

Formulation Strategies for Oral and Long-Acting GLP-1 Receptor Agonists: Recent Advances and Translational Challenges

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Abstract—Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have moved from a twice-daily diabetes injection to the most commercially and clinically significant drug class in metabolic medicine. Much of this shift was driven by pharmaceuticals rather than by new pharmacology. Fatty-acid acylation, Fc fusion and polymer microspheres extended the dosing interval from hours to a week; permeation-enhancer technology made the first oral peptide GLP-1 RA possible; and non-peptide agonists now bypass peptide delivery barriers altogether. In December 2025 the US Food and Drug Administration (FDA) approved oral semaglutide 25 mg for weight management, and in April 2026 it approved the small-molecule agonist orforglipron, so oral delivery is now an established part of the class rather than a prospect. This review describes the formulation strategies behind oral and long-acting GLP-1 RAs: molecular engineering for albumin binding, absorption enhancement with salcaprozate sodium (SNAC), non-peptide agonists, mechanical oral devices, biodegradable microspheres, implants and monthly-dosing concepts. The strategies are compared using half-life, dose burden and weight-loss data from pivotal trials. We then discuss the unresolved translational challenges: low and variable oral bioavailability, the active pharmaceutical ingredient (API) burden of oral peptides, dosing restrictions, drug interactions, stability, device-related failures, manufacturing capacity and gastrointestinal tolerability. We close with directions most likely to shape the next generation of products.

Index Terms—GLP-1 receptor agonist; oral peptide delivery; semaglutide; permeation enhancer; SNAC; long-acting injectable; PLGA microspheres; orforglipron; obesity; type 2 diabetes

I. INTRODUCTION

Native GLP-1 is an incretin hormone with a plasma half-life of only a few minutes because dipeptidyl

peptidase-4 (DPP-4) cleaves it and the kidney clears it rapidly [1]. Turning it into a medicine was therefore a formulation and molecular-design problem before it was a clinical one. The first approved agent, exenatide (2005), was dosed twice daily. Since then the class has expanded to include once-weekly injectables, an oral peptide tablet and a non-peptide oral molecule, and the indications have broadened from glycaemic control to chronic weight management and cardiovascular risk reduction [2-4].

The clinical evidence has raised the stakes for formulation. Subcutaneous semaglutide 2.4 mg reduced body weight by 14.9% at 68 weeks in STEP 1 [16], and tirzepatide, a dual GIP/GLP-1 agonist, produced reductions above 20% at the highest dose in SURMOUNT-1 [17].

Cardiovascular benefit was first shown in people with type 2 diabetes in SUSTAIN-6 [19], and semaglutide also reduced major adverse cardiovascular events in people with overweight or obesity and established cardiovascular disease in SELECT [20]. Demand for these drugs now far exceeds the capacity of injectable pen manufacturing and of clinic-based delivery. Formulation choices therefore determine who can realistically be treated, how often, at what cost, and with what adherence.

Two formulation goals dominate current development. The first is oral delivery, which would remove injections, the cold chain and needle aversion, but must overcome the enzymatic and permeability barriers that give peptides an oral bioavailability of well under 1% [3,35]. The second is extended release, which seeks to reduce dosing frequency from weekly to monthly or longer, supporting adherence and potentially steadier exposure. This review follows both lines, compares

the resulting products and identifies the barriers that still limit translation.

II. SCOPE AND APPROACH

This is a narrative review. It covers GLP-1 RAs and related incretin agonists that have reached late-stage clinical development or approval, with emphasis on the formulation and delivery technology rather than on clinical pharmacology in general. Regulatory status was checked against FDA and manufacturer announcements available through October 2026 [30,32,33]. Pivotal-trial weight-loss figures are reported using the treatment-policy (intention-to-treat) estimand where published, so that cross-trial comparison is as fair as possible. Even so, differences in populations, durations (64 to 72 weeks) and doses mean these comparisons are indicative and not head-to-head.

III. MOLECULAR ENGINEERING AS A FORMULATION STRATEGY

The first lever for durability is the molecule itself, and it is best understood as formulation by design. Three approaches reached the market (Figure 1). Fatty-acid acylation and albumin binding. Liraglutide carries a C16 fatty acid that promotes self-association

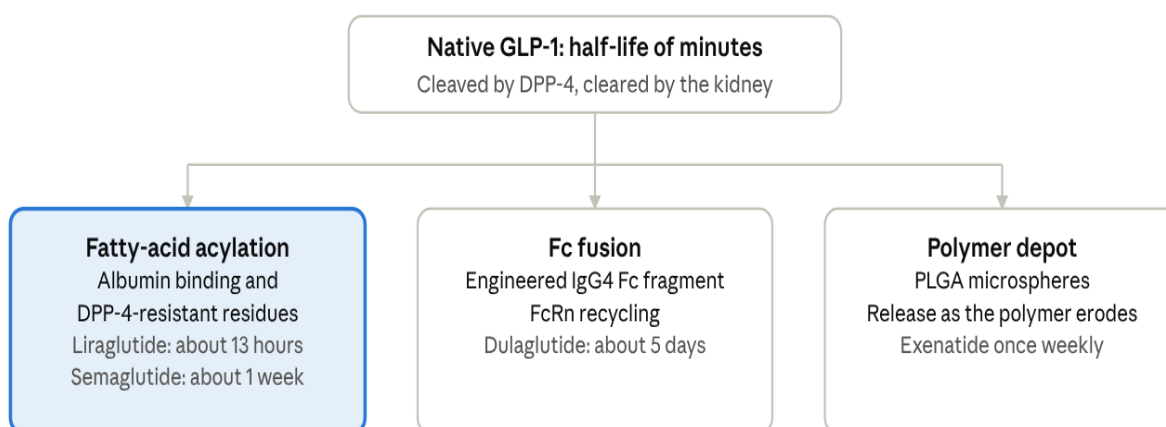
at the injection site and reversible albumin binding, giving a half-life of about 13 hours [4]. Semaglutide extends this: an Aib substitution at position 8 blocks DPP-4 cleavage, and a C18 fatty diacid attached through a spacer at lysine 26 produces strong albumin affinity, a half-life of roughly one week and about 89% subcutaneous bioavailability [4,5]. Tirzepatide uses a C20 diacid for the same purpose [17,18].

Fc fusion. Dulaglutide fuses a modified GLP-1 analogue to an engineered IgG4 Fc fragment, exploiting FcRn recycling to reach a half-life near five days [6]. Albiglutide, an albumin fusion, was withdrawn from the market in 2018 for commercial rather than safety reasons, showing that a good long-acting design can still fail on potency per dose and market position.

Polymer encapsulation. Exenatide once weekly encapsulates the unmodified peptide in poly(D,L-lactide-co-glycolide) (PLGA) microspheres (see Section 5.2) [7,8].

The lesson for formulators is that albumin binding gave semaglutide not only a weekly profile but also the properties that later made oral delivery feasible, because high albumin affinity and enzymatic stability tolerate the low and variable absorption of the gastrointestinal route [3,9].

Three molecular strategies extend GLP-1 action from minutes to days



drawn for this review from refs 3-9 · 3 strategies

Figure 1. Molecular and formulation strategies that extend the action of GLP-1 receptor agonists beyond the minutes-long half-life of the native hormone. Half-lives are approximate.

IV. ORAL DELIVERY

4.1 Barriers to oral peptide absorption

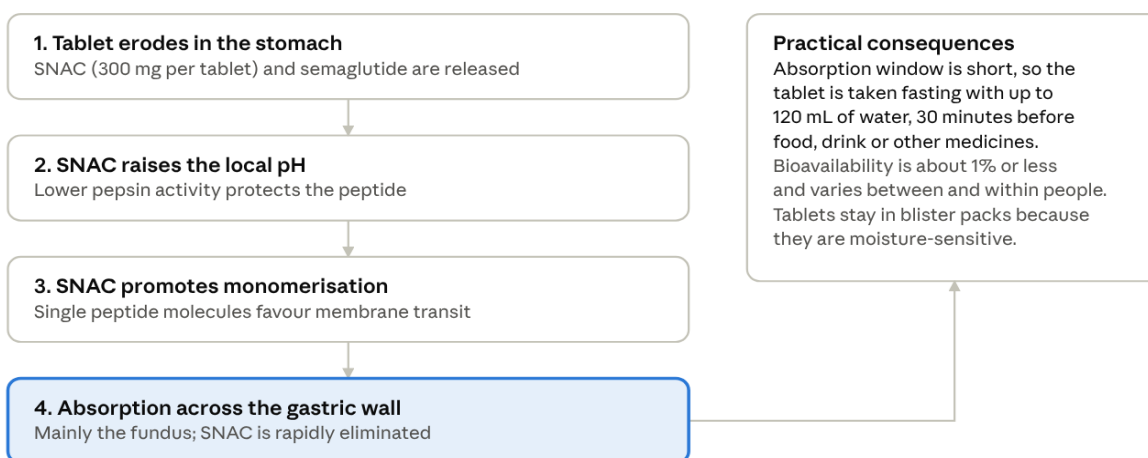
A 4 kDa peptide faces acid and pepsin in the stomach, pancreatic proteases in the duodenum, a mucus layer, and a tight epithelium that excludes hydrophilic molecules above roughly 0.5 kDa by the paracellular route. Oral bioavailability of unmodified peptides is usually below 1% [3,35]. Formulation strategies fall into four groups: permeation enhancers, protease inhibitors, nanocarriers and mechanical devices. Permeation enhancers have so far delivered the only approved oral peptide GLP-1 RA [10,36].

4.2 SNAC-enabled oral semaglutide

Salcaprozate sodium (SNAC) is a medium-chain fatty acid derivative with a carboxylate and a

salicylamide group. In oral semaglutide it is combined with the peptide in a co-formulated tablet, and its mechanism is local and gastric [9,10]. After a tablet erodes in the stomach, SNAC (300 mg per tablet) raises the local pH around the dissolving tablet, which lowers pepsin activity, and it promotes monomerisation of semaglutide, which favours membrane transit. SNAC also transiently increases membrane fluidity and enables transcellular absorption across the gastric epithelium, particularly in the fundus. The effect is localised, and the semaglutide reaches the systemic circulation through gastric uptake and not through intestinal permeability changes [9]. The effect is also short-lived, and SNAC itself is rapidly absorbed and eliminated [10]. Figure 2 summarises the sequence.

SNAC lets semaglutide cross the stomach wall before it is degraded



drawn for this review from refs 9-12 · 4 steps

Figure 2. Mechanism of SNAC-assisted gastric absorption of oral semaglutide and the dosing rules that follow from it.

This mechanism explains the unusual administration requirements. Absorption occurs within a short window after dissolution, so the tablet must be taken fasting with a small volume of water (no more than about 120 mL) and at least 30 minutes before food, drink or other oral medicines. Larger water volumes or a shorter wait reduce exposure [11,12]. Absolute bioavailability is approximately 1% or less, and pharmacokinetic variability between and within individuals is high [11,12]. Oral semaglutide tablets

are also moisture-sensitive and are dispensed in their original blister packaging for that reason.

4.3 Clinical translation of oral semaglutide

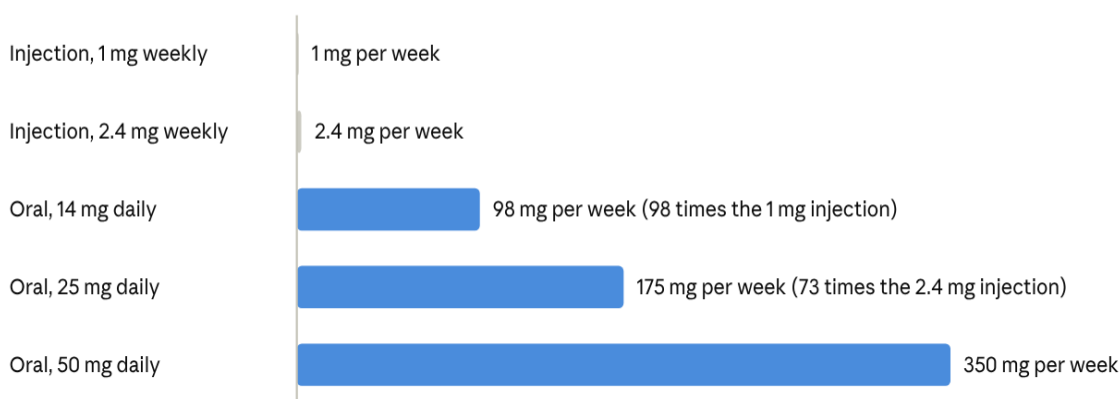
The PIONEER programme established efficacy and safety in type 2 diabetes. PIONEER 1 showed glycaemic benefit as monotherapy [13], and PIONEER 6 showed cardiovascular safety (non-inferiority) [14]. For obesity, OASIS 1 tested 50 mg daily and reported a 15.1% mean weight reduction at 68 weeks versus 2.4% with placebo [15]. A 25 mg

tablet was then developed and tested in OASIS 4, where the treatment-policy weight loss at 64 weeks was 13.6% versus 2.4% with placebo, and the on-treatment (adherent) figure was 16.6% [29]. On 22 December 2025 the FDA approved oral semaglutide 25 mg (Wegovy pill) for weight reduction, long-term weight maintenance and reduction of major adverse cardiovascular events, based on OASIS 4 and the SELECT trial [30]. It is the first oral GLP-1 RA approved for weight management.

The formulation price of this success is API burden. A 14 mg daily oral dose equals 98 mg per week against 1 mg per week subcutaneously, and the 25 mg obesity dose equals 175 mg per week against 2.4 mg per week for the injection (Figure 3). That is a roughly 70- to 100-fold higher peptide requirement per patient, with consequences for manufacturing capacity and cost of goods.

Oral semaglutide needs 70 to 100 times the weekly peptide of the injection

Semaglutide dose per week in mg (daily oral dose multiplied by 7)



labelled semaglutide doses; weekly oral dose = daily dose x 7

Figure 3. Weekly peptide exposure with subcutaneous and oral semaglutide at labelled and trial doses [15].

4.4 non-peptide oral agonists

Small molecules sidestep most peptide delivery problems because they are absorbed through conventional pathways, are chemically stable at room temperature, and are made by standard synthetic chemistry instead of solid-phase or recombinant peptide manufacture. Danuglipron, an earlier oral small-molecule GLP-1 RA, showed efficacy in early trials [24], but Pfizer discontinued its development in 2025 following a case of drug-induced liver injury, a reminder that small-molecule agonists carry their own safety risks.

Orforglipron (LY3502970) is a non-peptide agonist whose binding mode within the receptor has been characterized structurally [21]. It was tested in phase 2 trials in obesity and type 2 diabetes [22,23] and in phase 3 programmes ACHIEVE and ATTAIN [27,28]. In ATTAIN-1 the treatment-policy mean weight loss at 72 weeks was 11.1% against 2.1% with

placebo [28]. The FDA approved orforglipron (Foundayo) on 1 April 2026 for chronic weight management, reportedly the first new molecular entity cleared under the Commissioner's National Priority Voucher pilot [32,33]. Its formulation advantage is practical: it can be taken at any time of day without food or water restrictions, which removes the main usability limitation of oral semaglutide. The trade-off is lower mean weight loss than the highest-efficacy injectables (Figure 4) and a requirement for dose titration.

4.5 Mechanical and device-based oral delivery

Ingestible devices avoid permeability enhancement by delivering the peptide directly into tissue. A self-orienting capsule, designed on the shape of a leopard tortoise shell, reorients in the stomach and injects an insulin dose through the gastric wall in large-animal studies [25]. A luminal unfolding microneedle

injector delivers macromolecules into the small-intestinal wall in swine [26]. These approaches achieve bioavailability well above permeation-enhanced tablets in animals, but no GLP-1 device has reached human efficacy trials, and questions of reliability, transit variability and manufacturing cost remain open.

V. LONG-ACTING INJECTABLE DELIVERY

5.1 Weekly injectables through molecular design

Once-weekly dosing is now the standard for injectables. Semaglutide (weekly half-life, 1 mg and 2.4 mg), dulaglutide and tirzepatide all depend on the molecular strategies in Section 3, supplied in pre-filled pens with a simple aqueous formulation. For formulators these products are attractive because the peptide is dissolved, so there is no release-rate engineering, no initial burst and no polymer degradation chemistry. Their dose-response properties are well characterized in large trials [16-18].

5.2 PLGA microspheres

Exenatide once weekly (Bydureon) is the reference example of sustained release for the class. Exenatide is encapsulated in PLGA microspheres that release peptide through an initial surface-associated phase, followed by bulk erosion of the polymer [7]. DURATION-1 showed superior HbA1c reduction versus twice-daily exenatide [8]. The later autoinjector presentation suspends the microspheres in an oil vehicle to avoid reconstitution at the point of use. PLGA systems illustrate the classic technical challenges: control of the initial burst, acylation and degradation of peptide inside the acidic microenvironment of eroding particles, injectability with a fine-gauge needle, and manufacturing reproducibility of particle-size distribution [37]. The product's modest potency, with weight loss much smaller than with semaglutide or tirzepatide, meant its commercial position weakened as the more potent weekly molecules arrived.

5.3 Implants and osmotic pumps

The ITCA 650 device placed an osmotic mini-pump under the skin to deliver exenatide continuously for several months, with removal at the end. FREEDOM-1 showed glycaemic benefit [31], but the product was not approved by the FDA. Implants offer the longest dosing intervals and removable exposure, which is useful in the event of an adverse reaction, but they bring procedural burden, peptide stability at body temperature for months, and device-related regulatory scrutiny.

5.4 Monthly dosing

The most active frontier is once-monthly dosing. Maridebart cafraglutide, an antibody-peptide conjugate that agonises the GLP-1 receptor and antagonizes the GIP receptor, achieved substantial weight loss with monthly administration in a phase 2 trial [34]. It is not a formulation trick, since the long half-life comes from the antibody scaffold, but it shows that the main route to monthly dosing is again molecular design, and not depot technology.

5.5 Microneedles and other approaches

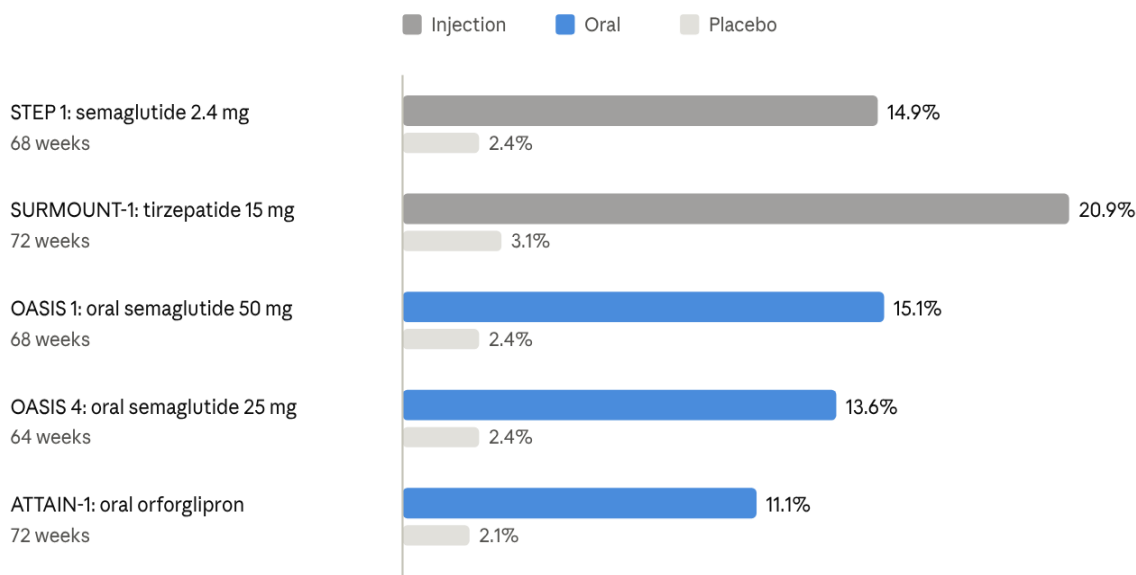
Microneedle patches can deliver peptides through the skin without a hypodermic needle and may allow self-administration and dry storage [38]. Dissolving or coated microneedles loaded with GLP-1 RAs have been studied in animals, but peptide dose capacity per patch is limited, and pharmacokinetic reproducibility across skin sites has not been established in humans. Weekly GLP-1 RA doses are low enough in milligram terms that microneedles remain plausible, but this is a research direction, not a development programme at the clinical stage.

VI. COMPARATIVE ANALYSIS

Table 1 compares the main approaches on formulation features. Figure 4 compares pivotal-trial weight loss, and Figure 5 compares the pharmacokinetic half-lives that determine the dosing interval.

Oral agents approach injectable weight loss, but tirzepatide still leads

Mean body-weight change in pivotal trials, percent, treatment-policy estimand

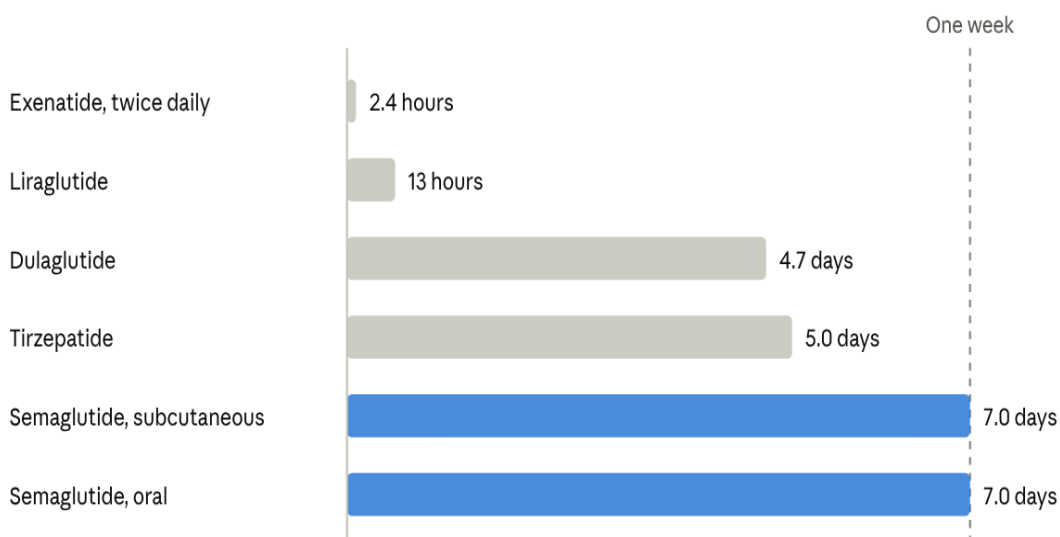


refs 15-17, 28, 29 · 5 pivotal trials, 64 to 72 weeks

Figure 4. Mean weight change versus placebo in pivotal trials of injectable and oral GLP-1 receptor agonists [15-17,28,29]. Trial durations, populations and doses differ, so the comparison is indicative and not head-to-head. ATTAIN-1 is shown as reported for all participants regardless of adherence.

Only albumin-bound and Fc-fused agents reach half-lives of several days

Approximate half-life in days; bars start at zero



approximate half-lives, rounded · refs 4, 6, 17 and product labelling

Figure 5. Approximate elimination half-lives of GLP-1 receptor agonists, which set the dosing interval [4,6,17].

Table 1. Formulation strategies for oral and long-acting GLP-1 receptor agonists.

Strategy	Example	Route and interval	Core technology	Main advantages	Main limitations
Acylation and albumin binding	Semaglutide, liraglutide, tirzepatide	SC, daily to weekly	Fatty-acid chain with spacer, DPP-4-resistant residues	Simple aqueous pen, high potency, strong outcomes data	Injection, cold chain, pen manufacturing capacity
Fc fusion	Dulaglutide	SC, weekly	IgG4-Fc fusion, FcRn recycling	Weekly dosing, proven	Lower weight loss, larger protein
PLGA microspheres	Exenatide once weekly	SC, weekly	Biodegradable polymer depot	Uses unmodified peptide	Burst release, nodules, lower potency
Osmotic implant	ITCA 650	SC implant, months	Mini-pump, continuous delivery	Longest interval, removable	Procedure, regulatory outcome, stability
SNAC co-formulation	Oral semaglutide	Oral, daily	Permeation enhancer, local gastric absorption	No injection	Fasting rules, about 1% bioavailability, API burden
Non-peptide agonist	Orforglipron	Oral, daily	Small-molecule synthesis	No food restriction, no cold chain, scalable	Lower mean efficacy, small-molecule safety risks
Antibody-peptide conjugate	Maridebart cafraglutide	SC, monthly	Antibody scaffold	Monthly interval	Phase 2 data, immunogenicity unknown
Ingestible devices	Self-orienting capsule	Oral, preclinical	Mechanical tissue injection	High animal bioavailability	No human data, cost

VII. TRANSLATIONAL CHALLENGES

Low and variable bioavailability. SNAC-based tablets deliver around 1% of the dose, with high within-subject variability [11,12]. For a drug dosed chronically this is tolerable only because the molecule is highly potent and has a long half-life, so variable absorption is buffered. Regulatory bioequivalence assessment for such products is difficult, which complicates generic and second-generation development.

API burden and cost of goods. The ratio of oral to injected weekly dose (Figure 3) means a population-scale oral peptide programme needs far more peptide than an injectable one. Semaglutide is produced by recombinant expression of a precursor followed by chemical acylation, so this load falls on a specialized and capacity-limited supply chain. Small molecules such as orforglipron avoid this constraint, which is a major strategic argument for them.

Administration restrictions and adherence. Fasting, a defined water volume and a 30-minute wait are demanding for chronic therapy. Adherence lapses

reduce exposure directly, which is why the on-treatment and treatment-policy weight-loss results differ by three percentage points in OASIS 4 [29]. Food-independent small molecules address this directly.

Drug interactions and the gastric environment. Oral semaglutide increases exposure to co-administered levothyroxine, with an increase of about a third in area under the curve reported on the product label, so thyroid function monitoring is advised. Delayed gastric emptying, acid-suppressive therapy or gastric surgery can in principle alter local absorption. These are interactions specific to the delivery strategy and are not seen in the injectable.

Stability and storage. Peptide formulations must control aggregation, oxidation, deamidation and adsorption to surfaces. Oral tablets are moisture-sensitive, PLGA depots risk acid-catalyzed degradation of peptide in the eroding matrix, and pens require a cold chain. Room-temperature stable small molecules have a distribution and wastage advantage.

Device and delivery-system risk. Implants and ingestible devices introduce procedural, retrieval and reliability concerns that go beyond conventional drug-product quality. The outcome of ITCA 650 shows how device-drug combination products can fail on regulatory grounds even with positive efficacy data.

Tolerability. Nausea, vomiting, diarrhoea and constipation affect every GLP-1 RA regardless of route, and they are dose and titration dependent. Long-acting formulations cannot be withdrawn quickly if tolerability problems arise, which favours short-acting oral dosing for patients at risk. Conversely, a depot or implant that removes peaks in plasma concentration might improve gastrointestinal tolerability, but that hypothesis needs direct comparison.

Long-term maintenance. Weight regained after treatment withdrawal is a consistent finding across the class, so formulation development must support chronic therapy at acceptable cost. Switching between injectable and oral agents for maintenance is an active research area.

Environmental and supply considerations. Single-use pens and autoinjectors generate plastic and device waste at population scale, and oral tablets with small-molecule actives have a smaller packaging and cold-chain footprint.

VIII. FUTURE PERSPECTIVES

Several developments are likely to shape the next decade. First, small-molecule and orally optimised peptides will compete with SNAC tablets on convenience and cost, and the field will learn from the safety record of danuglipron. Second, improved permeation-enhancer systems and ingestible devices may reduce the API burden of oral peptides, although this will need human efficacy data to be credible. Third, monthly and longer dosing is likely to rely on antibody and protein scaffolds, with polymer depots and implants reserved for specific indications such as adherence-challenged populations. Fourth, combination incretin products (dual and triple agonists, amylin combinations) raise formulation questions about co-formulation, compatibility and dose ratios. Fifth, quality-by-design and digital tools can help to predict peptide stability, release profile and bioequivalence, particularly for the variable-

absorption oral class. Finally, the regulatory pathway for generic and follow-on versions of complex peptide products will require validated analytical and pharmacokinetic approaches.

IX. CONCLUSIONS

The history of GLP-1 RAs shows that formulation and molecular engineering, not receptor pharmacology alone, determined which agents became practical medicines. Albumin binding gave weekly injections, PLGA microspheres showed the limits of depot technology for a lower-potency molecule, and SNAC enabled the first oral peptide in the class, at the cost of strict dosing rules and a very high peptide requirement. With the approval of oral semaglutide 25 mg in December 2025 and orforglipron in April 2026, oral delivery is now an established option, and the competition among them will be decided by efficacy, convenience, safety and cost of goods. The main unresolved challenges are bioavailability variability, API burden, interaction management, tolerability and long-term maintenance. Progress on these will determine how widely incretin therapy can be delivered.

REFERENCES

- [1]. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab.* 2018;27(4):740-756.
- [2]. Muttenthaler M, King GF, Adams DJ, Alewood PF. Trends in peptide drug discovery. *Nat Rev Drug Discov.* 2021;20:309-325.
- [3]. Drucker DJ. Advances in oral peptide therapeutics. *Nat Rev Drug Discov.* 2020;19:277-289.
- [4]. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. *Front Endocrinol.* 2019;10:155.
- [5]. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem.* 2015;58(18):7370-7380.
- [6]. Glaesner W, Vick AM, Millican R, et al. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. *Diabetes Metab Res Rev.* 2010;26(4):287-296.

- [7]. DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P. Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther.* 2011;13(11):1145-1154.
- [8]. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study (DURATION-1). *Lancet.* 2008;372:1240-1250.
- [9]. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med.* 2018;10(467):eaar7047.
- [10]. Twarog C, Fattah S, Heade J, Maher S, Fattal E, Brayden DJ. Intestinal permeation enhancers for oral delivery of macromolecules: a comparison between salcaprozate sodium (SNAC) and sodium caprate (C10). *Pharmaceutics.* 2019;11(2):78.
- [11]. Granhall C, Donsmark M, Blicher TM, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. *Clin Pharmacokinet.* 2019;58:781-791.
- [12]. Bækdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Effect of various dosing conditions on the pharmacokinetics of oral semaglutide, a human glucagon-like peptide-1 analogue in a tablet formulation. *Diabetes Ther.* 2021;12:1915-1927.
- [13]. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care.* 2019;42:1724-1732.
- [14]. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes (PIONEER 6). *N Engl J Med.* 2019;381:841-851.
- [15]. Knop FK, Aroda VR, do Vale RD, et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2023;402:705-719.
- [16]. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity (STEP 1). *N Engl J Med.* 2021;384:989-1002.
- [17]. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity (SURMOUNT-1). *N Engl J Med.* 2022;387:205-216.
- [18]. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes (SURPASS-2). *N Engl J Med.* 2021;385:503-515.
- [19]. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes (SUSTAIN-6). *N Engl J Med.* 2016;375:1834-1844.
- [20]. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes (SELECT). *N Engl J Med.* 2023;389:2221-2232.
- [21]. Kawai T, Sun B, Yoshino H, et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *Proc Natl Acad Sci USA.* 2020;117:29959-29967.
- [22]. Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med.* 2023;389:877-888.
- [23]. Frias JP, Hsia S, Eyde S, et al. Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *Lancet.* 2023;402:472-483.
- [24]. Saxena AR, Frias JP, Brown LS, et al. Efficacy and safety of oral small molecule glucagon-like peptide 1 receptor agonist danuglipron for glycemic control among patients with type 2 diabetes: a randomized clinical trial. *JAMA Netw Open.* 2023;6(5):e2314493.
- [25]. Abramson A, Frederiksen MR, Vegge A, et al. An ingestible self-orienting system for oral delivery of macromolecules. *Science.* 2019;363:611-615.
- [26]. Abramson A, Caffarel-Salvador E, Soares V, et al. A luminal unfolding microneedle

- injector for oral delivery of macromolecules. *Nat Med.* 2019;25:1512-1518.
- [27]. Rosenstock J, Hsia S, Nevarez Ruiz L, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes (ACHIEVE-1). *N Engl J Med.* 2025.
- [28]. Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, for obesity treatment (ATTAIN-1). *N Engl J Med.* 2025.
- [29]. Wharton S, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity (OASIS 4). *N Engl J Med.* 2025.
- [30]. Novo Nordisk. FDA approves Wegovy pill (oral semaglutide 25 mg) for weight management and cardiovascular risk reduction. Press release, 22 December 2025.
- [31]. Rosenstock J, Denham D, Rodbard H, et al. Efficacy and safety of ITCA 650, a novel drug-device GLP-1 receptor agonist, in type 2 diabetes uncontrolled with oral antidiabetes drugs: the FREEDOM-1 trial. *Diabetes Care.* 2016;39:1318-1328.
- [32]. US Food and Drug Administration. FDA approves first new molecular entity under national priority voucher program (orforglipron, Foundayo). Press announcement, 1 April 2026.
- [33]. Eli Lilly and Company. FDA approves Lilly's Foundayo (orforglipron) for chronic weight management. Press release, 1 April 2026.
- [34]. Jastreboff AM, et al. Once-monthly maridebart cafraglutide for the treatment of obesity: a phase 2 trial. *N Engl J Med.* 2025.
- [35]. Brayden DJ, Hill TA, Fairlie DP, Maher S, Mrsny RJ. Systemic delivery of peptides by the oral route: formulation and medicinal chemistry approaches. *Adv Drug Deliv Rev.* 2020;157:2-36.
- [36]. Maher S, Mrsny RJ, Brayden DJ. Intestinal permeation enhancers for oral peptide delivery. *Adv Drug Deliv Rev.* 2016;106:277-319.
- [37]. Kapoor DN, Bhatia A, Kaur R, Sharma R, Kaur G, Dhawan S. PLGA: a unique polymer for drug delivery. *Ther Deliv.* 2015;6(1):41-58.
- [38]. Prausnitz MR, Langer R. Transdermal drug delivery. *Nat Biotechnol.* 2008;26:1261-1268.