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"ORAL VS INJECTABLE PEPTIDE THERAPIES IN DIABETES MELLITUS: A COMPARATIVE REVIEW."

Mr. Sahil Todkar[1], Ms.Megha Mohite[2], Mr.Suyog Bodake[3] , Ms.Shrushti Nalawade[4], Ms. Pratiksha Kambale[5], Mrs.Savita Bhise[6]

[26]Assistant Professor, Late ADV. Dadasaheb Chavan Memorial Institute Of Pharmacy Malwadi Masur, Maharashtra 415 106.

[1345]Students, Late ADV. Dadasaheb Chavan Memorial Institute Of Pharmacy Malwadi Masur, Maharashtra 415 106.

Abstract

The present treatment of chronic illnesses, particularly type 2 diabetic mellitus (T2DM), relies heavily on peptide therapies. Peptides have historically been given parentally, although there are significant obstacles to oral distribution (enzymatic breakdown, limited epithelial permeability, acidic gastrointestinal environment). Oral peptide therapy is now possible thanks to developments in formulation science, permeability enhancers (like SNAC), enteric and nanoparticle carriers, and innovative devices; the first extensively used example is oral Semaglutide. With an emphasis on diabetes, this paper offers a thorough comparison of injectable and oral peptide methods in the treatment of chronic diseases. Pharmacology, pharmacokinetics, clinical efficacy and safety, patient choice and adherence, health economics, regulatory environments, and future directions are all integrated in this review.

Keywords

Peptide Tharapies , Oral Peptide Delivery , Injectable Peptide ,GLP – 1 Receptor agonists , Semaglutide , Glycemic control , Regulatory considerations

1.Introduction

Peptide therapies are becoming more important for the long-term management of chronic diseases like type 2 diabetes, because of their strong biological effects and great specificity. Although injectable peptides (such as insulin and GLP-1 receptor agonists) have proven safety and efficacy profiles, injection aversion, the demand for a cold chain, and training requirements are obstacles to their implementation. In order to achieve therapeutic systemic exposure, oral peptide formulations must overcome several physiological challenges [1,5]. This study summarizes the available data and offers researchers and physicians a useful framework.

Table 1. Comparison of Oral Vs Injectable Peptide Therapies in Diabetes Mellitus

Parameter	**Oral Peptide Therapy (e.g., Oral Semaglutide)**	**Injectable Peptide Therapy (e.g., SC Semaglutide, Insulin)**
Route of Administration	Oral (tablet/capsule)	Subcutaneous / Intramuscular
Bioavailability	Very low (<1%), variable	High and predictable
Dosing frequency	Usually once daily	Daily or once weekly
Patient convenience	High (no needles)	Moderate (needle use required)
Adherence potential	Higher for needle-averse patients	Higher for patients preferring less frequent dosing
Cold chain Requirement	Generally not required	Often required
Onset and Consistency	Slower, variable absorption	Consistent absorption
Administration constraints	Fasting, water limits, timing	Minimal
Injection - its reactions	None	Possible
Overall efficacy	Moderate–high	High

1. Peptide therapeutics in diabetes: classes and mechanisms

The principal peptide classes used in diabetes are:

- **Insulin (human, rapid-acting, long-acting analogues):** To control the absorption of glucose, replace or enhance natural insulin. Insulin is mostly injectable; it can be breathed, although its absorption is restricted. [6, 7]
- **Glucagon-like peptide-1 receptor agonists (GLP-1 RAs):** Reduce hunger, decrease stomach emptying, increase glucose-dependent insulin secretion, and frequently cause weight reduction; some peptide are initially administered (daily or weekly) via injection and they are now available in oral form. Oral Semaglutide is approved as a tablet formulation with an absorption enhancer. [2, 8–10]
- **Dual and tri-agonists (GLP-1/GIP, GLP-1/glucagon):** Newlydeveloped peptides with promising metabolic effects that are mostly injectable at the moment. [11, 12]

The efficacy and adverse-effect profiles of peptides and conventional small-molecule antidiabetics differ due to mechanistic differences, which also influence delivery methods.

Table 2. Major Peptide Drug Classes Used in Diabetes Management

Peptide Class	Examples	Mechanism of Action	Route
Insulin analogues	Insulin glargine, lispro	Replace/supplement insulin	Injectable
GLP-1 receptor agonists	Liraglutide, Semaglutide	↑ insulin secretion, ↓ appetite	Oral or Injectable
Dual agonists	Tirzepatide (GLP- 1/GIP)	Enhanced incretin effect	Injectable
Amylin analogues	Pramlintide	↓ gastric emptying, ↓ glucagon	Injectable

2. Biological barriers to oral peptide delivery

Major hurdles for oral peptide absorption include:

- **Proteolytic degradation:** Peptidases throughout the oral cavity, stomach, and small intestine rapidly cleave peptide bonds. [3,13]
- **Acid denaturation:** Low gastric pH can denature many peptides. [3]
- **Mucus and glycocalyx:** Limit contact between drug and absorptive epithelium. [14]
- **Epithelial barrier:** Tight junctions and lo transcellular permeability limit macromolecule transit. [14]
- **First-pass hepatic metabolism:** Even absorbed peptides may face hepatic clearance before reaching systemic circulation. [15]

These mechanisms typically limit oral bioavailability of unmodified peptides to fractions of a percent, necessitating delivery innovations.

3. Enabling technologies for oral peptides

Multiple strategies have been developed to enhance oral peptide delivery. These include:

1. **Permeation enhancers (PEs):** Small molecules that transiently increase mucosal uptake. SNAC (sodium N-(8-[2-hydroxybenzoyl]amino)caprylate) is a notable example used with oral Semaglutide; SNAC appears to increase local pH and promote transcellular absorption in the stomach. [7,16,23]
2. **Protease inhibitors and stabilizers:** Co-formulation with protease inhibitors or chemical modification (D-amino acids, cyclization) to reduce enzymatic degradation. [3,13,15]
3. **Enteric coatings and targeted release:** Protect peptides from stomach acid and release them in targeted intestinal segments. [3,17]
4. **Nano- and micro-particles, lipid carriers:** Use of lipid nanoparticles, polymeric systems, or mucoadhesive carriers to improve stability and uptake. [18]
5. **Device-based approaches:** Swallowable devices (e.g., RaniPill®, self-orienting capsules) that physically deliver peptides across the gastric mucosa by micro-needle or deployable injection. First-in-human data are emerging. [6,19,22]
6. **Chemical modification and half-life extension:** Fatty-acylation, PEGylation, or fusion to albumin- binding moieties to increase plasma half-life and reduce dosing frequency— commonly used for injectable peptides and applicable to oral candidates when systemic exposure is achieved. [11,12]

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4. Pharmacokinetic and pharmacodynamic comparison

injectable peptides typically yield higher and more consistent systemic exposures as compared to oral version. Strong HbA1c and weight effects are made possible by weekly injectable GLP-1 RAs, which generate consistent plasma concentrations with minimal daily variability. As with oral Semaglutide, oral formulations frequently exhibit low absolute bioavailability and increased interindividual variability, necessitating daily dose and particular delivery conditions (e.g., fasting state, restricted water, waiting 30–60 minutes before food) to maximize absorption. [8, 9, 16, 23] Exposure is followed by pharmacodynamic differences: more exposure is associated with stronger cardiovascular benefits seen in outcome trials (which depend on both exposure and trial populations), as well as greater glycemic and weight-loss effects. [2, 10]

Table 3. Pharmacokinetic Differences Between Oral and Injectable GLP-1 RAs6

Feature	Oral Semaglutide	Injectable Semaglutide
Bioavailability	~0.4–1%	~100%
Peak concentration (Cmax)	Lower	Higher
Variability	High interindividual	Low
Half-life	~1 week (systemic)	~1 week
Food effect	Significant	Minimal

5. Clinical efficacy: glycemic control, weight, and cardiovascular outcomes

Glycemic control and weight

GLP-1 RAs, regardless of route, reduced HbA1c and body weight when compared to a placebo or numerous oral glucose-lowering medications, according to randomized controlled trials (RCTs) and meta- analyses. There are few head-to-head RCTs that explicitly compare injectable with equal-exposure oral peptide formulations. Although oral Semaglutide maintains clinically meaningful efficacy and provides an oral option for those unwilling to inject, indirect comparisons indicate that weekly injectable Semaglutide (and higher-dose formulations used for obesity) produces greater reductions in HbA1c and body weight than the currently approved daily oral Semaglutide doses. [1, 8, 9, 17]

Key trial programs

- **SUSTAIN program:** Pivotal trials of subcutaneous Semaglutide demonstrating significant HbA1c and weight reductions and cardiovascular outcome benefits (SUSTAIN 6). [2,10]
- **PIONEER program:** Pivotal trials for oral Semaglutide showing significant HbA1c and weight reductions vs placebo and some active comparators; administration constraints apply and effect sizes are generally smaller than those observed with higher-exposure injectable regimens. [1,8,17]

Table 4 . Key Clinical Trials of Injectable Vs Oral Semaglutide

Trial Program	Formulation	Population	Primary Outcome	Key Findings
SUSTAIN 6	Injectable Semaglutide	T2DM with CV risk	MACE	↓CV events, ↓ HbA1c
SUSTAIN 1–7	Injectable Semaglutide	T2DM	HbA1c, weight	Superior glycemic control
PIONEER 1	Oral Semaglutide	T2DM (drug- naive)	HbA1c	Significant reduction vs placebo
PIONEER 6	Oral Semaglutide	T2DM with CV risk	CV safety	Non-inferior CV safety

Cardiovascular outcomes

Several GLP-1 RAs given parenterally have been demonstrated to reduce MACE in cardiovascular outcome trials (CVOTs) (e.g., Semaglutide subcutaneous in SUSTAIN-6; other drugs in LEADER, REWIND). Dedicated CV safety programs that show non-inferiority for major adverse cardiovascular events provide evidence for the cardiovascular outcomes of oral Semaglutide; superiority signals are less developed than in injectable datasets. When utilizing GLP-1 RAs to lower cardiovascular risk, clinicians should take the formulation-specific evidence base into account. [2, 10, 24]

Hypoglycemia

GLP-1 Unless combined with insulin or insulin secretagogues, RAs have a minimal inherent risk of hypoglycemia. The treatment with the highest risk of hypoglycemia is still injectable insulin, which calls both cautious titration and patient education. [6, 25]

6. Safety, tolerability and immunogenicity

Gastrointestinal problems, including as nausea, vomiting, diarrhea, constipation, and decreased appetite, are common side effects of GLP-1 RAs. Injection-site reactions are examples of injection-specific occurrences. In certain people, oral formulations may cause local stomach discomfort due to permeation enhancers; nevertheless, when used as directed in clinical trials, major side effects are rare. Because injectable formulations have longer follow-up periods across programs, long-term safety data are more comprehensive. Immunogenicity (anti-drug antibodies) varies; the peptide and assay sensitivity determine the clinical outcomes. [8, 9, 26]

Table 5. Common Adverse Effects of Peptide Therapies

Adverse Effect	Oral Peptides	Injectable Peptides
Nausea	Common	Common
Vomiting	Moderate	Moderate
Diarrhea	Common	Common
Injection-site reactions	Not applicable	Possible
Gastric irritation	Possible	Rare
Hypoglycemia (monotherapy)	Rare	Rare

7. Adherence, patient preference, and quality of life

Patient preference is significantly influenced by the mode of administration. Many patients prefer once-daily oral drugs over injections, according to surveys and discrete-choice experiments; nevertheless, preferences differ by population and by trade-offs such dosage frequency, efficacy, and adverse effects. Injectables once a week are preferred by some individuals over daily oral medications. Side effects, cost, difficulty of administration instructions, and perceived benefit all influence real-world adherence and persistence. According to new real- world investigations, GLP 1 RA durability varies, and some cohorts frequently stop using them because of side effects, cost, or accessibility concerns. [4,5,13,20]

Table 6. patient preference and adherence consideration

Factor	Oral Therapy	Injectable Therapy
Needle anxiety	None	Present
Dosing burden	Daily	Daily/Weekly
Training required	Minimal	Injection training
Quality of life impact	Often improved	Variable
Long-term persistence	Moderate	Moderate–High

8. Health economics and access

Economic value is driven by acquisition cost, comparative effectiveness including glycemic control, weight loss, cardiovascular event prevention, and subsequent reduction in microvascular and macrovascular complication . Despite greater initial prices, injectable peptides with larger effect sizes and demonstrated cardiovascular benefits may be more affordable for high-risk patients.
Pricing and payer policies will have a significant impact on real-world uptake; oral versions could increase access in areas where injections are stigmatized or cold chain logistics are restricted. Long-term results, administrative expenses, and variations in adherence should all be included in cost-effectiveness models. [27–29]

9. Regulatory and manufacturing considerations

Regulatory agencies use established procedures to assess oral peptide products for effectiveness, safety, and bioavailability. To guarantee uniform absorption profiles across populations, manufacturers must deal with formulation difficulties (specific excipients like SNAC), scale-up issues, and strict quality control. While certain oral formulations may have less rigorous storage requirements, injectable medications frequently require cold chain storage—a distribution benefit in low-resource situations. In order to achieve optimal bioavailabilty it is essential that patient adhere to labeled administration requirement for oral peptide , including fasting . [16, 30]

10.Special populations

- **Renal impairment:** Many GLP-1 RAs can be used across a wide range of renal function; specific dose adjustments are agent-dependent. Injectables often have clearer data in severe impairment; clinicians should consult product labels and trial data. [31]
- **Elderly:** Increased risk of dehydration from GI adverse events and polypharmacy considerations warrant careful initiation and monitoring. [32]
- **Pregnancy and lactation:** Data are limited; many peptides are not recommended unless benefits outweigh risks. [33]
- **Pediatrics:** Evidence in children is evolving; injectable liraglutide and certain agents have pediatric approvals for obesity in selected age groups, but caution is required. [34]

11. Practical guidance for clinicians

- **Individualize therapy:** Consider efficacyneeds, cardiovascular risk, tolerability, patient preference, access, and cost when selecting oral vs injectable peptides. [2,8,9]
- **Educate on administration:** For oral Semaglutide, they must wait at least 30 min before eating or taking other oral medication to maximize absorption. [16]
- **Titrate to reduce GI effects:** Where possible, upward titration can improve tolerability. [8]
- **Monitor and coordinate:** Check renal function, counsel on hypoglycemia risk when combining with insulin or sulfonylureas, and monitor weight and GI tolerability. [31,25]
- **Document rationale for payer approvals:** For high-cost injectable therapies, document clinical indications (e.g., ASCVD, inadequate control) to support access. [27]

Table 7. advantages and limitations of oral Vs injectable peptides

Aspect	Oral Peptides	Injectable Peptides
Advantages	Non-invasive, patient-friendly	Strong efficacy, robust evidence
Limitations	Low bioavailability, strict dosing	Needle use, cold chain
Best suited patients	Needle-averse, early T2DM	Advanced T2DM, high CV risk

12. Future directions and research priorities

- **Improved oral delivery platforms:** New permeation enhancers, stabilizers, and capsule technologies may increase oral bioavailability and reduce administration constraints. [3,11,18]
- **Non-peptide small molecule GLP-1 agonists:** These could provide oral agonism without peptide limitations. [35]
- **Oral dual/tri-agonists:** If oral delivery of multi-agonists becomes possible, therapeutic potency could increase substantially. [12]
- **Device innovations:** Further clinical testing of ingestible microdevice systems (RaniPill, self-orienting systems) is warranted. [19,22]
- **Head-to-head trials:** Direct comparisons of matched-exposure oral vs injectable peptides and long-term CVOTs for oral formulations will clarify their relative roles. [2,8,24]

13. Limitations

There are few head-to-head RCTs comparing equal doses across routes, and long-term comparative CV data for oral peptides lag injectable programs. This review is based on published trials, reviews, and growing real-world evidence.

14. Conclusions

For many diseases, injectable peptide treatments are still the gold standard because of their strong effectiveness, reliable pharmacokinetics, and wealth of long-term evidence. Although oral peptides, which are clinically represented by oral Semaglutide, are a significant advancement that increases treatment options and improves acceptability for many patients, they currently frequently result in lower systemic exposure, have more stringent administration requirements, and may have higher interindividual variability. Efficacy, safety, patient choice, adherence likelihood, cardiovascular risk, and cost should all be taken into consideration when choosing a route. Clinical decision-making will be improved by direct comparative studies and ongoing innovation in oral administration.

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