and survodutide.

Claim 81. The capsule of Claim 79, for co-primary embodiment of exenatide per Claim 40, wherein the exenatide dose is 0.05 to 0.5 milligrams per capsule and the capsule is administered twice daily.

Claim 82. The capsule of Claim 79, for semaglutide delivery at 0.25 milligrams per capsule administered once weekly, exploiting the 168-hour plasma elimination half-life for an oral weekly-dosing regimen unavailable in the tablet embodiments.

Claim 83. The capsule of Claim 79, wherein the pulse frequency is selected from the group consisting of 10, 20, 30, 50, 75, 100, 150, 200, and 300 kilohertz, the pulse amplitude is selected from the group consisting of 0.1, 0.25, 0.5, 1, 2, 5, 10, 15, and 25 volts per centimeter, the duty cycle is selected from the group consisting of 0.1, 0.25, 0.5, 1, 2, 2.5, 5, and 10 percent, and the electrode separation is selected from the group consisting of 2, 3, 5, 7, and 10 millimeters.

Claim 84. The capsule of Claim 79, wherein the pulse activation window is 30 to 120 minutes after capsule arrival in the stomach, triggered by gastric-pH sensor on the capsule surface.

Claim 85. The capsule of Claim 79, wherein the enteric polymer body comprises hydroxypropyl methylcellulose phthalate (HPMCP), Eudragit L100-55, Eudragit S100, or equivalent FDA-approved enteric polymer.

Claim 86. The capsule of Claim 79, further comprising an on-capsule Bluetooth-low-energy beacon for delivery confirmation and dose-compliance logging.

Claim 87. The capsule of Claim 79, co-administered with the tablet dosage form of Claim 1 per Claim 4 at the reduced Component A tablet dose.

Claim 88. A method of operating the capsule of Claim 79, comprising: (a) activation of the pulse-generator circuit upon gastric-fluid contact; (b) sub-electroporative iontophoretic drift of Component B, Component C, and Component A into the gastric-corpus epithelium adjacent to the capsule during the activation window; (c) transient tight-junction-protein rearrangement at the device-adjacent epithelial surface; and (d) payload release by passive dissolution over 30 to 120 minutes.

§ 11.5 Combination and co-formulation claims

Claim 89. An oral semaglutide-plus-liraglutide co-tablet per Claim 6, wherein semaglutide is at 0.5 to 2.0 milligrams and liraglutide is at 2.0 to 10.0 milligrams, administered once daily, for dual GLP-1-receptor-agonist exposure-smoothing combining semaglutide's long half-life with liraglutide's titratable daily dosing.

Claim 90. An oral semaglutide-plus-tirzepatide co-tablet per Claim 6, wherein semaglutide is at 0.5 to 2.0 milligrams and tirzepatide is at 1.0 to 10.0 milligrams, administered once daily, for combined GLP-1 and GIP/GLP-1 receptor engagement without requiring two separate injectable devices.

Claim 91. An oral semaglutide-plus-exenatide co-tablet per Claim 6 at semaglutide 1.0 milligram once daily plus exenatide 0.05 milligrams twice daily, exploiting exenatide's rapid-onset prandial effect with semaglutide's sustained background exposure.

Claim 92. An oral CagriSema co-tablet per Claims 49 to 52, in all enumerated mass ratios and dose combinations.

Claim 93. An oral semaglutide-plus-retatrutide co-tablet per Claim 6, wherein semaglutide is at 0.5 to 2.0 milligrams and retatrutide is at 1.0 to 8.0 milligrams, administered once daily, for dual GLP-1 and GLP-1/GIP/glucagon triple agonism.

Claim 94. An oral semaglutide-plus-survodutide co-tablet per Claim 6, wherein semaglutide is at 0.5 to 2.0 milligrams and survodutide is at 1.0 to 5.0 milligrams, administered once daily, for combined GLP-1 and GLP-1/glucagon dual agonism particularly targeted at MASH plus obesity comorbid indications.

Claim 95. An oral tirzepatide-plus-cagrilintide co-tablet per Claim 6, wherein tirzepatide is at 2.0 to 10.0 milligrams and cagrilintide is at 1.0 to 3.0 milligrams, administered once daily, for combined GLP-1/GIP plus amylin agonism delivering three distinct receptor-class mechanisms in a single oral dose.

Claim 96. An oral split-dose regimen per Claim 6 combining tirzepatide and exenatide, wherein tirzepatide at 2.0 to 10.0 milligrams is administered once daily in a first dosage form and exenatide at 0.05 to 0.5 milligrams is administered twice daily in a separate dosage form or a separate pulsed-field ingestible capsule per Claim 81, the split-dose architecture reflecting the approximately 50-fold half-life mismatch between tirzepatide (120 hours) and exenatide (2.4 hours) that precludes a single-tablet co-dose optimized for both peptides simultaneously.

Claim 97. An oral retatrutide-plus-cagrilintide co-tablet per Claim 6, wherein retatrutide is at 2.0 to 8.0 milligrams and cagrilintide is at 1.0 to 3.0 milligrams, administered once daily, for combined triple-agonist plus amylin quadruple-receptor-class engagement.

Claim 98. An oral survodutide-plus-cagrilintide co-tablet per Claim 6, wherein survodutide is at 1.0 to 5.0 milligrams and cagrilintide is at 1.0 to 3.0 milligrams, administered once daily.

Claim 99. An oral triple-peptide co-tablet per Claim 6, comprising semaglutide, cagrilintide, and tirzepatide at individual doses specified in § 11.2, administered once daily, for the broadest receptor-class coverage in a single oral dosage form.

Claim 100. An oral combination of any of Claims 89 to 99 with the pulsed-field ingestible capsule of Claim 79 per Claim 4, for maximum-throughput metabolic-peptide oral delivery.

§ 11.6 Component C ionic-liquid analog species claims

The following claims elevate the § 12.3 Component C analog variants to explicit species-level preemption, closing the design-around space on choline-and-geranate via non-geranate choline ionic liquids and betaine-based deep-eutectic-solvent systems. Each species substitutes for choline-and-geranate in the Claim 1 architecture at equivalent function, placing the species claim explicitly outside the literal scope of Mitragotri WO 2019/099837 claim 22 (“choline-and-geranate”) by fatty-acid-anion identity or by substitution of the choline cation itself.

Claim 101. The dosage form of Claim 1, wherein Component C comprises choline and octanoate ionic liquid (CAOT) at choline-to-octanoate molar ratio from 1:1 to 1:4 and total dose 10 to 100 milligrams per tablet, the C8 fatty-acid-anion variant providing enhanced bilayer interaction relative to geranate per Neville 2024 neutron-reflectometry and QCM-D characterization at DMPC phospholipid bilayers.

Claim 102. The dosage form of Claim 1, wherein Component C comprises choline and decanoate ionic liquid at choline-to-decanoate molar ratio from 1:1 to 1:4 and total dose 10 to 100 milligrams per tablet, providing a saturated C10 fatty-acid-anion variant intermediate in chain length between CAOT (C8) and CAGE geranate (branched C10 unsaturated).

Claim 103. The dosage form of Claim 1, wherein Component C comprises choline and laurate ionic liquid at choline-to-laurate molar ratio from 1:1 to 1:4 and total dose 10 to 100 milligrams per tablet, providing a saturated C12 fatty-acid-anion variant of higher hydrophobic potency.

Claim 104. The dosage form of Claim 1, wherein Component C comprises choline and oleate ionic liquid at choline-to-oleate molar ratio from 1:1 to 1:4 and total dose 10 to 100 milligrams per tablet, providing an unsaturated C18 fatty-acid-anion variant with fluidity-enhancing membrane-interaction properties.

Claim 105. The dosage form of Claim 1, wherein Component C comprises a betaine-based deep-eutectic-solvent system at betaine-to-hydrogen-bond-donor molar ratio from 1:1 to 1:10 with hydrogen-bond-donor selected from glycerol, urea, lactic acid, malonic acid, and ethylene glycol, at total dose 10 to 100 milligrams per tablet, providing a non-choline ionic-liquid variant entirely outside the Mitragotri WO 2019/099837 choline-and-geranate scope.

Claim 106. The dosage form of Claim 1, wherein Component C comprises a choline-anion ionic liquid at molar ratio selected from the group consisting of 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:8, and 1:10, for any of the fatty-acid anions recited in Claims 101, 102, 103, and 104, covering the full Mitragotri-adjacent ratio space for design-around preemption under the doctrine of equivalents.

Class overview: seven-peptide architecture matrix

Component B (SNAC 200-500 mg), C (CAGE 30-80 mg), D (PIP640/chitosan 2-20 mg), E (PLGA-PEG NP 30-80 mg), F (thiolated chitosan 20-50 mg) are common across all peptides

Peptide (class / MW in Da)	Primary PO label	Disclosed envelope	SC reference dose / interval	t½ (h)	F_theor nominal	F_eff pre-bench	Mitragotri scope WO 2019/099837 cl.22	US CoM status (expiration / generic)	Device role (§ 11.4 capsule)	Key structural feature
Semaglutide GLP-1 RA 4113.58 Da *reference peptide*	**1.0 mg** QD	0.25–5.0 mg QD (7 species)	~0.68 mg QW (Ozempic)	**168**	**8.6 %** (4.2–14)	3.6 %	**LITERAL** GLP-1 sequence *license-critical*	Active expires 2033	Optional QW @ 0.25 mg *§11.4 Claim 82*	C18 at Lys26 γGlu-2xOEG Aib2 DPP-4r
Liraglutide GLP-1 RA 3751.20 Da	**10 mg** QD	0.5–55 mg QD (13 spp) + BID/TID	1.38 mg QD (Victoza)	**12.6**	**7.6 %** (3.7–13)	3.0 %	**LITERAL** GLP-1 sequence *license-critical*	**EXPIRED** Aug 2025 (US) *HIKMA, Teva gen.*	Optional tablet primary	C16 at Lys26 γGlu only albumin binding
Tirzepatide GLP-1/GIP dual 4813.48 Da	**12 mg** QD	0.5–50 mg QD (14 spp) + BID/TID	9.4 mg QW (Mounjaro)	**120**	**8.91 %** (4.4–14)	3.87 %	**OUTSIDE** GIP-derived dual *(FTO opinion rec.)*	Active Jan 2036 (US 9,474,780)	Optional tablet primary	C20 at Lys20 γGlu + miniPEG Aib2 + Aib13
Exenatide GLP-1 RA (exendin-4) 4186.57 Da	**0.1 mg** BID	0.025–5 mg QD / BID / TID *(28 total species)*	~9 µg BID (Byetta)	**2.4**	**6.93 %** (3.4–11)	2.49 %	**LITERAL** enumerated in cl.22 *license-critical*	**EXPIRED** 2017 (US) / 2024 (EU) *Amneal gen. Nov 2024*	**CO-PRIMARY** unlipidated + short t½	**UNLIPIDATED** Gly2 DPP-4r HIP counterion
Cagrilintide amylin analog 4409.01 Da	**3 mg QD** or 3+3 mg CagriSema	0.25–15 mg QD (13 spp) + BID / co-tablet	2.4 mg QW (Phase 3) *REDEFINE NDA 2025*	**170**	**8.91 %** (4.4–14)	3.87 %	**OUTSIDE** amylin-derived *(FTO opinion rec.)*	Active ~2035–2040 (Novo)	**Co-tablet** oral CagriSema *primary §11.5 (49-52)*	C20 N-terminal γGlu + miniPEG Cys2–Cys7 disulfide
Retatrutide GLP-1/GIP/GCG triple 4731.33 Da	**10 mg** QD	0.5–50 mg QD (14 spp) + BID/TID	~7.8 mg QW (Phase 3) *TRIUMPH NDA Q4'26*	**144**	**8.91 %** (4.4–14)	3.87 %	**OUTSIDE** GIP-derived triple *(FTO opinion rec.)*	Active ~2040 (Lilly)	Optional tablet primary *MASH co-indication*	C20 at Lys16/17 γGlu + AEEA Aib2 + Aib20
Survodutide GLP-1/GCG dual 4231.63 Da	**5 mg** QD	0.25–20 mg QD (13 spp) + BID	~3.6 mg QW (Phase 3) *SYNCHRONIZE H1'26*	**150**	**8.25 %** (4.0–13)	3.43 %	**OUTSIDE** glucagon-derived 29aa *(FTO opinion rec.)*	Active ~2035–2040 (Zealand/BI)	Optional MASH indication *FDA Breakthrough '24*	C18 at Lys24 γGlu only, no OEG Acbc2 (cyclobutane)

Mitragotri literal (license-critical) Mitragotri outside / CoM expired (FTO clear) Envelope "spp" = species enumerated in § 11.2 per-peptide claims.

F_eff pre-bench applies CAGE gastric-translation penalties (ionic-liquid state at pH 1–2, local concentration, gastric-corpus claudin profile vs Caco-2). Effective band scales with future bench data; theoretical band is the upper envelope.

Figure 7. Class-overview matrix. Seven peptides × nine architecture attributes: molecular weight, lipidation chemistry, SC bioavailability, plasma half-life, oral dose envelope, F_theor nominal, F_eff nominal, Mitragotri WO 2019/099837 claim 22 scope, composition-of-matter status.

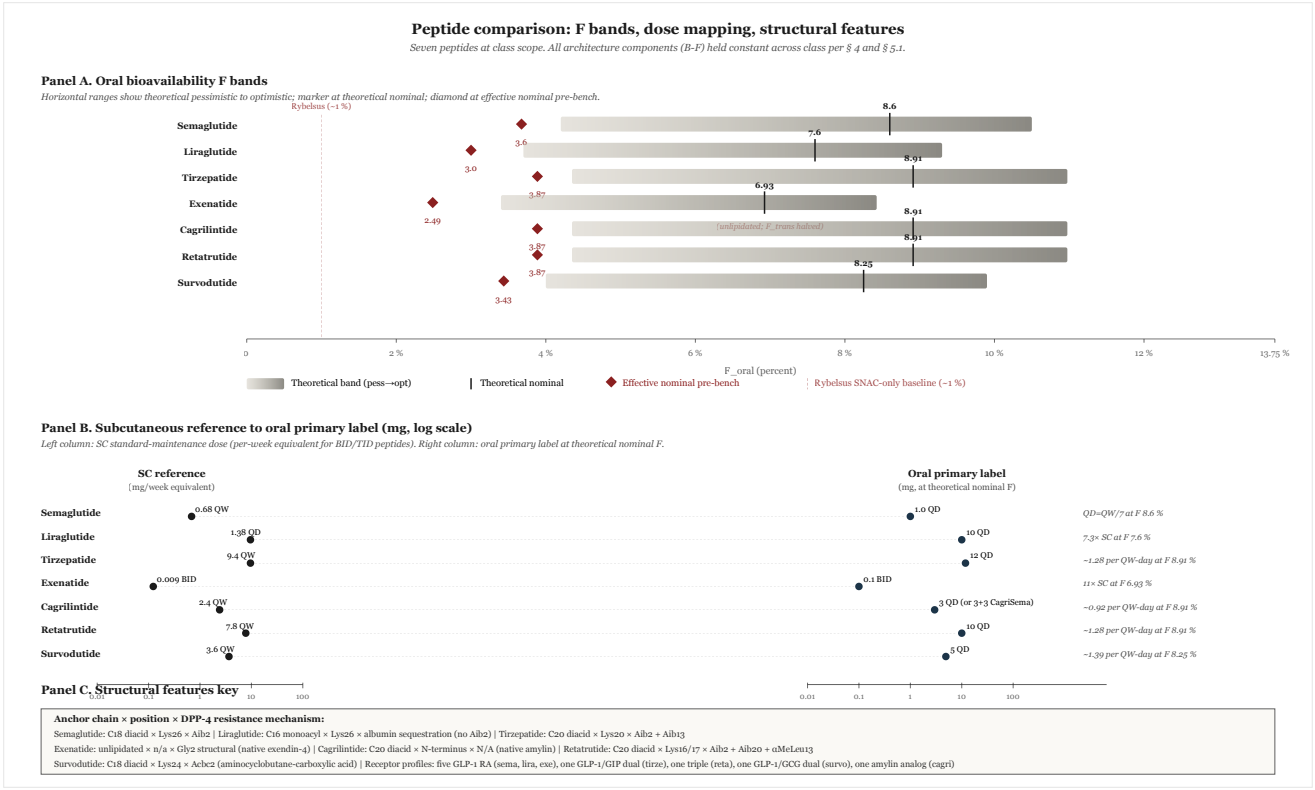

Figure 8. Peptide comparison chart. F bands theoretical and effective per peptide; subcutaneous-to-oral dose mapping under one-compartment PK; structural features; regulatory milestones (REDEFINE 1, TRIUMPH, SYNCHRONIZE/LIVERAGE).

§ 12

Variants and alternative components

This section enumerates compositional variants at each component position and at the excipient, dosage-form, and administration levels. Each variant is compatible with the route-additive F_epithelium = F_transcellular + F_paracellular mechanism of the primary embodiment; bench validation of each variant is warranted. All variants are placed into the public domain as of the publication date.

§ 12.1 Peptide variants (Component A)

§ 12.1.1 Lipidation chain-length variants. For each of the seven enumerated peptides, variants with C12, C14, C16, C18, C20, or C22 fatty-acyl or fatty-diacyl modification at any lysine residue, at the N-terminus, or at the C-terminus, attached via direct amide bond, gamma-glutamate spacer, 2-(2-

aminoethoxy)ethoxyacetyl (AEEA / OEG) mini-PEG spacer, double-OEG spacer, triple-OEG spacer, or equivalent polyether linker of up to 50-angstrom contour length.

§ 12.1.2 Lipidation-position variants. For each peptide, lipidation at alternative lysine positions beyond the preferred position (semaglutide and liraglutide Lys26; tirzepatide Lys20; retatrutide Lys16 or Lys17; survodutide Lys24; cagrilintide N-terminal). Variants with multiple lipidation sites on the same peptide.

§ 12.1.3 DPP-4 resistance variants. Peptides with Aib (aminoisobutyric acid), alpha-methyl-leucine (αMeLeu), 1-aminocyclobutane-1-carboxylic acid (Acbc), or N-methylated amino acid substitutions at position 2 or position 13 (semaglutide, tirzepatide, retatrutide, survodutide analog positions). D-amino acid substitutions at cleavage-susceptible positions. N-terminal modifications providing steric or electronic DPP-4 blocking.

§ 12.1.4 Glycosylated peptide variants. Peptides with N-linked or O-linked glycans at any residue, of glycan mass 200 to 3000 daltons.

§ 12.1.5 PEGylated peptide variants. Peptides with polyethylene glycol conjugates at any residue, of PEG molecular weight 500 to 20,000 daltons, attached via succinimidyl ester, maleimide, or click-chemistry triazole chemistry.

§ 12.1.6 Prodrug variants. Peptides with protective-group, ester, or amide cleavable linkage to a masking moiety, cleavable under gastric pH 5 to 6 conditions or by intestinal enzyme cleavage.

§ 12.1.7 Salt form variants. Peptide acetate, hydrochloride, trifluoroacetate, sodium, potassium, zinc, or pharmaceutically acceptable salt forms; peptide in zwitterionic neutral form; peptide as mixed-salt co-crystal.

§ 12.1.8 Stereochemistry variants. L-amino acid peptides per preferred embodiment; variants comprising at least one D-amino acid substitution at positions compatible with receptor binding.

§ 12.2 Component B variants

§ 12.2.1 SNAC analogs. Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC, preferred). Sodium N-[10-(2-hydroxybenzoyl)amino]decanoate (5-CNAC). Sodium N-[8-(5-chloro-2-hydroxybenzoyl)amino]caprylate. Sodium N-[8-(2-hydroxy-4-methoxybenzoyl)amino]caprylate. N-acyl-amino-acid permeation-enhancer analogs with 6-to-12-carbon fatty-acid tail and salicylate or substituted-salicylate head group.

§ 12.2.2 Sodium caprate (C10). As alternative transcellular enhancer at 100 to 300 milligrams per tablet.

§ 12.2.3 Sodium caprylate (C8). At 100 to 300 milligrams per tablet.

§ 12.2.4 Sodium laurate (C12). At 100 to 300 milligrams per tablet.

§ 12.2.5 Sucrose laurates and sucrose esters. Sucrose monolaurate, sucrose dilaurate, sucrose monocaprate at 50 to 200 milligrams per tablet.

§ 12.2.6 Hydrophobic ion pairing (HIP) variants. Peptide hydrophobic ion pairing with sodium deoxycholate, sodium dodecyl sulfate, sodium taurocholate, sodium cholate, or medium-chain fatty-acid anion at 1:5 to 1:20 peptide-to-counterion molar ratio, as alternative transcellular carrier for unlipidated peptides.

§ 12.2.7 Dual-enhancer combinations. SNAC plus sodium caprate at combined 400 to 600 milligrams per tablet. SNAC plus sucrose monolaurate. Sodium caprate plus sodium caprylate.

§ 12.2.8 Component B dose variants. 150, 200, 250, 300, 350, 400, 450, 500 milligrams per tablet.

§ 12.3 Component C variants

§ 12.3.1 CAGE analogs (alternative fatty-acid anions). Choline and geranate 1:2 (preferred). Choline and octanoate (CAOT). Choline and decanoate. Choline and laurate. Choline and oleate. Choline and myristate. Choline and palmitate.

§ 12.3.2 Choline-anion molar ratio variants. 1:1, 1:2 (preferred), 1:3, 1:4.

§ 12.3.3 Substituted choline variants. 2-hydroxyethyl-trimethylammonium (choline, preferred). 2-hydroxyethyl-diethylmethylammonium. 2-hydroxyethyl-triethylammonium. Acetylcholine. Betaine.

§ 12.3.4 Substituted geranate and related terpenoid anion variants. Geranic acid (preferred). Neric acid. Citronellic acid. Linalyl acid. Perillic acid. Hydroxycitronellic acid. Geranyl-propionic acid.

§ 12.3.5 Deep-eutectic solvent (DES) variants. Choline chloride plus urea at 1:2 molar ratio. Choline chloride plus oxalate at 1:2 molar ratio. Choline chloride plus glycerol at 1:2 molar ratio. Choline chloride plus malonic acid at 1:1 molar ratio. Betaine-based DES systems.

§ 12.3.6 Non-choline ionic liquid variants. 1-methyl-3-butylimidazolium acetate. 1-ethyl-3-methylimidazolium chloride. Ammonium geranate. Phosphonium geranate. Pyridinium-based room-temperature ionic liquids with fatty-acid anions.

§ 12.3.7 Component C dose variants. 10, 20, 30, 40, 50, 60, 80 milligrams per tablet.

§ 12.4 Component D variants

§ 12.4.1 PIP peptide family variants. PIP640 analog decapeptide (preferred). PIP250 parent peptide. PIP640 analog with single amino-acid substitutions at positions compatible with MYPT1 binding. PIP640 analog with extended (12-residue) or truncated (8-residue) sequences. Cyclized-PIP analog forms.

§ 12.4.2 Chitosan variants. Low-molecular-weight (5 to 20 kilodalton) chitosan at 75 to 95 percent deacetylation. Medium-molecular-weight (50 to 150 kilodalton) chitosan. Trimethyl chitosan (quaternized) at 20 to 80 percent quaternization. Thiolated chitosan (chitosan-thioglycolic acid, chitosan-cysteine, chitosan-glutathione).

§ 12.4.3 Zonulin-pathway modulator variants. Zonula occludens toxin (ZOT) fragments at 50 to 200 nanograms per tablet. AT1002 zonulin-agonist octapeptide at 20 to 100 micrograms per tablet. Larazotide acetate (zonulin-receptor antagonist, included for completeness though opposite mechanism).

§ 12.4.4 Claudin-family-targeted modulators. Clostridium perfringens enterotoxin C-terminal fragment (C-CPE) claudin-3/4/18 binders at 50 to 200 micrograms per tablet. Anti-claudin antibody fragments.

§ 12.4.5 Component D dose variants. 1, 2, 5, 10, 15, 20 milligrams per tablet for PIP640 or chitosan alternatives.

§ 12.4.6 Absent Component D. Formulations omitting Component D and relying solely on Component C paracellular effect, per § 11.1 Claim 3 minimum viable variant.

§ 12.5 Component E variants

§ 12.5.1 Nanoparticle polymer variants. PLGA 50:50 (preferred). PLGA 75:25. PLGA 25:75. Poly(lactic acid) (PLA). Poly(glycolic acid) (PLG). Polycaprolactone (PCL). Poly(lactic-co-caprolactone). Poly(lactic-co-trimethylene carbonate).

§ 12.5.2 PEG molecular-weight variants. 2 kilodalton (preferred). 1 kilodalton. 1.5 kilodalton. 3 kilodalton. 5 kilodalton. Note: to retain clearance outside the granted Hanes WO 2017/075565 MPP patent (polyalkylene oxide MW > 5 kilodalton), preferred embodiments use PEG at or below 3 kilodalton.

§ 12.5.3 Alternative hydrophilic coatings. Polyvinyl pyrrolidone (PVP). Poly(vinyl alcohol) (PVA). Dextran. Poly(2-oxazoline). Mucoadhesive polysaccharide coating (chitosan-based).

§ 12.5.4 Acid-trigger crosslinker variants. Acetal crosslinker (preferred). Orthoester crosslinker. Phosphoramidate crosslinker. pH-sensitive hydrazone linker. Boronate ester crosslinker.

§ 12.5.5 Nanoparticle size variants. 50, 75, 100, 125, 150, 175, 200 nanometers nominal diameter.

§ 12.5.6 Core composition variants. PLGA plus Component A plus Component B (preferred). PLGA plus Component A plus Component B plus Component C. PLGA plus Component A plus sodium caprate (in place of SNAC). PLGA plus Component A plus HIP counterion (unlipidated peptide variant per § 12.2.6).

§ 12.5.7 Surface charge variants. Near-neutral zeta potential (-2 ± 4 millivolts, preferred). Mildly negative (-10 to -5 millivolts). Mildly positive (+5 to +10 millivolts).

§ 12.5.8 Encapsulation efficiency variants. 30, 40, 50, 60, 70, 80 percent of Component A dose encapsulated. 20, 30, 40, 50 percent of Component B dose co-encapsulated.

§ 12.6 Component F variants

§ 12.6.1 Chitosan outer-matrix variants. Chitosan (preferred). Thiolated chitosan. Chitosan-glutathione copolymer. Quaternized (trimethyl) chitosan. Chitosan-EDTA conjugate.

§ 12.6.2 Alginate outer matrix. Sodium alginate. Calcium alginate. Propylene glycol alginate. Chemically modified alginate.

§ 12.6.3 Carbomer outer matrix. Carbopol 971P. Carbopol 974P. Carbopol 934P.

§ 12.6.4 Polyacrylic acid outer matrix. Including cross-linked polyacrylic acid (PAA) variants.

§ 12.6.5 Cellulose ether outer matrix. Hydroxypropyl methylcellulose (HPMC). Hydroxypropyl cellulose (HPC). Sodium carboxymethylcellulose (NaCMC).

§ 12.6.6 Thiolated polymer outer matrices. Thiolated polyacrylic acid. Thiolated carbomer. Thiolated hydroxyethyl cellulose.

§ 12.6.7 Sialic-acid-binding lectin outer coating. Wheat-germ agglutinin. Tomato lectin. Ulex europaeus agglutinin.

§ 12.6.8 Component F dose variants. 10, 15, 20, 25, 30, 35, 40, 45, 50 milligrams per tablet.

§ 12.7 Standard excipient variants

§ 12.7.1 Filler. Microcrystalline cellulose grades PH101, PH102, PH105, PH200, PH301. Dibasic calcium phosphate anhydrous and dihydrate. Lactose monohydrate and anhydrous. Mannitol.

§ 12.7.2 Binder. Povidone K30 (preferred). Povidone K17, K25, K60, K90. Hydroxypropyl cellulose. Hydroxypropyl methylcellulose. Pregelatinized starch.

§ 12.7.3 Lubricant. Magnesium stearate (preferred). Sodium stearyl fumarate. Glyceryl behenate. Talc.

§ 12.7.4 Flow aid. Colloidal silicon dioxide (preferred). Talc. Calcium silicate.

§ 12.7.5 Disintegrant (if added). Croscarmellose sodium. Sodium starch glycolate. Crospovidone.

§ 12.8 Dosage form variants

§ 12.8.1 Immediate-release tablet (preferred per § 5.1).

§ 12.8.2 Multi-layer tablet per § 11.1 Claim 7.

§ 12.8.3 Enteric-coated tablet for pH-triggered duodenal release, as alternative to the gastric-corpus primary target.

§ 12.8.4 Delayed-release tablet with pH-sensitive outer coating targeting intestinal rather than gastric deposition.

§ 12.8.5 Dissolvable film for sublingual or buccal pre-deposition.

§ 12.8.6 Effervescent tablet for rapid dissolution in water before administration.

§ 12.8.7 Orally-disintegrating tablet (ODT) for patients with swallowing difficulty.

§ 12.8.8 Chewable tablet.

§ 12.8.9 Hard-gelatin capsule or HPMC capsule containing equivalent granulate.

§ 12.8.10 Sachet of granulate for reconstitution in water before administration.

§ 12.8.11 Ingestible pulsed-field capsule per § 11.4 (secondary embodiment).

§ 12.9 Administration variants

§ 12.9.1 Once-daily (QD) administration per preferred embodiments for semaglutide, liraglutide, tirzepatide, cagrilintide, retatrutide, and survodutide.

§ 12.9.2 Twice-daily (BID) administration for short-half-life peptides (exenatide primary label) and for dose-fractionation of long-half-life peptides where patient-level exposure smoothing is desired.

§ 12.9.3 Thrice-daily (TID) administration for very-short-half-life embodiments (exenatide variant) or for maximum dose-fractionation.

§ 12.9.4 Once-weekly (QW) administration for semaglutide pulsed-field capsule embodiment per Claim 82, exploiting the 168-hour plasma elimination half-life.

§ 12.9.5 Fasted-state administration at least 30 minutes before first meal (preferred per § 5.1).

§ 12.9.6 Fed-state administration with the architecture retaining substantial efficacy per § 8.4 and Claim 75.

§ 12.9.7 Bedtime administration.

§ 12.9.8 Multi-drug co-administration with oral proton pump inhibitors, H2 receptor antagonists, statins, metformin, SGLT2 inhibitors, or other oral chronic therapies.

§ 12.9.9 Pediatric administration at weight-adjusted dose, ages 10 to 17 years per available pharmacokinetic data.

§ 12.9.10 Geriatric administration at renal-function-adjusted dose for exenatide (renal-cleared), and standard dose for the other six peptides (minor renal contribution to total clearance).

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§ 13

Anticipate-and-preempt

This section addresses specific forward-looking patent filings that third parties might attempt after the publication date of this disclosure. Each subsection enumerates a hypothetical narrow future claim and places the relevant subject matter explicitly into the public domain, such that any such later filing

would fail United States Patent and Trademark Office §102 novelty examination on the enumerated subject matter and would face §103 non-obviousness challenges on related subject matter. This section establishes the defensive perimeter of the publication against targeted follow-on filings.

§ 13.1 Novo narrow oral cagrilintide and oral CagriSema claim preemption

Novo Nordisk's Phase 3 REDEFINE program filed an NDA for subcutaneous CagriSema in December 2025. No public Novo oral cagrilintide monotherapy or oral CagriSema fixed-dose combination program has been disclosed as of April 2026. Should Novo file any patent claim on oral cagrilintide or oral CagriSema after the publication date of this disclosure, the following subject matter is in the public domain:

- Oral cagrilintide monotherapy at any dose in the envelope 0.125 to 15.0 milligrams once daily or 0.25 to 5.0 milligrams twice daily per § 11.2.5 Claims 44 to 46, in the six-component architecture per § 11.1 Claim 1.
- Oral CagriSema fixed-dose combination at cagrilintide 0.5 to 6.0 milligrams plus semaglutide 0.5 to 6.0 milligrams in a single unit dosage form once daily per § 11.2.5 Claims 49 to 52, at 1:1 mass ratio matching the subcutaneous CagriSema 2.4-plus-2.4-milligram-weekly regimen, and at 1:0.5, 1:2, and 2:1 mass ratio variants.
- Dose-escalation regimen for oral CagriSema initiating at 0.5 plus 0.5 milligrams and escalating to 6.0 plus 6.0 milligrams over 12 to 24 weeks per § 11.2.5 Claim 52.
- Oral cagrilintide Mitragotri-independent (no-CAGE) variant per § 11.2.5 Claim 48, avoiding Harvard / Cage Bio license dependency given the amylin-derived parent sequence places cagrilintide plausibly outside literal Mitragotri WO 2019/099837 claim 22 scope.
- Oral cagrilintide in triple-peptide co-tablet with semaglutide plus tirzepatide or with semaglutide plus retatrutide per § 11.5 Claim 99.

§ 13.2 Lilly narrow oral tirzepatide claim preemption

Lilly's current oral GLP-1 path is orforglipron (FDA-approved Foundayo, April 2026). No public Lilly oral tirzepatide peptide-delivery program has been disclosed as of April 2026. Should Lilly pivot from orforglipron to oral tirzepatide (for indications where peptide mechanism is preferred over small-molecule) and file a patent claim on oral tirzepatide after the publication date of this disclosure, the following subject matter is in the public domain:

- Oral tirzepatide at any dose in the envelope 0.25 to 75 milligrams once daily, 1.0 to 15 milligrams twice daily, or 1.0 to 5.0 milligrams thrice daily per § 11.2.3 Claims 25 to 28.

- Primary label 12 milligrams once daily matching subcutaneous 9.4 milligrams weekly mid-maintenance per § 11.2.3 Claim 29.
- Dose-escalation regimen initiating at 2 milligrams daily and escalating to 12 milligrams daily over 12 to 16 weeks per § 11.2.3 Claim 30.
- Mitragotri-independent (no-CAGE) variants for oral tirzepatide per § 11.2.3 Claim 32, leveraging the plausibly-outside-scope reading of WO 2019/099837 claim 22 for GIP-derived dual agonists.
- Oral tirzepatide in co-tablet combinations with exenatide, cagrilintide, semaglutide, or survodutide per § 11.5 Claims 90, 95, and 96.

§ 13.3 Lilly oral retatrutide program preemption

Lilly's retatrutide Phase 3 TRIUMPH NDA is expected Q4 2026, for subcutaneous administration. No public Lilly oral retatrutide program has been disclosed. Should Lilly decide that oral retatrutide is a commercial priority (parallel to or succeeding the subcutaneous product) and file a patent claim on oral retatrutide after the publication date, the following subject matter is in the public domain:

- Oral retatrutide at any dose in the envelope 0.25 to 75 milligrams once daily or 1.0 to 15 milligrams twice daily per § 11.2.6 Claims 53 to 55.
- Primary label 10 milligrams once daily matching subcutaneous 7.8 milligrams weekly per § 11.2.6 Claim 56.
- Dose-escalation regimen following the TRIUMPH titration (1, 3, 6, 10 milligrams at four-week steps) per § 11.2.6 Claim 59.
- Mitragotri-independent variants for oral retatrutide per § 11.2.6 Claim 57.
- Oral retatrutide in MASH indication at specific subset of dose envelope per § 11.2.6 Claim 58.
- Oral retatrutide in combination co-tablet with cagrilintide per § 11.5 Claim 97, with semaglutide per § 11.5 Claim 93.

§ 13.4 Boehringer Ingelheim and Zealand Pharma oral survodutide preemption

Boehringer Ingelheim and Zealand Pharma are in Phase 3 SYNCHRONIZE (obesity) and LIVERAGE (MASH) with subcutaneous survodutide; FDA Breakthrough Therapy designation for MASH was granted October 2024; H1 2026 readout expected. No public BI or Zealand oral survodutide program has been disclosed. Should either filer attempt an oral survodutide patent claim after the publication date, the following subject matter is in the public domain:

- Oral survodutide at any dose in the envelope 0.1 to 30 milligrams once daily or 0.5 to 5 milligrams twice daily per § 11.2.7 Claims 61 to 63.
- Primary label 5 milligrams once daily matching subcutaneous 3.6 milligrams weekly per § 11.2.7 Claim 64.
- Oral survodutide for the MASH indication at specific dose range per § 11.2.7 Claim 66, leveraging the FDA Breakthrough designation.
- Oral survodutide for obesity per § 11.2.7 Claim 67.
- Mitragotri-independent variants for oral survodutide per § 11.2.7 Claim 65, leveraging the plausibly-outside-scope reading of WO 2019/099837 claim 22 for glucagon-derived dual agonists and the 29-amino-acid length.
- Oral survodutide in co-tablet combinations with semaglutide or cagrilintide per § 11.5 Claims 94 and 98.

§ 13.5 AstraZeneca / generic / third-party oral exenatide preemption

The exenatide United States composition-of-matter patent expired in 2017 and the European equivalent expired in 2024. Amneal Pharmaceuticals launched the first US generic exenatide injectable (referencing Byetta) in November 2024. AstraZeneca discontinued Bydureon in the US market in March 2021. Oramed Pharmaceuticals ORMD-0901 oral exenatide (SNAC-enhanced) is in Phase 2 development via a different architecture. No other public oral exenatide program has been disclosed as of April 2026. Should any party file a patent claim on oral exenatide beyond Oramed's SNAC-based platform after the publication date, the following subject matter is in the public domain:

- Oral exenatide at any dose in the envelope 0.01 to 7.5 milligrams once daily, 0.025 to 1.5 milligrams twice daily, or 0.025 to 1.0 milligrams thrice daily per § 11.2.4 Claims 34 to 37.
- Primary label 0.1 milligrams twice daily per § 11.2.4 Claim 38.
- Unlipidated-peptide-specific architecture adjustments including hydrophobic ion pairing compensation for absence of fatty-acid anchor per § 11.2.4 Claim 39.
- Co-primary pulsed-field ingestible capsule embodiment for exenatide per § 11.2.4 Claim 40 and § 11.4 Claim 81, compensating for short 2.4-hour plasma elimination half-life.
- Exenatide in oral co-tablet combinations per § 11.5 Claims 91 and 96.

§ 13.6 Novel CAGE-analog plus any peptide combination preemption

Should any party file a patent claim on a novel choline-based ionic liquid (CAGE analog) combined with any of the seven enumerated peptides in an oral formulation, the following subject matter is in the public domain:

- Choline plus any fatty-acid anion (octanoate, decanoate, laurate, oleate, myristate, palmitate) at any choline-to-anion molar ratio from 1:1 to 1:4, combined with any of the seven enumerated peptides at any dose within the § 11.2 envelope, in the six-component architecture per § 11.1 Claim 1. Corresponds to § 12.3.1 through § 12.3.4.
- Non-choline ionic liquid variants (imidazolium, ammonium, phosphonium, pyridinium, with fatty-acid anion) in combination with any peptide. Corresponds to § 12.3.6.
- Deep-eutectic solvent (DES) variants (choline chloride plus urea, choline chloride plus oxalate, choline chloride plus glycerol, betaine-based) in combination with any peptide. Corresponds to § 12.3.5.
- Any substituted-choline or substituted-terpenoid-anion ionic-liquid variant in combination with any peptide per § 12.3.3 and § 12.3.4.

§ 13.7 Pulsed-field ingestible device plus any peptide preemption

Should any party file a patent claim on a device-based pulsed-field oral peptide delivery architecture beyond the existing Rani RaniPill platform (US 10,814,114 B2 and continuations, microneedle actuation) and the Traverso-Langer SOMA platform (US 10,639,226 B2, needle penetration), the following subject matter is in the public domain:

- Any of the seven enumerated peptides in a pulsed-field ingestible capsule operating at 10 to 300 kilohertz frequency, 0.1 to 25 volts per centimeter amplitude, 1 to 100 millisecond pulse duration, 0.1 to 10 percent duty cycle, with electrode separation of 2 to 10 millimeters, per § 11.4 Claims 79 to 88.
- Co-administration protocol of § 11.1 Claim 1 tablet plus § 11.4 Claim 79 capsule per Claim 4 and Claim 87.
- On-capsule Bluetooth beacon for dose-compliance logging per § 11.4 Claim 86.
- Gastric-pH-sensor-triggered activation window per § 11.4 Claim 84.
- Pulsed-field semaglutide once-weekly oral dosing exploiting 168-hour half-life per § 11.4 Claim 82.

§ 13.8 Multi-peptide oral co-formulation preemption

Any two-peptide, three-peptide, or four-peptide oral co-formulation within the seven-peptide class, at the individual doses specified in § 11.2, in the six-component architecture per § 11.1 Claim 1 or Claim 6. The anticipate-and-preempt subject matter includes but is not limited to:

- Semaglutide plus liraglutide co-tablet per § 11.5 Claim 89.
- Semaglutide plus tirzepatide co-tablet per § 11.5 Claim 90.
- Semaglutide plus exenatide co-tablet (QD / BID) per § 11.5 Claim 91.
- Semaglutide plus cagrilintide co-tablet (oral CagriSema) per § 11.5 Claim 92 and § 11.2.5 Claims 49 to 52.
- Semaglutide plus retatrutide co-tablet per § 11.5 Claim 93.
- Semaglutide plus survodutide co-tablet per § 11.5 Claim 94.
- Tirzepatide plus cagrilintide co-tablet per § 11.5 Claim 95.
- Tirzepatide plus exenatide co-tablet per § 11.5 Claim 96.
- Retatrutide plus cagrilintide co-tablet per § 11.5 Claim 97.
- Survodutide plus cagrilintide co-tablet per § 11.5 Claim 98.
- Triple-peptide oral co-tablet (semaglutide plus cagrilintide plus tirzepatide) per § 11.5 Claim 99.
- Quadruple-peptide and higher-order oral co-formulations within the class at individual doses per § 11.2.

§ 13.9 Formulation-boundary preemption

Should any party attempt to file a narrow tablet-parameter claim that places the filing outside the Novo WO 2013/189988 / US 9,993,430 / US 11,033,499 composition space by the same tablet-mass, SNAC-weight-fraction, or disintegration-time tightening employed in this disclosure, the following tightening combinations are in the public domain:

- Tablet mass at or above 650 milligrams with SNAC weight fraction at or below 46.2 percent.
- Bulk density 0.90 to 1.00 grams per cubic centimeter (below Novo US 9,993,430 “at least 1.0” independent-claim element).
- Disintegration time at or above 23 minutes (above Novo US 11,033,499 “22 minutes or less” continuation-claim ceiling).

- Any combination of the three tightening parameters.
- Peptide weight fraction at or below 15 percent of tablet mass.

§ 13.10 Route-additive mechanism preemption

Any claim that recites the route-additive absorption mechanism F_epithelium = F_transcellular + F_paracellular as an engineering principle for oral peptide delivery, combined with any of the seven enumerated peptides, in any architecture comprising at least one transcellular enhancer and at least one paracellular enhancer, is preempted by § 4 Feature-level novelty claim (i) and § 11.1 Claim 8. The route-additive engineering is placed into the public domain at the class level.

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§ 14

Publication intent and disclosure status

This document is published as prior art under 35 U.S.C. §102 for defensive purposes as of the publication date stated in the masthead. The integrated architecture disclosed herein, together with the parameter windows, the dose envelope, the operations sequences, the alternative embodiments, the claims-style enumeration of § 11, the variant enumeration of § 12, and the anticipate-and-preempt enumeration of § 13, is placed into the public domain as of the publication date. This disclosure does not constitute an offer to license or an assignment of rights. No prior patent filing or provisional application by the filer is in force on the subject matter. The filer's intent is defensive publication to preempt any third-party claim on the combined architecture at the seven-peptide class payload and at the per-peptide species dose and embodiment variants enumerated throughout.

Individual subsystem mechanisms (SNAC pH buffering and transcellular hydrophobization; CAGE ionic liquid for paracellular enhancement and mucus fluidization; PIP640 analog for selective claudin-2 tight-junction modulation; diblock PLGA-PEG mucus-penetrating nanoparticle architecture; thiolated-chitosan mucoadhesive outer matrix; pulsed-field ingestible device for sub-electroporative delivery) are variously claimed or unclaimed in the prior art cited in § 3. The combined architecture at the seven-peptide class as disclosed herein is believed not to be covered by any issued patent known to the filer. The feature-level novelty claims enumerated in § 4, the integrated claims matrix of § 11, the variants of § 12, and the anticipate-and-preempt subject matter of § 13 are all presented for examiner reference and for unambiguous inclusion in the §102 public-domain corpus.

Commercial deployment of any embodiment containing choline-and-geranate (CAGE) remains subject to the Harvard / Cage Bio WO 2019/099837 license requirement for the three GLP-1-sequence-derived peptides (semaglutide, liraglutide, exenatide) and is recommended for FTO opinion for the four non-

GLP-1-sequence-derived peptides (tirzepatide, cagrilintide, retatrutide, survodutide) given the plausibly-outside-literal-scope reading of claim 22. The Mitragotri-independent variants per § 11.1 Claim 2 and per-peptide Claims 13, 22-bis, 32, 43-bis, 48, 57, 65 avoid the license dependency entirely.

Composition-of-matter license considerations per peptide: semaglutide CoM expires 2033 (Novo); liraglutide CoM expired August 2025 (generic available); tirzepatide CoM expires January 2036 (Lilly); exenatide CoM expired 2017 (US; Amneal generic injectable launched November 2024); cagrilintide CoM active 2035 to 2040 (Novo); retatrutide CoM active approximately 2040 (Lilly); survodutide CoM active 2035 to 2040 (Zealand and Boehringer Ingelheim).

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§ 15

Discretionary follow-on defensive publication

Coracle Research may, at its discretion and without a committed schedule, publish follow-on defensive disclosures under 35 U.S.C. §102 if narrowing patent claims are subsequently filed at adjacent ranges of the architecture, claims, parameters, or species disclosed in § 4 through § 14 above.

This statement is unilateral and discretionary. It does not commit Coracle Research to any specific monitoring obligation, follow-on-publication obligation, license-grant obligation, opposition or post-grant defense obligation, litigation obligation, or freedom-to-operate legal-advice obligation. No correspondence or follow-on publication issued at Coracle Research's discretion shall be construed as legal advice, as a license grant, or as an assignment of rights.

The defensive-publication effect of the present disclosure under 35 U.S.C. §102 is established by publication itself and is independent of any subsequent follow-on activity.

End of Technical Disclosure 03.

Companion research note, references, supplementary figures, pharmacokinetic simulation code, molecular-dynamics input files, and the full audit log are deposited on Zenodo under DOI 10.5281/zenodo.19768434, with additional public mirrors as announced at the primary venue.