Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 09 May 2026
Revised 24 June 2026
Accepted 04 July 2026

Natural Resources for Human Health 2026, Vol. 6 (11s): 1068–1085

KEYWORDS:
GLP-1, ADME, DMPK, Pharmacokinetic, Multireceptor.

Pharmacokinetic and ADME challenges of GLP-1 based Multireceptor therapeutics: mechanisms, models and development strategies.

Srinivas Lenkalapelly[1], Ravi Akkireddy[1], Bhagheeradha. L[2], P. Venkata Suresh[3], Maharshi Thalla[4], Muralimohan Devalapalli[5], Manikantha Dunna[1], Sandhya Rani Chennupati[6]

[1]Texas Tech University of Health Sciences Center, Lubbock, TX, USA.
[2]JSS College of Pharmacy, Mysore, Karnataka, India.
[3]Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India.
[4]Irma Lerma Rangel College of Pharmacy, Texas A&M University, Kingsville, TX, USA.
[5]Advanced Analytical Research Institute, Health Research Institute, Fairfield, Iowa, USA.
[6] Harrisburg University of Science and Technology, Pennsylvania,USA.
Correspondence: srinipharma2002@gmail.com

ABSTRACT: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a paradigm shifting class of therapeutics for type 2 diabetes, obesity and associated cardiometabolic conditions. This review integrates a pharmacokinetic and ADME (absorption, distribution, metabolism, and excretion)-focused analysis of the challenges that have guided the design and delivery of GLP-1-based drugs, particularly multi-receptor analogues. we review the impact of receptor targeting, delayed gastric emptying, and transporter interactions on drug absorption, and the structural approaches, such as lipidation, PEGylation, and Fc-fusion, that prolong half-life and improve plasma stability. Formulation strategies targeting enhanced permeability and resistance against enzymatic degradation are discussed, including oral delivery systems, depot technologies and nano carrier systems. It covers biodistribution, plasma protein binding, and depot formation as determinants of tissue targeting and drug accumulation, and their significance for efficacy and long-term safety. Drug–drug interaction liability driven by prolonged half-lives and protein-binding characteristics is discussed within the context of regulatory requirements with respect to DMPK profiling, safety evaluation, and clinical trial conduct. Emerging new dual-agonists and combination therapy (eg Tirzepatide) are evaluated for their distinctive metabolic effects and regulatory implications. Finally, we provide context for the accelerated clinical and commercial ascent of GLP-1 analogues, including their continually widening therapeutic use, including in CNS and addiction research, and the regulatory templates that enable rapid development. Collectively, these findings emphasize the importance of integrated DMPK strategies to help define the next generations of GLP-1-based therapeutics across a spectrum of disease states.

Natural Resources for Human Health
eISSN: 2583-1194

INTRODUCTION

The worldwide market value of GLP-1 receptor agonists was USD 53.46 billion in 2024, and its CAGR (compound annual growth rate) has been estimated at 17.46% up to 2030 [1–8]. Clinical efficacy of glucagon-like peptide-1 (GLP-1) receptor agonists has substantially changed the field of therapeutic options towards type 2 diabetes and obesity, and its further scope is determined by glycemia and weight control. Increased competition from the likes of Eli Lilly, AstraZeneca and Novo Nordisk has hastened the rate of development of the next-generation GLP-1-based agents. Brand names such as Mounjaro, Zepbound, Ozempic, Wegovy, and Victoza are increasingly being assessed not only for better efficacy in lowering glucose but also for comorbidities such as lipids, liver, and kidney and broader cardiometabolic and renal impacts [1]. Given the limitations of targeting only one receptor subunit of GLP-1 agonists for therapy, research efforts have broadened to encompass other metabolic targets, especially the amylin and calcitonin receptors. Amylin, a parallel product of insulin secretion, plays a role in gastric emptying, satiety and glucagon release, and is thus an intriguing target for metabolic modulation(2). Also, the endocrine calcitonin receptor, which is classically implicated in calcium homeostasis, has recently emerged as a significant effector in energy metabolism and appetite regulation.(3) describing novel therapeutic agents' pleiotropic benefits on one or two multi-agonists, targeting dual or multiple receptors with a single peptide ligand have emerged as potential new agents that modulate more than one axis of physiology simultaneously. These advances represent a move from mono-targeted to multi-receptor strategies in the design of peptide drugs, to improve efficacy and tolerability.

The range of therapeutic indications for GLP-1 analogues has also broadened with drugs such as tirzepatide, cotadutide, and retatrutide, which act concurrently on a larger number of metabolic targets. These include the glucagon receptor (GCGR), glucose-dependent insulinotropic polypeptide receptor (GIPR), amylin receptors (AMY1R–3R), and calcitonin receptor (CTR) functionally involved in the regulation of glycemia, suppression of appetite and energy balance(4) . Other interesting targets are the melanocortin-4 receptor (MC4R) (1-13), the cholecystokinin (CCK) receptors (CCK1R, CCK2R) and the free fatty acid receptor 1 (FFAR1/GPR40), which also regulate satiety and lipid metabolism. In addition, central nervous system–related targets, such as dopamine (D2R), serotonin (5-HT2C, 5-HT1B) and the ghrelin receptor (GHSR), emphasize the intricate neuroendocrine control of energy balance, providing further potential for future multimodal therapeutic approaches(5).

The diversity in the receptor classification has added to the complexity of drug pharmacokinetics and drug disposition science. The progressing clinical standards care for GLP-1–based therapies, now incorporating weight loss, cardiovascular risk reduction, and hepatic steatosis, require a level of precision and specificity in drug design that is enhanced (6). To meet these endpoints, developers need to consider advanced pharmacokinetic strategies to optimize systemic exposure, prolong receptor engagement and achieve tissue-selective distribution. As such, ADME and DMPK is now an integral part of the drug discovery process. Avoiding enzymes breaking down (e.g., DPP-4, neprilysin), decreasing clearance by kidneys, and enhancing bioavailability through structural changes (e.g., PEGylation, lipidation, Fc-fusion, albumin-binding domains) are today fundamental design principles (7-9). These progressive steps reposition DMPK not as a conduit, but as a foundational driver of innovation, driving multi-receptor peptide drug discovery. Among the various pharmacokinetic determinants influenced by receptor engagement, modulation of the gastric emptying represents a consecutive sequential mechanism that impacts key contributors of T_{max}, C_{max} and absorption variability especially in the case of treatments with GLP-1 analogues or related peptides.

Natural Resources for Human Health
eISSN: 2583-1194

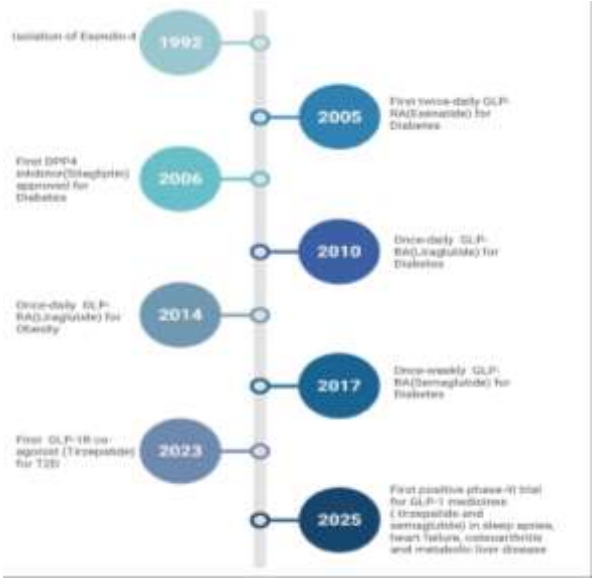

Fig. 1: GLP1 drug development history

RECEPTOR TARGETING, ALTERS PEPTIDE PHARMACOKINETICS THROUGH GASTRIC EMPTYING MODULATION

GLP-1 and related peptides based on their action at receptors have provided a shift in PK thinking and understanding, especially regarding their effect on gastric emptying, a major driver for drug absorption. The slower emptying of the stomach, mainly due to the stimulation of receptors related to satiety hormones (GLP-1.c, peptide YY (PYY), cholecystokinin (CCK), and oxyntomodulin), changes the kinetics of the rate at which the orally administered drugs reach to the small intestine, where most drugs are absorbed. This delay results in delayed (Tmax) and attenuated (Cmax) peak plasma concentrations without changing total amount of exposure (AUC) **(10, 11)**. These modifications distort absorption kinetics and demands special attention in term of drug metabolism and pharmacokinetic (DMPK) profiling in peptide therapeutic development (12).

From a mechanistic standpoint, (13) described that GLP-1 receptor stimulation in the intestine and brainstem decelerates gastric emptying through the upper gastrointestinal tract (by inhibiting antral motility and increasing pyloric tone) and gastric peristalsis (by inducing direct suppression). PYY and CCK both act on G-protein coupled receptors (NPY2R and CCK1R, respectively) and potentiate the inhibition of gastric transit (14, 15). This hormonal symphony prolongs gastric residence time, shifting the absorption window distally. For drugs absorbed in the upper small intestine, such a displacement may impair absorption efficiency especially for drugs that have pH-dependent solubility or limited permeability. These effects are best demonstrated in orally co-administered agents, such as metformin or acetaminophen, where GLP-1R agonists have been shown to have a dramatic influence on Tmax and/or Cmax, while not producing similar changes in bioavailability (AUC) [16-18].

While ghrelin and motilin agonists have the opposite effect, promoting motility through GHSR and motilin receptors, and resulting in faster gastric emptying and transit often in the context of earlier Tmax and possibly greater Cmax (19). The latter, antagonistic, hormonal profile becomes especially relevant in obese or diabetic subjects treated with GLP-1-based therapies, which will abolish endogenous ghrelin and hence further accentuate the retarded gastric emptying (20). The interaction of these hormones can impart a significant degree of variability between individuals for drug absorption, which, in turn, makes it a difficult variable to model and predict for pharmacokinetic purposes, particularly in the context of fed versus fasted status(21).

These effects can be further expanded by multi-agents that act at multiple satiety and energy-regulating pathways, including: tirzepatide (GLP-1/GIP), cotadutide (GLP-1/glucagon) and cagrilintide (amylin/calcitonin) **(22).** Although GIPR activation is considered to have little influence on gastric emptying by itself, due to its central effects, it may facilitate or modify the GLP–1–induced delay, contributing to the heterogeneity(23). Alternatively, Glucagon receptor stimulation may increase motility and lipolysis and may negate the actions of GLP-1(14). These opposing pharmacodynamic influences in multi-receptor peptides, result in very subtle, sometimes hard-to-predict, pharmacokinetics.

In addition to receptor binding, delayed gastric emptying alters drug solubility, pH-mediated degradation, and enzymatic contact. Drugs that are acid-labile and dependent on rapid gastric transit for protection against acid are likely to experience a reduction in bioavailability varies with formulation and pH and varies with gender (24-26) alternatively noted that, prolonged gastric retention may improve the solubilization of poorly soluble drugs by increasing the exposure to the gastric fluid. This two-faced effect complicates the development of orally co-administered drugs together with GLP-1-based agents (27). Significantly, these PK changes are not only drug-specific but also patient-specific. The gastric delay, as well as its effects on drug exposure, can be influenced by receptor expression, gastric tone, metabolic status, and concomitant medication use (e.g., PPI, prokinetic) reducing the delay (28).

The degree of between-patient variability, as described by (29), illustrates the challenges in applying PK parameters to clinical dosing as well as the need for personalized therapy in both drug development and therapeutic optimization. Gastric emptying, which is modulated by hormone-activated receptors, constitutes a major but commonly overlooked factor underlying changes in drug pharmacokinetics in pharmacotherapy involving GLP-1 action. This results in direct impact on Tmax and Cmax and thus influences the uniformity and reproducibility of oral drug absorption. It is important for DMPK scientists to recognize and consider these receptor-mediated delays when designing, profiling and modelling the PK of not only peptide therapeutics, but also co-administered agents.

STRATEGIES TO ENHANCE PEPTIDE STABILITY AND IMPROVE BIOAVAILABILITY THROUGH STRUCTURAL MODIFICATIONS

GLP-1 receptor agonists, their biological potency and target specificity have already revolutionized clinical practice, but native linear peptide sequences have some profound limitations, notably poor stability, rapid renal clearance, and low oral bioavailability. These issues have been addressed with structural modifications, and several different types of structural modifications have been proposed, with different strengths in half-life, reducing clearance and bioavailability.

Backbone Modifications

Backbone modifications such as the introduction of N-alkylated residues, D-amino acids, and reduced-beta amino acids, provide resistance to proteolysis by the closure of peptide bonds or by the modification of enzymatic recognition sites. By enzymatic reaction incorporation of lanthipeptides, By replacement of peptide bonds by isosteric or isoelectronic options for instance, azapeptides, retro-inverso peptides, peptoids, etc. Azapeptides are a class of compounds with similarities to endogenous peptides in which one of the amino carbons is substituted with nitrogen, improving plasma half-life and delaying biological biodegradation. Furthermore, nanomaterial-based immunomodulation strategies help in beneficial delivery (30, 31). Although it has not been broadly applied in commercially produced GLP-1 analogues, Vargason, Anselmo, and Mitragotri (2021) highlighted backbone engineering as an attractive strategy for future analogues designed for oral delivery with improved intracellular longevity(32, 33).

Side Chain Modifications

Making innovation as a tool in chemistry, the side chain modifications can be considered a strategic movement to improve peptides for bioavailability and stability. Among those AAs, His7, Ala8, Gly10, Ser12, Glu13, Asp15, Ser17, Phe28, and Ile29 should be preserved without upseting GLP-1 activity. Phenylalanine28 and isoleucine29 are critical for receptor binding and receptor activation, and aspartic acid15 and serine17 are responsible for insulinotropic activity. The alanine8 and glycine35 residues affect metabolic stability; their replacement increases resistance to DPP-IV cleavage (27, 33, 34). Substitutions of these positions are to designed to be approached cautiously as they impact receptor binding, signaling profile and peptide washout rates heavily. Such residues are essential structural features which, if generally conserved or selectively altered, are useful in the rational design of potent stable GLP-1 analogs suitable for use as medicaments (35).

The addition of non-natural amino acid analogues—such as β-phenylalanine or homoarginine- improves receptor affinity, selectivity, and physicochemical properties, including solubility and permeability. Although Sno-dGe side chain alteration has only modest effects on modified RNA half-life, it has a profound impact on PD, resulting in a more effective drug at lower concentrations. For GLP-1 analogues, such changes are especially important to adjust the receptor binding kinetics and specificity(36). Furthermore, glycine35 is a crucial residue and its replacement by Aib (ψ[CH 2 NH]NH-Gly35) upon the

insertion of Aib at position 8 resulted in a more active analog, called taspoglutide, which exhibited strong resistance to DPPIV(6).

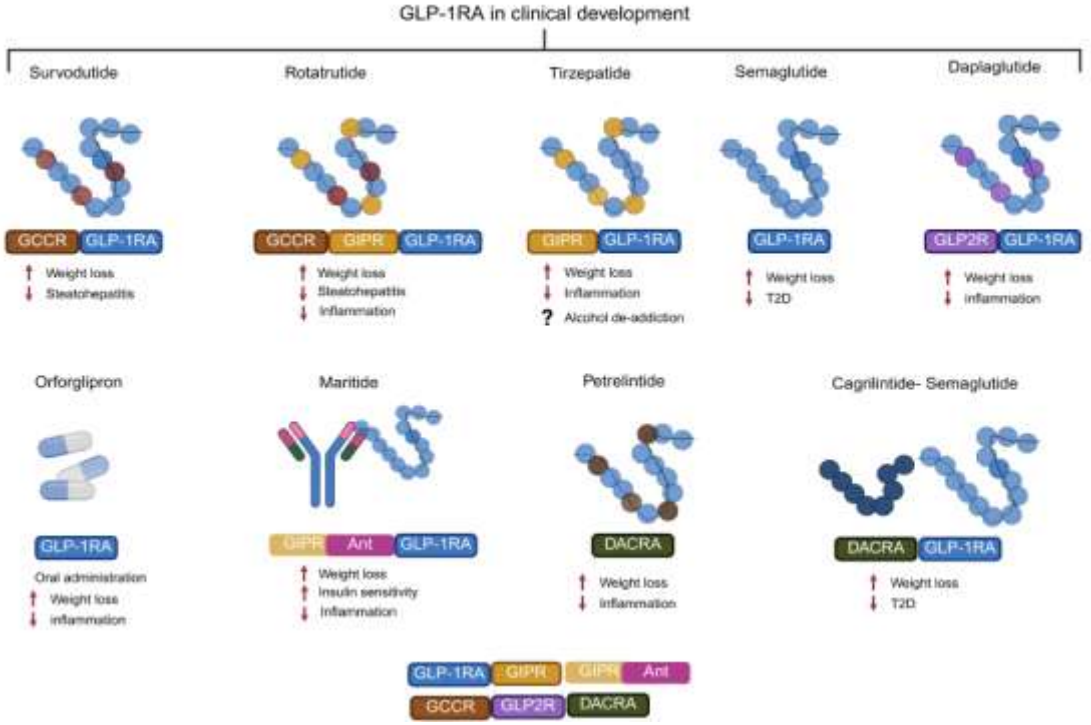

Fig.2. GLP1 Side chain modifications and their clinical significances

Cyclic Peptide Macrocyclization and Secondary Structure Optimization

The important characteristics of cyclic peptides lie in their pharmacokinetics. Special properties such as the stability, the property of the hydrophilic-lipophilic balance, cell permeation, etc., make cyclic peptides an important subject for the design of peptide drugs administrable via the oral route. Cyclization decreases protease susceptibility, increases conformational rigidity, improves membrane permeabilization, cyclization through head-to-tail, side chain-to-side chain, or stapled configuration (37). These alterations have the effect of securing α-helices and β-sheets, which are frequently an important determinant for certain receptor bindings such as evident in the stapled peptide designs. Cyclization contributes to extended half-life and improved tissue penetration. Although not yet a feature of any GLP-1 drugs on the market, cyclic peptides such as MK-0616 are becoming the focus of investigation as orally bioavailable candidates in clinical development (38).

Conjugation Approaches (Lipid and Polymer)

As Alavi (39) reported that lysine26 is a critical residue for Fatty acid conjugation where conjugation of a fatty acid chain to the amino group activates prolonged systemic exposure. Attachment of a fatty acid (e.g., C18 in liraglutide, C18-diacid in semaglutide) leads to albumin binding and reduced renal clearance. Conjugation with a polymer chain, especially poly (ethylene glycol) (PEGylation), protects peptides against enzymatic degradation and immune system clearance, leading to increased circulating half-lives. These are cornerstones in GLP-1 analogues and have a direct impact on dosing intervals which can be as long as once-weekly (semaglutide, dulaglutide) (36).

TERMINAL MODIFICATIONS

A commonly accepted two-step activation model suggests that the C-terminus of GLP-1 interaction with the receptor NTD is followed by the N-terminus of peptide insertion into the receptor TMD core. It was also reported that the partial agonist activity exhibited by short peptide fragments, GLP (9-36), GLP (15-36 is N-terminal-dependent and is involved in the full activation of the receptor for G protein signaling (40). C-terminal of GLP-1 binds to the behind the membrane part of the receptor, respectively. The Ala scan identified the N-Terminal (position 7, 8, 9, 10, 12, 13 and 15) and particular residues in the

C-terminal (position 28 and 29) to be important for the activity of GLP-1(41). The second important residue in the GLP-1 peptide is alanine -8, as a result of the DPPIV processing site at the C-terminus (39). N-terminal acetylation, C-terminal amidation, and albumin fusion are used to protect peptides from exopeptidase cleavages. The albumin fusion strategy used by dulaglutide yields very long plasma elimination half-lives (~5 days), potentially altering the patient treatment burden (42). These modifications are also important to control distribution volume and enhance the predictability of pharmacokinetics. The structural optimization is important for improving the DMPK profiles of the peptide drugs.

Every approach targets a specific target PK liability, (enzymatic stability, renal clearance, or absorption) significantly improving clinical efficacy, patient convenience and market potential. The GLP-1 analogues are well established as an exemplar for which combined application of these strategies has generated best-in-class drugs boasting outstanding therapeutic properties.

3.1 Absorption Related Issues in GLP-1 Based Therapeutics

GLP-1 analogue absorption (as well as for its multi-receptor analogues derivatives) is highly dependent on delayed gastric emptying, which constitutes a pharmacological action inherent to GLP-1 pathway modulation. This delay retards the passage of orally administered drugs to the small bowel, where the majority of absorption takes place; Tmax and Cmax are thus adjusted. Preliminary clinical studies have already been able to demonstrate change in the absorption kinetics of co-administered drugs across the entire BCS due to liraglutide, for example, since it has major effects on gastric motility as well as rates of emptying (43). These were more striking for dulaglutide and tirzepatide with similar effects at times delaying Tmax without affecting AUC in proportion to that delay, highlighting the importance of kinetically based dose regimen design (44-46). This modified pharmacokinetics is also indirectly involved in the interindividual differences in drug response as well as in the PGx-related potential adverse event profiles, as reported in the FAERS-based studies (47).

Novel formulations have been developed to overcome the low bioavailability of oral peptide therapy. SNAC (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) technology enables stomach absorption through increased drug permeability and has peptide-protective characteristics, such as protecting against enzymatic digestion. This methodology has been critical to the market launch of oral semaglutide and has enabled the qualitative systemic exposure despite the peptide being a target for GI degradation (3, 40, 48)In addition to SNAC, other types of delivery systems such as BIOJET and self-emulsifying drug delivery system (SEDDS) and enteric coatings in conjunction with fatty acid-based enhancers have shown good results in improving absorption of GLP-1 analogues (45, 49, 50). As orally available non-peptidic GLP-1RAs, Orforglipron and Danuglipron are novel agents breaking through permeability and enzymatic barriers via structural rather than formulation invention (48, 51).

Multi-receptor peptide agonists (e.g., tirzepatide [GLP-1/GIP], BGM0504 [GLP-1/GIP], cotadutide [GLP-1/glucagon]) further complicate this by involving multiple gut and CNS signalling pathways, leading to increased absorption variability. The variability in the modulation of gastric motility and intestinal transit (3, 46, 52) determines drug residence time and permeability across the gastrointestinal barriers. Structural characterization of non-peptidic agonists, such as RGT1383, illuminates new binding pockets and stability mechanisms which can be applied in the design of dual- or tri-agonists with optimal uptake pathways(53)

Mechanistic modeling and simulation are now at the core of addressing these issues. Molecular dynamics, in vitro permeability and PBPK modelling aid in quantifying the contribution of receptor engagement, transporter activity and drug solubility on absorption. For example, dual agonists as GLP-1/GLP-2 etc., have different intestinal permeability profiles based on the activity and structural alterations of these compounds(54-56). Population variability of drug absorption has also been documented under clinical dosing in actual conditions, e.g., in observational registries and economic assessments of semaglutide and dulaglutide medications (57, 58).

Finally, co-administration effects, patient comorbidities, and inter-animal anatomical heterogeneities (e.g., gastric pH, mucosal thickness, GI motility) further complicate the absorption-related ADME issues for this class of compounds. Abdominal side-effects are not only implicated in tolerability, but in local permeability and dose consistency as well(47, 57). Considering the broadening landscape of oral peptide delivery, comprehension of such multi-variant absorption mechanisms, especially for structurally diverse GLP-1 analogues is crucial for rational formulation and clinical interpretation.

Natural Resources for Human Health
eISSN: 2583-1194

3.2 Metabolic Stability and Hepatic Clearance Challenges of GLP-1 Analogues 671

Metabolism of GLP-1 receptor agonists (GLP-1RAs) is closely related to their molecular structure, receptor affinity, and sensitivity to hepatic and renal clearance. Although these peptides are highly efficacious for controlling glycemia and reducing body weight, their clinical pharmacokinetic profile is usually limited by enzymatic degradation, poor oral bioavailability, and species differences in hepatic metabolism(9). An appreciation of these limitations is indispensable for DMPK staff to maximize drug design and extrapolate therapeutic effectiveness across pre-clinical and clinical applications.

The natural GLP-1 is quickly degraded through the activities of dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP) with a plasma half-life of 1–2 minutes(59, 60). Consequently, the currently marketed GLP-1 analogues (exenatide, liraglutide, dulaglutide, semaglutide, etc.) all include modifications to the peptide to prevent cleavage by proteases and/or clarifying properties designed to extend the half-life in circulation. For example, liraglutide carries an acylated fatty acid side chain that confers binding to albumin and steric protection against DPP-4 attacking, resulting in a human half-life of 13 hr (57, 61, 62). Semaglutide also contains a spacer and C-18 fatty acid to achieve a half-life of approximately 165 h, predominantly via sustained albumin binding and relatively low renal filtration(63, 64).

However, with these alterations hepatic metabolism still plays a major role in determining pharmacokinetic variability. Although they are all rated as low metabolizers compared to small molecules, there are some differences between different GLP-1 analogues. For instance, dulaglutide and semaglutide have markedly divergent hepatic and biliary clearance trends in rodents and primates compared with humans, which confound translatability (64)(**National Institute of Diabetes and Digestive and Kidney Diseases, 2025**). Liver specificity in uptake, through OATP transporters and/or receptor-mediated endocytosis, can lead to sequestration or different degradation rates that may not be adequately calculated in standard microsome or hepatocyte assays.

Different molecular design approaches have been used to overcome metabolic instability. Amongst widely used methods are PEGylation and lipidation, while new possibilities for site-specific conjugation nowadays even allow the adjustment of receptor affinity and metabolic stability without loss in efficacy (36, 65, 66). Furthermore, Fc-fusion and albumin-binding domains have extended half-life of peptides through the masking of proteolytic enzymes and the reduction of renal filtration. Such structural refinements, however, are effective, but add formulation and production challenges, such as immunogenicity, aggregation, and scalability (58) **(42).**

Interestingly, the non-peptidic GLP-1 agonists including danuglipron and orforglipron belong to another category with improved oral bioavailability and different metabolic liabilities. In contrast to the peptide agents these compounds are metabolized by cytochrome P450 (CYP) mediators and thus present an opportunity for drug-drug interaction, first pass hepatic clearance and risk of hepatotoxicity (67-69). First-in-human data have indicated wide exposure variability and marked inter-individual differences in metabolism of elobixibat, which have led to the generation of in vitro and in vivo metabolism data in the early stages of development.

The problem of species variation is also a translational bottleneck. Hepatic uptake and metabolism in rodents is frequently very different from humans secondary to different peptidase expression, albumin binding and transporter systems. Accordingly, IVIVE of hepatic clearance profiles are being increasingly preferred using human-based systems of cryopreserved human hepatocytes, liver microsomes, or sandwich-cultured human hepatocyte platforms(70, 71). These systems also facilitate mechanistic modeling which enables the prediction of metabolic clearance and potential liabilities.

From a regulatory perspective, hepatic safety is an area of focus for both injectable and oral GLP-1RAs. Although the association of GLP-1 analogues with hepatotoxicity has not been common, slight increases in liver enzymes and few reports of liver damage have been reported, and hence caution should be exercised during long- term use especially in those with presence of underlying liver disease or in patients presumptively receiving multiple medications(72). As such, inclusion of patients with hepatic impairment in phase 1/2 studies, and the conduct of thorough exposure-response analyses, are considered necessary for registration.

The metabolic disposition of GLP-1 analogues, either peptidic or nonpeptidic, is a field in constant evolution, thanks to the advancements in drug development and analytical measurements. Although various chemical modifications such as PEGylation, lipidation and fusion technologies have reduced in vivo enzymatic degradation and improved half-life, hepatic metabolism is

still a significant challenge in clearance prediction and safety. Incorporating high resolution in vitro models, species bridging data, and mechanistic PK modeling are key to refine these agents. As the field progresses to multi-receptor and orally bioavailable GLP-1RA platforms, hepatic metabolism will continue to be a focus for DMPK scientists and developers with the aim of recognizing and controlling this issue.

3.3 Permeability and Transporter-Mediated Challenges in GLP-1 Analogues

Intestinal permeability of GLP-1 analogs is a major obstacle in the development of oral peptide drugs, owing to their molecular weight, hydrophilicity and enzymatic stability. The passive permeability across epithelial barrier of most GLP-1RAs such as semaglutide, liraglutide, dulaglutide, etc., are naturally low and require the transport systems such as Caco-2 and MDCK to evaluate permeability profiles and prediction for the absorption during early-stage of their development(46, 73).

In Caco-2 and MDCK-MDR1 studies, multiple GLP-1 analogs display low apparent permeability coefficients (Papp); these low values are primarily derived by the absence of passive diffusion and/or interactions with efflux transporters. It has been reported that P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 2 (MRP2) are involved in efflux transport of peptidic drugs, leading to low intestinal absorption of peptidic drugs(74). The selectivity of inhibitors, including zosuquidar (P-gp), fumitremorgin C (BCRP) and MK571 (MRP2) across Caco-2 and MDCK-MDR1 cells yields additional information concerning the degree of efflux liability for GLP-1 analogues(75).

A number of GLP-1-related projects reported on how the intestinal transporters influence peptide transport. Peptide transporter PepT1 (SLC15A1) In addition to its traditional function in intestinal di- and tripeptide transport, interest was raised in its ability to facilitate the uptake of some GLP-1 mimetics or have indirect action towards through boosting endogenous GLP-1 chapter (76, 77). New findings indicate that peptone-induced activation of L-cells that excrete GLP-1 is also dependent on PepT1 activity, highlighting an intriguing interplay between transporter activity and endogenous hormone regulation (78).

Formulation engineering is of central importance to address these permeability limitations. We previously demonstrated that delivery systems based on SNAC (sodium N-[8-(2-hydroxybenzoyl)amino] caprylate) and BIOJET have effectively contributed to the increased oral bioavailability of semaglutide, through active and temporary modulation of tight junctions and local changes in pH, to provide the transcellular uptake in the stomach (45, 79). Similarly, lipid nanocarriers and ion-pairing techniques have exhibited a potential to circumvent efflux transporter barriers and promote the lymphatic transport of GLP-1 analogues (80, 81). Non-peptidic GLP-1 receptor agonists, for example danuglipron and orforglipron, provide another approach to circumventing permeability-related issues using small molecule design(82).

The interactions between efflux transporters and GLP-1 analogues are also confounded with co-administered drugs and disease-induced alteration in transporter abundance. For example, patients suffering from diabetes or metabolic syndrome are likely to have disturbed transporter profiles in their intestine and the pharmacokinetic profile of orally administered GLP-1-based therapies may be affected accordingly (36). Additionally, concomitant administration of efflux transporter inhibitors or nutritional compounds can affect drug exposure leading to variation in the absorption and efficacy of drugs (83).

Novel modulators of intracellular accumulation of peptide drugs have been identified in recent intracellular metabolomics studies in Caco-2 cells (84). When combined with mechanistic models predicting passive permeability and transcytosis across monolayers, such tools facilitate an improved understanding of GLP-1 analogue behavior across the intestinal barrier(85, 86).

To measure permeability profiles accurately and predictions in vivo outcomes, it will be necessary to use in vitro transporter assays, for example, the bidirectional flux studies, in combination with advanced modelling platforms. Techniques such as physiologically based pharmacokinetic (PBPK) modeling and in silico simulations with consideration of transporter kinetics, cooperating parameters, structure information and regional absorption rates have become necessary for ADME profiling of GLP-1-based drugs (87, 88).

Permeability and transport interactions represent a multi-dimensional challenge for the design of oral active GLP-1 analogues. Strategic refinement of formulation technologies and an in-depth understanding of the mechanistic aspects related to transporter interactions, disease-specific modulation, and predictive in vitro–in vivo correlation models is required for optimizing the transport of compounds across the intestinal barriers.

Natural Resources for Human Health
eISSN: 2583-1194

Section 3.4: Plasma Protein Binding, Depot Effects, and Biodistribution Barriers

The pharmacokinetics of GLP-1 receptor agonists are largely influenced by their structural alterations, mainly those that increase protein binding to the plasma and formation of the depot. Agonists such as semaglutide and dulaglutide display long half-lives attributed predominantly to albumin binding or Fc-fusion approaches, thereby limiting the degree of renal clearance and resulting in an extended systemic exposure. For instance, semaglutide utilizes a C18 fatty acid linker for reversible binding to albumin, thereby yielding a half-life of around 168 hours, whereas dulaglutide employs an Fc-fusion to the IgG4 domain for FcRn-mediated recycling, hence prolonging plasma retention with a t1/2 of ~90 hours(89, 90). Liraglutide, which has a smaller C16 chain, possesses a shorter half-life (~13 hours) and weaker affinity for albumin (91).

These binding modalities not only serve to extend circulation, they modulate biodistribution by reducing penetration in certain tissues and supporting depot formation at subcutaneous sites of administration. Depot activity, particularly in lipidated peptides, could modify systemic release kinetics and could give rise to concern about accumulation in, for example, adipose-rich tissues throughout chronic treatment. Although there is no evidence of clinical depot-related toxicity, animal studies and imaging data suggest depot metabolism is a major contributor to sustained exposure, especially for agents like tirzepatide (42, 92).

Ultimately, despite the contribution of albumin binding to reduced glomerular filtration rate and enzymatic degradation, 'plasma stability' does not equate to 'protein binding'. Plasma stability characterizes resistance against degradation enzymes (e.g., DPP-4, NEP) while protein binding relates to the reversible binding to carriers, such as albumin. Each of these parameters independently contributes to half-life, clearance, and free-drug fraction, and needs to be characterized in early development using techniques such as equilibrium dialysis and ultracentrifugation (91, 93).

Uniqueness of the patient's trait further complicates the nature of biodistribution. Elevated volume of subcutaneous fat in obesity may affect depot kinetics and tissue distribution. Hepatic and renal insufficiency: Changes in albumin levels or filtration rates can have an impact on systemic exposure in patients with hepatic or renal impairment. Because of its high albumin binding, semaglutide retains stable pharmacokinetics, even in mild hepatic impairment, and non-steady-state peptides may require a dose adjustment in the population (42, 94).

Concomitant administration of other drugs that bind albumin, such as warfarin, NSAIDs, or sulfonylureas, could in theory lead to displacement of GLP-1 analogues and an increase in the unbound fraction, with changes in pharmacodynamics or toxicity. Further, absorption enhancers including SNAC or jet-delivery platforms may in fact perturb not only uptake but early tissue exposure, potentially biasing distribution toward lymphatics or gastrointestinal compartments (91, 93).

The different structural modifications of GLP-1 analogues further determine their biodistribution pattern. Lipidation-based strategies, such as semaglutide and liraglutide, enhance depot binding and sustained release to the systemic circulation. Fc-fusion molecules such as dulaglutide, in contrast, do not accumulate in depots but instead use receptor-mediated recycling for persistence. Peptides that are not acylated (eg, exenatide) that do not bind to albumin and do not form a depot, exhibit poor systemic clearance with a requirement for frequent administration (93). These differences have not just an impact on pharmacokinetics, but also on suitability for various co-formulated regimens and for chronic diseases.

3.5 Enzymatic Degradation and Elimination Pathways

The native form of GLP-1 is rapidly degraded by enzymes and has a short plasma half-life of 1–2 min, therefore not well suited to therapeutic use without some level of modification. The main pathway responsible for this instability is cleavage by dipeptidyl peptidase-4 (DPP-4), which inactivates GLP-1 completely, due to removing the N-terminal dipeptide (His7-Ala8), to an inactive metabolite(95, 96). DPP-4 binds to the penultimate alanine residue and cleaves GLP-1 at position 8 thereby greatly reducing its potency to activate the GLP-1 receptor (97). In addition to DPP-4, acid degradation in the stomach and NEP-mediated hydrolysis of internal peptide bonds contribute to GLP-1 inactivation and instability in the circulation(95, 98).

To overcome this enzymatic degradation, various resistance-increasing approaches have been used in the design of GLP-1 analogues. Early alterations implanted replacing Ala8 with a D-form amino acid or nonlabile amino acid that would resist recognition and cleavage by DPP-4(58). Also, C-terminal modifications such as amidation and unnatural amino acids help improve stability as well as receptor binding(97). These backbone alterations also confer resistance to peptidase action and affect drug-receptor binding kinetics.

In addition to the exchange of amino acid residues, conjugation-based methods, e.g., PEGylation, lipidation, or fusing with albumin binding domains or Fc fragments have efficiently improved protease resistance. Lipidation in semaglutide, for instance, allows non-covalent binding with albumin and forms a steric interference preventing enzyme interaction and, hence, enhances circulation half-life (94, 99). PEGylation also raises the hydrodynamic size and decreases the renal filtration and protease recognition of antibodies (6). These modifications are important in providing for dosing intervals, e.g., once a week or longer, or more, to avoid degradation.

Nevertheless, not all of these ploys are applicable outside of a species. Significant inter-species differences in the rates of enzymatic degradation have been shown in preclinical investigations, which place difficulties on translational pharmacokinetics. Murine proteolytic clearance is higher than in man, which may cause the difference in half-life, including exposure and efficacy, in early studies (100-103). These results highlight the critical need for connecting studies and humanized in vitro systems to increase predictive power.

Renal filtration, besides enzymatic degradation, is involved in the dissolution of both GLP-1 and its analogues. Free peptide fragments and unaltered analogues are usually eliminated by the kidneys. In patients with renal impairment, the exposure to some GLP1 analogues can be increased, which may bolster therapeutic effects or side effects(46, 104-106). In fact, dulaglutide and semaglutide demonstrate less dependence on renal clearance following albumin binding and depot formation, both of which result in safer pharmacokinetics in this patient group.

The method of delivery also determines degradation exposure. Oral drugs consisting of semaglutide with SNAC needs to survive a hostile environment of the stomach, with harsh proteases such as trypsin and chymotrypsin before being absorbed(46, 107, 108). By comparison, subcutaneous depots induce a reservoir with slow release that minimizes exposure to systemic proteases with a resulting decrease in degradation (109).

Novel DMPK tools such as in vitro extended plasma stability assays and PBPK modeling allow for a more detailed understanding of degradation kinetics for peptides. Such models include enzyme kinetics, transporter information, and inter-compartmental distribution for the purpose of predicting in vivo behavior (110). These types of methodologies are important to the targeting of the next generation of GLP-1 analogues with superior resistance and clearance characteristics.

3.6 Drug–Drug Interactions with GLP-1 –Based Therapies

The transition from short-acting to long-acting GLP-1RAs has increased the importance of DDIs, as one must consider their prolonged systemic exposure. Exenatide, having a half-life of ~2.4 h, presented little DDI risk, but further consideration is warranted for semaglutide or tirzepatide, with half-lives of ~7 days, considering its long circulation and depot effects(95, 111).

Delayed gastric emptying, a PDE effect of GLP-1RAs, is a significant DDI issue. This may retard the rate of absorption of per orally administered drugs with a consequent effect on Tmax and Cmax, but without that on AUC. Drugs such as acetaminophen and metformin are known to have inconsistent absorption patterns when they are co-administered with GLP-1RAs (112, 113). Depot preparations, with microspheres or acylated chains, can extend this delay even more(46).

Plasma protein binding is an additional factor. Semaglutide and liraglutide show significant albumin binding, thereby prolonging their pharmacokinetics, but also present theoretical risks for displacement by further co-medications which bind to albumin (e.g., NSAIDS, warfarin) with high affinity (42, 94, 114, 115). Although clinically significant displacement is infrequent, such interactions should be used judiciously in polypharmacy. Dual agonists such as tirzepatide could indirectly regulate the activity of enzymes or transporters via biased receptor signaling that involves CYP or transporter-mediated clearance of concomitantly administered drugs (109, 116, 117). While clear evidence of CYP inhibition by GLP-1RAs is scarce, the influence of hepatic/renal clearance in patients with organ insufficiency is not known (94).

Taken together, although the DDI risk with GLP-1RAs in clinical practice is not high in general, individualized consideration should be made owing to their long half-life, depot effect, and effects on GI motility, especially in the situation of patients taking complex regimens or narrow therapeutic index drugs.

Oral Delivery Technologies

Progress in drug-delivery technologies has facilitated the reengineering of GLP-1 analogues towards oral and non-invasive routes. An example is Rybelsus®, the first oral semaglutide formulation, which utilizes SNAC as an absorption enhancer and

pH modifier rition gel), local pH increases transiently and allows for transcellular absorption of semaglutide in the stomach without degradation by gastric enzymes (32). Although innovative, this strategy is constrained by poor bioavailability and safety at higher dose. To address these limitations, new classes of ingestible robots have been developed, which include the L-SOMA and Robotic Pill (RP). The Microneedle-based capsules and gastric-resident systems such as SOMA are other mechanical delivery platform, which can autonomously eject up to a 4 mg drug into the stomach wall(117, 118), while the RP injects peptides directly into the vascularized intestinal mucosa, and delivers peptides through autonomous injection in the small intestine. Safety, Tolerability and Bioavailability trials in Humans and RP was well tolerated and bioavailable at a level equivalent to subcutaneous injection, circumventing degradation and exposure of the mucosal epithelium (119).

Depots of controlled-release microparticles are a promising tool to prolong the pharmacological effect of GLP-1 analogues, thus lowering the number of injections and potentially enhancing patient compliance. These systems employ hydrogels and polymeric implants that function through dissolution, diffusion, osmosis, and ion exchange to control the release of the drug. Surface modifications of microparticles and nanoparticles can enable the development of peptide-surface modified microparticles and nanoparticles to stabilize the peptide, increase circulation time, target its delivery, enhance its efficacy, and minimize systemic side effects by interaction with the tissue microenvironment (32).

Additionally, strategy which can be supported by devices and new chemical approaches such as ionic liquids (ILs), called cum (CAGE), breaks tight junctions for insulin but meanwhile prevents its enzymatic breakdown and mucus penetration and stabilizes the insulin structure, where a multidisciplinary approach obliterates complex formulation strategies (120). These are devices that open up oral delivery to bigger biologics that used to be confined to parenteral administration.

Injectable depot formulations

Conventionally long-acting preparations easily cause the drug concentration to fluctuate, so the effect is reduced and immunogenicity is even caused. To overcome this, a thermogelling ELP was conjugated to a stable GLP-1 analog TRULICITY and serves to create a subcutaneous depot capable of zero-order release kinetics. This strategy prolongs systemic exposure – up to 10 days in mice and 17 days in monkeys – and provides sustained therapeutic exposure, promoting continuous glycaemic control and metabolic enhancement in diabetic models(121). This stability and long action of the formulation, when administered once a month, may be advantageous for chronic diseases that need long-term peptide therapy (60).

Long-acting injection depot formulations of glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed the treatment of type 2 diabetes (T2D) and obesity. Such depots, including those of exenatide once weekly (PLGA microspheres), dulaglutide (Fc-fusion), and semaglutide (albumin binding), facilitate continued drug release which allows for weekly dosing (60, 122). Depot formulations require the less frequent administration and may increase the convenience and improve patients' compliance compared with short-acting agents, such as exenatide twice daily. They not only keep drug levels more constant in the blood, allowing for fewer GI side effects and better fasting glucose control. Several studies have demonstrated that depots achieve better or similar HbA1c reductions and weight loss compared with injections. For example, in AWARD-1, dulaglutide was superior over exenatide BID, and in LEAD-6, liraglutide was superior to exenatide BID(104). Depot injections also have better, or equivalent glycemic control compared with oral GLP-1RAs, although oral agents such as semaglutide allow for non-invasive administration. But strict food timing may be needed and this could impact on compliance. Injection site reactions are more frequent with depot injections, but they are typically of mild severity. GLP-1 depot formulations represent a compelling balance between efficacy, tolerability, and ease of use and are therefore an attractive choice for long-term treatment of patients seeking simplified treatment regimens without compromising on metabolic control(123).

Novel drug delivery systems

Novel GLP-1 Receptor Agonist Delivery Systems As new delivery systems, based on GLP-1 receptor agonists (GLP-1 RAs), are being developed to overcome the drawbacks of standard injectable treatments in terms of pharmacokinetics, patient-friendly administration and treatment results. An emerging transdermal approach, under development, is the injection-free method utilizing transdermal technology, such as a microneedle patch system for biologic administration, e.g., Zosano Pharma's microneedle patch technology that delivers biologics for nearly painless delivery via skin penetration for potential control or pulsatile release of GLP-1(124). Nanoparticle oral systems, including chitosan-coated nanoparticles are also under investigation for their mucoadhesive properties and influence on intestinal peptide transport(125).

Moreover, implantable mini-pumps such as Intarcia Therapeutics' ITCA 650, a matchstick-sized osmotic pump that provides a continuous exenatide payload for up to 12 months, represent extreme long-acting delivery with low user intervention(126). Inhalable peptides, while originally created for insulin (e.g., Afrezza), provide an avenue for the lung delivery of GLP-1 analogues due to the lung's high surface area and fast systemic absorption. New frontiers include hybrid LP (lipo-polymer) nanoparticles that can encapsulate GLP-1 analogues in order to increase their oral bioavailability and protect them from enzymatic degradation(122). Ingestible robots (ie, devices that are swallowed and can perform autonomous physical interaction with an organ) including the Rani Therapeutics RaniPill have been designed to inject GLP-1 analogues into the small intestine wall post oral consumption, avoiding stomach degradation(127) **.** Another frontier is represented by electrospun nanofiber mats already loaded with GLP-1 analogues that, when sublingually (or even buccally) applied may deliver the drug in a sustained manner exploiting mucoadhesive features. Moreover, smart hydrogel-based depots sensitive to the physiological glucose levels are under development to deliver GLP-1 analogues according to the need, which will mimic the endogenous incretin patterns(128). Intelligent delivery systems, such as sense-and-respond technologies, release drugs in a responsive manner to the physiological cues, whereas pulsatile-release (PLGA-based core-shell microparticles), mimics the multi-dose from a single administration(122) . Peptide-Based co-agonists for the treatment of T2D and associated co-morbidities GLP-1/GIP co-agonists that activate the receptors for both GLP-1 and GIP and led to significant improvements in glucose- and energy control in preclinical studies as well as in patients with T2D and in obese T2D patients, due to the complementary biological activities of the two hormones. Ultimately, these novel platforms share the goal of improving the pharmacokinetic profile, reducing patient burden, and ultimately improving efficacy, patient adherence, and convenience and extending the clinical application of GLP-1 analogues.

Regulatory standpoint on GLP-1 therapeutics

The regulatory environment for GLP-1-based therapies and multi-receptor peptide modalities, in general, has evolved significantly with global escalation of their clinical use in diabetes, obesity and metabolic syndromes(95). Regulatory authorities, including the US FDA, European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA) of Japan and National Medical Products Administration (NMPA) of China had recognized this need and have sought to provide an accelerated development and approval process, through such mechanisms as Fast Track or Breakthrough Therapy designation, particularly for candidates with large beneficial effects on weight and glycemic control(40, 129). More recently, drugs such as semaglutide and tirzepatide are illustrative of this trend, reaching the regulatory finish line by leveraging strong efficacy and extended pharmacokinetic (PK) profiles enabled by innovative molecular design and delivery approaches.

For new GLP-1 formulations (long-acting injectables, oral peptides, and depot-based systems), regulatory agencies seek complete data packages on formulation stability, bioequivalence, device compatibility, and dose reproducibility. For semaglutide as an oral preparation with SNAC, this meant developing specific measurements for pH-dependence and local absorption, while long-acting injectables like exenatide in PLGA microspheres required kinetic modeling of peptide release(48, 130). A persistent issue from a regulatory standpoint relates to verifying similar biodistribution and circulation profiles across modified analogues, especially in cases where formulation approaches influence Tmax, Cmax, or variability in systemic exposure.

The safety issue is still at the forefront of concern, particularly for agents with prolonged systemic exposure. Regulatory agencies require cardiovascular outcome trials (CVOTs) and long-term endocrine safety studies with a specific focus on thyroid C-cell carcinoma and pancreatitis. Trials like SUSTAIN-6 of semaglutide, and REWIND of dulaglutide have set a precedent linking sustained exposure to cardio protection, however, regulators are continuing to follow these classes for longer-term adverse effects related to sustained receptor activation(131). Real-world data and long-term registry use are increasingly impacting on post-approval risk–benefit re-evaluations. Perhaps unrealistically, also, expectations of DMPK have multiplied. Today's modern approvals demand in-depth ADME profiles including an understanding of factors such as gastric emptying delays, enzymatic degradation pathways (DPP-4 and NEP cleavage) and renal/hepatic clearance in special populations. Modeling and simulation including PBPK techniques now drive dose selection and the content of labeling and allow for extrapolation to special populations (e.g., pediatric, obese, and renally impaired) without the need for redundant trials. Regulatory authorities look closely at drug–drug interaction risks, such as the role of delayed gastric transit or competitive metabolism on co-administered therapies(48). US FDA Fast Track and Breakthrough Therapy designations have facilitated shortened timelines that can be up to 1–2 years earlier if early efficacy or surrogate endpoints are robust. Sponsors do, however, still need to meet substantial NDA requirements, e.g. modeling and simulation data to aid in selecting dose and labelin**.**

Dual- or multi-agonism combinations, including tirzepatide, must provide appropriate reasons for the additional benefit and safety of each combination with regard to the combination-specific protocol. Post-approval, regulators have emphasized the need for REMS programs for tracking longer-term risks such as pancreatitis, thyroid tumors, and weight-related outcomes. These criteria mirror the growing yet still immature regulatory environment for peptide-based metabolic therapies.

CONCLUSION AND FUTURE TRENDS

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were once niche therapies for diabetes, but they have transformed to multi-target drugs with wide-ranging prospects in metabolic, cardiovascular, neurological and even addiction indications. Advances in formulation, structural modification, and delivery techniques have greatly prolonged half-lives, improved bioavailability, and permitted once weekly or even oral dosing, revolutionizing treatment options for the management of type 2 diabetes and obesity. Of particular significance are the lead compounds semaglutide and tirzepatide, which have begun to lead the way as therapies that can offer double-digit weight loss and durable glycemic control, outcomes that have not hitherto been achievable with traditional modalities(105).

Nevertheless, the interindividual variations continue to be a problem even if achieving positive results. Response to treatment with respect to HbA1c lowering and weight loss frequently varies greatly, which indicates that pharmacokinetic variations, genetic differences, and specific patient characteristics play a role (132). Early response markers and responders' stratification have been investigated; however, a predictive model is not available. This emphasizes the importance of further translation and personalized dosing algorithms. The future of GLP-1 drugs is not only in maximizing their metabolic effects but in discovering new uses. The expression of GLP-1 receptors in the brain has stimulated research concerning neuropsychiatric and reward-related conditions. Early studies have been promising for alcohol use disorders, opioids, and even smoking cessation, but the data are early and there is little consistency between trials (133, 134). These results suggest a systemic influence of GLP-1 on satiety, motivation and neuroinflammation, suggesting that this pharmacological strategy might open new therapeutic avenues beyond the control of glycemia.

Simultaneously, the regulatory environment is evolving to nurture this progression. From expedited approval pathways to novel risk monitoring systems, real-world evidence, modeling, and long-term risk are being folded into protocols as a matter of routine. Moreover, the arrival of GLP-1Ras in psychiatric and addiction medicine will demand new trial endpoints and cross-disciplinary regulatory cooperation. Forty years after the discovery of GLP-1, the class isn't just thriving but evolving in function. The next 10 years will also provide treatments that combine metabolic, neuroendocrine, and behavioral effects - heralding a second generation of multi-system precision medicine.

ACKNOWLEDGMENTS

The authors sincerely thank the Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India, for providing institutional support and access to scientific resources that facilitated the preparation of this review article. The authors also acknowledge the valuable discussions and academic environment that contributed to the completion of this work.

REFERENCE:

[1] Zhao, X., et al., *GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects.* Frontiers in Endocrinology, 2021. **Volume 12 - 2021**.
[2] Drucker, D.J., *Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1.* Cell Metabolism, 2018. **27**(4): p. 740-756.
[3] Singh, A., A. Sohal, and A. Batta, *GLP-1, GIP/GLP-1, and GCGR/GLP-1 receptor agonists: Novel therapeutic agents for metabolic dysfunction-associated steatohepatitis.* World Journal of Gastroenterology, 2024. **30**(48): p. 5205-5211.
[4] Michael, A.N., et al., *GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art.* Molecular Metabolism, 2021. **46**: p. 101102.
[5] Clément, K., et al., *MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency.* Nature Medicine, 2018. **24**(5): p. 551-555.
[6] Alavi, S.E., P.J. Cabot, and P.M. Moyle, *Glucagon-Like Peptide-1 Receptor Agonists and Strategies To Improve Their Efficiency.* Molecular Pharmaceutics, 2019. **16**(6): p. 2278-2295.

[7] Mahapatra, M.K., M. Karuppasamy, and B.M. Sahoo, *Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes.* Reviews in Endocrine and Metabolic Disorders, 2022. **23**(3): p. 521-539.
[8] Zhu, L., et al., *The Role of Dipeptidyl Peptidase IV in the Cleavage of Glucagon Family Peptides: IN VIVO METABOLISM OF PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE-(1–38) **.* Journal of Biological Chemistry, 2003. **278**(25): p. 22418-22423.
[9] Joshi, G., et al., *Design and Synthesis of Topoisomerases-Histone Deacetylase Dual Targeted Quinoline-Bridged Hydroxamates as Anticancer Agents.* J Med Chem, 2025. **68**(3): p. 2849-2868.
[10] Nauck, M.A. and J.J. Meier, *Incretin hormones: Their role in health and disease.* Diabetes, Obesity and Metabolism, 2018. **20**(S1): p. 5-21.
[11] Kadouh, H., et al., *GLP-1 Analog Modulates Appetite, Taste Preference, Gut Hormones, and Regional Body Fat Stores in Adults with Obesity.* The Journal of Clinical Endocrinology & Metabolism, 2020. **105**(5): p. 1552-1563.
[12] Meier, J.J., *GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus.* Nature Reviews Endocrinology, 2012. **8**(12): p. 728-742.
[13] Holst, J.J., *The Physiology of Glucagon-like Peptide 1.* Physiological Reviews, 2007. **87**(4): p. 1409-1439.
[14] Karra, E., K. Chandarana, and R.L. Batterham, *The role of peptide YY in appetite regulation and obesity.* The Journal of Physiology, 2009. **587**(1): p. 19-25.
[15] Liddle, R.A., *Regulation of cholecystokinin secretion by intraluminal releasing factors.* American Journal of Physiology-Gastrointestinal and Liver Physiology, 1995. **269**(3): p. G319-G327.
[16] van Can, J., et al., *Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults.* Int J Obes (Lond), 2014. **38**(6): p. 784-93.
[17] Meece, J., *Pharmacokinetics and Pharmacodynamics of Liraglutide, a Long-Acting, Potent Glucagon-Like Peptide-1 Analog.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2009. **29**(12P2): p. 33S-42S.
[18] Marathe, C.S., et al., *Relationships between gastric emptying, postprandial glycemia, and incretin hormones.* Diabetes Care, 2013. **36**(5): p. 1396-405.
[19] Müller, T.D., et al., *Ghrelin.* Mol Metab, 2015. **4**(6): p. 437-60.
[20] Cummings, D.E., J. Overduin, and K.E. Foster-Schubert, *Roles for ghrelin in the regulation of appetite and body weight.* Current Opinion in Endocrinology, Diabetes and Obesity, 2005. **12**(1).
[21] Jones, K.L., et al., *Predictors of Delayed Gastric Emptying in Diabetes.* Diabetes Care, 2001. **24**(7): p. 1264-1269.
[22] Zhou, Q., et al., *Efficacy and safety of tirzepatide, dual GLP-1/GIP receptor agonists, in the management of type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials.* Diabetol Metab Syndr, 2023. **15**(1): p. 222.
[23] Ricardo, J.S., P.C. Matthew, and W.S. Kyle, *How May GIP Enhance the Therapeutic Efficacy of GLP-1?* Trends in Endocrinology & Metabolism, 2020. **31**(6): p. 410-421.
[24] Satish, K., et al., *Effect of modulation of alimentary and formulation pH on the pharmacokinetics of BCS-Class I, II, III, and IV compounds in rats following cassette dosing.* Drug Development and Industrial Pharmacy, 2026. **52**(5): p. 825--838.
[25] Mudie, D.M., G.L. Amidon, and G.E. Amidon, *Physiological Parameters for Oral Delivery and in Vitro Testing.* Molecular Pharmaceutics, 2010. **7**(5): p. 1388-1405.
[26] Yeshwant, S., et al., *Intersex and Interspecies Pharmacokinetics of Metoprolol After Oral and Intravenous Dose Administration in Rats and Mice.* International Journal of Pharmacokinetics, 2023. **7**(1): p. IPK04.
[27] Lawrence, X.Y., R.C. John, and L.A. Gordon, *Compartmental transit and dispersion model analysis of small intestinal transit flow in humans.* International Journal of Pharmaceutics, 1996. **140**(1): p. 111-118.
[28] Jiarong, L., L. Gongkai, and D. Zhijun, *The mechanism of esophagus dysmotility in diabetes and research progress of relating treatments.* Expert Review of Gastroenterology \& Hepatology, 2021. **15**(8): p. 919--927.
[29] Jennifer, E.S., et al., *Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification.* Drug Metabolism and Disposition, 2015. **43**(11): p. 1823-1837.
[30] Xiao, W., et al., *Advance in peptide-based drug development: delivery platforms, therapeutics and vaccines.* Signal Transduction and Targeted Therapy, 2025. **10**(1): p. 74.
[31] Thalla, M., et al., *Immunomodulatory Nanomaterials: Design Strategies, Mechanisms, Biomedical Applications, and Future Perspectives.* Biomedicines, 2026. **14**(5): p. 964.
[32] Vargason, A.M., A.C. Anselmo, and S. Mitragotri, *The evolution of commercial drug delivery technologies.* Nature Biomedical Engineering, 2021. **5**(9): p. 951-967.

[33] Kim, Y.M., S.M. Lee, and H.S. Chung, *Novel AGLP-1 albumin fusion protein as a long-lasting agent for type 2 diabetes.* BMB Rep, 2013. **46**(12): p. 606-10.
[34] Granhall, C., 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.* Clinical Pharmacokinetics, 2019. **58**(6): p. 781-791.
[35] Masri, E., et al., *Side-Chain Modification of Peptides Using a Phosphoranylidene Amino Acid.* Organic Letters, 2020. **22**(8): p. 2976-2980.
[36] Zheng, Z., et al., *Glucagon-like peptide-1 receptor: mechanisms and advances in therapy.* Signal Transduction and Targeted Therapy, 2024. **9**(1): p. 234.
[37] Linker, S.M., et al., *Lessons for Oral Bioavailability: How Conformationally Flexible Cyclic Peptides Enter and Cross Lipid Membranes.* Journal of Medicinal Chemistry, 2023. **66**(4): p. 2773-2788.
[38] Ballantyne Christie, M., et al., *Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616.* JACC, 2023. **81**(16): p. 1553-1564.
[39] Alavi, S.E., P.J. Cabot, and P.M. Moyle, *Glucagon-Like Peptide-1 Receptor Agonists and Strategies To Improve Their Efficiency.* Mol Pharm, 2019. **16**(6): p. 2278-2295.
[40] Ma, H., et al., *Structural insights into the activation of GLP-1R by a small molecule agonist.* Cell Research, 2020. **30**(12): p. 1140-1142.
[41] Knudsen, L.B. and J. Lau, *The Discovery and Development of Liraglutide and Semaglutide.* Frontiers in Endocrinology, 2019. **Volume 10 - 2019**.
[42] Huanbo, T., et al., *Albumin-binding domain extends half-life of glucagon-like peptide-1.* European Journal of Pharmacology, 2021. **890**: p. 173650.
[43] New, R.R.C., et al., *Glucagon-like peptide-1 receptor agonists for treatment of diabetes and obesity: advantage of oral delivery.* Frontiers in Drug Delivery, 2024. **Volume 4 - 2024**.
[44] Shapira-Furman, T., et al., *The Synthesis of SNAC Phenolate Salts and the Effect on Oral Bioavailability of Semaglutide.* Molecules, 2024. **29**(16): p. 3909.
[45] LEE, S.N., et al., *80-LB: Evaluation of the Pharmacokinetics of Glucagon-Like-Peptide-1 (GLP-1) Receptor Agonist Delivered through the BIOJET Oral Biotherapeutic Delivery Platform in Porcine Model.* Diabetes, 2023. **72**(Supplement_1).
[46] Buckley, S.T., et al., *Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist.* Science Translational Medicine, 2018. **10**(467): p. eaar7047.
[47] Ard, J., et al., *Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists.* Adv Ther, 2021. **38**(6): p. 2821-2839.
[48] Osei, S.P., et al., *Gastrointestinal Safety Assessment of GLP-1 Receptor Agonists in the US: A Real-World Adverse Events Analysis from the FAERS Database.* Diagnostics, 2024. **14**(24): p. 2829.
[49] Marques Vidas, M., et al., *Efficacy and Safety in a Real-World Study of the New Oral Formulation of Semaglutide in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus.* Journal of Clinical Medicine, 2024. **13**(17): p. 5166.
[50] Nissen b, e.a., *Tablets comprising GLP-1 agonist and enteric coating with permeation enhancers* . . Vol. U.S. Patent No. 10,265,384 B2. Patent.
[51] Urva, S., et al., *The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists.* Diabetes, Obesity and Metabolism, 2020. **22**(10): p. 1886-1891.
[52] Meier, J.J., et al., *Effect of upper gastrointestinal disease on the pharmacokinetics of oral semaglutide in subjects with type 2 diabetes.* Diabetes, Obesity and Metabolism, 2022. **24**(4): p. 684-692.
[53] Granhall, C., 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**(6): p. 781-791.
[54] Pratt, E., et al., *Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants.* Diabetes, Obesity and Metabolism, 2023. **25**(9): p. 2634-2641.
[55] Yuan, J., et al., *Molecular dynamics-guided optimization of BGM0504 enhances dual-target agonism for combating diabetes and obesity.* Scientific Reports, 2024. **14**(1): p. 16680.
[56] Abdalqadir, N. and K. Adeli, *GLP-1 and GLP-2 Orchestrate Intestine Integrity, Gut Microbiota, and Immune System Crosstalk.* Microorganisms, 2022. **10**(10): p. 2061.

[57] Holst, J.J., *Pharmacology of GLP-1-based therapies.* The British Journal of Diabetes & Vascular Disease, 2008. **8**(2_suppl): p. S10-S18.
[58] Knudsen, L.B. and J. Lau, *The Discovery and Development of Liraglutide and Semaglutide.* Front Endocrinol (Lausanne), 2019. **10**: p. 155.
[59] Collins, L. and R.A. Costello, *Glucagon-Like Peptide-1 Receptor Agonists*, in *StatPearls*. 2026, StatPearls Publishing
[60] Copyright © 2026, StatPearls Publishing LLC.: Treasure Island (FL).
[61] Veiseh, O., *Drug delivery: Week-long diabetes therapy.* Nature Biomedical Engineering, 2017. **1**(6): p. 0090.
[62] Aroda, V.R., *A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials.* Diabetes Obes Metab, 2018. **20 Suppl 1**: p. 22-33.
[63] Sawyer, J.R., et al., *Design, Structure–Activity Relationships, and Computational Modeling Studies of a Series of a-Helix Biased, Ultra-Short Glucagon-like Peptide-1 Receptor Agonists.* Molecules, 2025. **30**(1): p. 12.
[64] Yang, X.D. and Y.Y. Yang, *Clinical Pharmacokinetics of Semaglutide: A Systematic Review.* Drug Des Devel Ther, 2024. **18**: p. 2555-2570.
[65] Baptist, G., et al., *GLP-1-analogues resistant to degradation by dipeptidyl-peptidase IV in vitro.* Regulatory Peptides, 2000. **86**(1): p. 103-111.
[66] Han, J., et al., *Design, Synthesis, and Biological Activity of Novel Dicoumarol Glucagon-like Peptide 1 Conjugates.* Journal of Medicinal Chemistry, 2013. **56**(24): p. 9955-9968.
[67] Nischan, N. and C.P.R. Hackenberger, *Site-specific PEGylation of Proteins: Recent Developments.* The Journal of Organic Chemistry, 2014. **79**(22): p. 10727-10733.
[68] Choe Hun Jee, C.Y.M., *Peptidyl and Non-Peptidyl Oral Glucagon-Like Peptide-1 Receptor Agonists.* Endocrinol Metab, 2021. **36**(1): p. 22-29.
[69] Bækdal, T.A., et al., *Pharmacokinetics, Safety, and Tolerability of Oral Semaglutide in Subjects With Hepatic Impairment.* The Journal of Clinical Pharmacology, 2018. **58**(10): p. 1314-1323.
[70] Ma, X., et al., *Effect of Food Consumption on the Pharmacokinetics, Safety, and Tolerability of Once-Daily Orally Administered Orforglipron (LY3502970), a Non-peptide GLP-1 Receptor Agonist.* Diabetes Therapy, 2024. **15**(4): p. 819-832.
[71] Jones, B., *The therapeutic potential of GLP-1 receptor biased agonism.* British Journal of Pharmacology, 2022. **179**(4): p. 492-510.
[72] Madsbad, S., *Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists.* Diabetes, Obesity and Metabolism, 2016. **18**(4): p. 317-332.
[73] Maria, J.J., K.K. Filip, and C. Mikkel, *GLP-1 agonists for type 2 diabetes: pharmacokinetic and toxicological considerations.* Expert Opinion on Drug Metabolism \& Toxicology, 2013. **9**(1): p. 17--29.
[74] Huadong, S., et al., *The Caco-2 cell monolayer: usefulness and limitations.* Expert Opinion on Drug Metabolism \& Toxicology, 2008. **4**(4): p. 395--411.
[75] Hubatsch, I., E.G.E. Ragnarsson, and P. Artursson, *Determination of drug permeability and prediction of drug absorption in Caco-2 monolayers.* Nature Protocols, 2007. **2**(9): p. 2111-2119.
[76] Naseem, A., et al., *Intracellular Metabolomics Identifies Efflux Transporter Inhibitors in a Routine Caco-2 Cell Permeability Assay—Biological Implications.* Cells, 2022. **11**(20): p. 3286.
[77] Bajraktari-Sylejmani, G., et al., *Evaluation of PepT1 (SLC15A1) Substrate Characteristics of Therapeutic Cyclic Peptides.* Pharmaceutics, 2022. **14**(8): p. 1610.
[78] Modvig, I.M., R.E. Kuhre, and J.J. Holst, *Peptone-mediated glucagon-like peptide-1 secretion depends on intestinal absorption and activation of basolaterally located Calcium-Sensing Receptors.* Physiological Reports, 2019. **7**(8): p. e14056.
[79] Yining, X., et al., *Targeted nanoparticles towards increased L cell stimulation as a strategy to improve oral peptide delivery in incretin-based diabetes treatment.* Biomaterials, 2020. **255**: p. 120209.
[80] Nissen, *TABLETS COMPRISING GLP - 1 AGONIST AND ENTERIC COATING* in *US patent*. 2019.
[81] Ruba, I., et al., *Hydrophobic ion pairing of a GLP-1 analogue for incorporating into lipid nanocarriers designed for oral delivery.* European Journal of Pharmaceutics and Biopharmaceutics, 2020. **152**: p. 10-17.
[82] Pinto, S., et al., *Nanoparticles targeting the intestinal Fc receptor enhance intestinal cellular trafficking of semaglutide.* J Control Release, 2024. **366**: p. 621-636.
[83] Karakasis, P., et al., *Safety and efficacy of the new, oral, small-molecule, GLP-1 receptor agonists orforglipron and danuglipron for the treatment of type 2 diabetes and obesity: systematic review and meta-analysis of randomized controlled trials.* Metabolism - Clinical and Experimental, 2023. **149**.

[84] Li, N., et al., *P-glycoprotein Substrate Assessment in Drug Discovery: Application of Modeling to Bridge Differential Protein Expression Across In Vitro Tools.* Journal of Pharmaceutical Sciences, 2021. **110**(1): p. 325-337.
[85] Huttunen, J., et al., *Comparison of Experimental Strategies to Study l-Type Amino Acid Transporter 1 (LAT1) Utilization by Ligands.* Molecules, 2022. **27**(1): p. 37.
[86] Patil, A.G., et al., *Development and validation of RP-HPLC-fluorescence method for quantitative determination of quinidine, a probe substrate for P-glycoprotein inhibition assay using Caco-2 cell monolayer.* Biomed Chromatogr, 2010. **24**(6): p. 620-5.
[87] Akkireddy, R., et al., *In Vitro characterization of narciclasine: solubility, metabolic stability, and P-glycoprotein substrate status.* Frontiers in Pharmacology, 2026. **Volume 17 - 2026**.
[88] Bu Tong, S.Z.P.Y.D.X.Y.G., *Glucagon-Like Peptide-1: New Regulator in Lipid Metabolism.* Diabetes Metab J, 2024. **48**(3): p. 354-372.
[89] Donnelly, D., *The structure and function of the glucagon-like peptide-1 receptor and its ligands.* British Journal of Pharmacology, 2012. **166**(1): p. 27-41.
[90] Lau, J., et al., *Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide.* Journal of Medicinal Chemistry, 2015. **58**(18): p. 7370-7380.
[91] Schneider, E.L., et al., *Long-Acting, Longer-Acting, and Ultralong-Acting Antiobesity Peptides.* Journal of Medicinal Chemistry, 2025. **68**(3): p. 2301-2306.
[92] Han, J., et al., *Novel coumarin modified GLP-1 derivatives with enhanced plasma stability and prolonged in vivo glucose-lowering ability.* British Journal of Pharmacology, 2014. **171**(23): p. 5252-5264.
[93] Martin, C.K., et al., *Tirzepatide on ingestive behavior in adults with overweight or obesity: a randomized 6-week phase 1 trial.* Nat Med, 2025. **31**(9): p. 3141-3150.
[94] Simone, E., et al., *A liquid chromatography high-resolution mass spectrometry in vitro assay to assess metabolism at the injection site of subcutaneously administered therapeutic peptides.* Journal of Pharmaceutical and Biomedical Analysis, 2018. **159**: p. 449-458.
[95] Uli, B. and S. Arne, *Strategies for extending the half-life of biotherapeutics: successes and complications.* Expert Opinion on Biological Therapy, 2025. **25**(1): p. 93--118.
[96] Deacon, C.F., *Circulation and degradation of GIP and GLP-1.* Horm Metab Res, 2004. **36**(11-12): p. 761-5.
[97] MENTLEIN, R., B. GALLWITZ, and W.E. SCHMIDT, *Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7–36)amide, peptide histidine methionine and is responsible for their degradation in human serum.* European Journal of Biochemistry, 1993. **214**(3): p. 829-835.
[98] van der Velden, W.J.C., et al., *GLP-1 Val8: A Biased GLP-1R Agonist with Altered Binding Kinetics and Impaired Release of Pancreatic Hormones in Rats.* ACS Pharmacology & Translational Science, 2021. **4**(1): p. 296-313.
[99] Plamboeck, A., et al., *Neutral endopeptidase 24.11 and dipeptidyl peptidase IV are both mediators of the degradation of glucagon-like peptide 1 in the anaesthetised pig.* Diabetologia, 2005. **48**(9): p. 1882-1890.
[100] Santhanakrishnan, K.R., J. Koilpillai, and D. Narayanasamy, *PEGylation in Pharmaceutical Development: Current Status and Emerging Trends in Macromolecular and Immunotherapeutic Drugs.* Cureus, 2024. **16**(8): p. e66669.
[101] Guo, W., et al., *Discovery of ecnoglutide - A novel, long-acting, cAMP-biased glucagon-like peptide-1 (GLP-1) analog.* Mol Metab, 2023. **75**: p. 101762.
[102] Glaesner, W., et al., *Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein.* Diabetes/Metabolism Research and Reviews, 2010. **26**(4): p. 287-296.
[103] Chodorge, M., et al., *Engineering of a GLP-1 analogue peptide/anti-PCSK9 antibody fusion for type 2 diabetes treatment.* Scientific Reports, 2018. **8**(1): p. 17545.
[104] Lene, J., et al., *Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species.* European Journal of Pharmaceutical Sciences, 2017. **104**: p. 31-41.
[105] Mosterd, C.M., P. Bjornstad, and D.H. van Raalte, *Nephroprotective effects of GLP-1 receptor agonists: where do we stand?* Journal of Nephrology, 2020. **33**(5): p. 965-975.
[106] Drucker, D.J., *GLP-1-based therapies for diabetes, obesity and beyond.* Nature Reviews Drug Discovery, 2025. **24**(8): p. 631-650.
[107] Hanefeld, M., et al., *Efficacy and safety of lixisenatide in patients with type 2 diabetes and renal impairment.* Diabetes, Obesity and Metabolism, 2017. **19**(11): p. 1594-1601.
[108] Twarog, C., et al., *Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10).* Pharmaceutics, 2019. **11**(2): p. 78.
[109] Al Musaimi, O., et al., *Strategies for Improving Peptide Stability and Delivery.* Pharmaceuticals, 2022. **15**(10): p. 1283.

[110] Xianyin, L., T. Jason, and E.H.E. Mohamed, *Recent advances in proteolytic stability for peptide, protein, and antibody drug discovery.* Expert Opinion on Drug Discovery, 2021. **16**(12): p. 1467--1482.
[111] Goles, M., et al., *Peptide-based drug discovery through artificial intelligence: towards an autonomous design of therapeutic peptides.* Briefings in Bioinformatics, 2024. **25**(4).
[112] Jensen, L., et al., *Pharmacokinetics and tolerability of semaglutide in people with hepatic impairment.* Diabetes, Obesity and Metabolism, 2018. **20**(4): p. 998-1005.
[113] Rajput, R., et al., *First-in-Class Oral Semaglutide: Overcoming Barriers of Incretinisation in the Indian Context.* Indian Journal of Endocrinology and Metabolism, 2022. **26**(5): p. 417-427.
[114] Ibeanu, N., et al., *Injectables and Depots to Prolong Drug Action of Proteins and Peptides.* Pharmaceutics, 2020. **12**(10): p. 999.
[115] Ilias, I., L. Zabuliene, and M. Rizzo, *GLP-1 receptor agonists in diabetes and weight loss: the double-edged sword of innovation and risks.* Frontiers in Clinical Diabetes and Healthcare, 2025. **Volume 5 - 2024**.
[116] Guru, R.V., et al., *Investigation of the inhibition of eight major human cytochrome P450 isozymes by a probe substrate cocktail in vitro with emphasis on CYP2E1.* Xenobiotica, 2019. **49**(12): p. 1396--1402.
[117] Simonsen, L., et al., *Preclinical evaluation of a protracted GLP-1/glucagon receptor co-agonist: Translational difficulties and pitfalls.* PLoS One, 2022. **17**(3): p. e0264974.
[118] Abramson, A., et al., *Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors.* Nat Biotechnol, 2022. **40**(1): p. 103-109.
[119] Alex, A., et al., *Quantifying the Value of Orally Delivered Biologic Therapies: A Cost-Effectiveness Analysis of Oral Semaglutide.* Journal of Pharmaceutical Sciences, 2019. **108**(9): p. 3138-3145.
[120] Dhalla, A.K., et al., *A robotic pill for oral delivery of biotherapeutics: safety, tolerability, and performance in healthy subjects.* Drug Delivery and Translational Research, 2022. **12**(1): p. 294-305.
[121] Banerjee, A., et al., *Ionic liquids for oral insulin delivery.* Proceedings of the National Academy of Sciences, 2018. **115**(28): p. 7296-7301.
[122] Luginbuhl, K.M., et al., *One-week glucose control via zero-order release kinetics from an injectable depot of glucagon-like peptide-1 fused to a thermosensitive biopolymer.* Nature Biomedical Engineering, 2017. **1**(6): p. 0078.
[123] Baryakova, T.H., et al., *Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems.* Nat Rev Drug Discov, 2023. **22**(5): p. 387-409.
[124] Tahrani, A.A., A.H. Barnett, and C.J. Bailey, *Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus.* Nature Reviews Endocrinology, 2016. **12**(10): p. 566-592.
[125] Thuy Trang, N., et al., *Progress in microneedle array patch (MAP) for vaccine delivery.* Human Vaccines \& Immunotherapeutics, 2021. **17**(1): p. 316--327.
[126] Fatemeh, S., T. Elnaz, and K. Khosro, *Development of chitosan coated calcium-alginate nanocapsules for oral delivery of liraglutide to diabetic patients.* International Journal of Biological Macromolecules, 2018. **120**: p. 460-467.
[127] Rosenstock, J., 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, 2017. **41**(2): p. 333-340.
[128] Myers, J.T., et al., *Preference for a Novel Oral Alternative to Parenterally Administered Medications.* Patient Prefer Adherence, 2024. **18**: p. 1547-1562.
[129] Maleki, H., et al., *Nanofiber-based systems intended for diabetes.* Journal of Nanobiotechnology, 2021. **19**(1): p. 317.
[130] Matsumoto, *Regulatory measures to promote fast patient access in Japan* Japan Medical Products Regulatory Symposium. Pharmaceuticals and Medical Devices Agency, 2023.
[131] Osei, S.P., et al., *Gastrointestinal Safety Assessment of GLP-1 Receptor Agonists in the US: A Real-World Adverse Events Analysis from the FAERS Database.* Diagnostics (Basel), 2024. **14**(24).
[132] Gupta, V., *Glucagon-like peptide-1 analogues: An overview.* Indian Journal of Endocrinology and Metabolism, 2013. **17**(3): p. 413-421.
[133] Emily, B., J.C. Daniel, and P.W. John, *Newer GLP-1 receptor agonists and obesity-diabetes.* Peptides, 2018. **100**: p. 61-67.
[134] Oesterle, T.S. and M.-F. Ho, *Glucagon-like Peptide-1 Receptor Agonists: A New Frontier in Treating Alcohol Use Disorder.* Brain Sciences, 2025. **15**(7): p. 702.
[135] Sheridan, C., *Not just obesity: GLP-1 receptor agonists advance on addiction.* Nature Biotechnology, 2025. **43**(4): p. 455-457.