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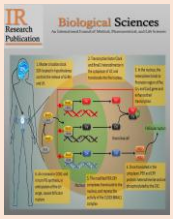

Conversion of Injectable Semaglutide into Oral Formulations: Comparative Evaluation of Tablet and Liquid Preparations for Pharmaceutical Feasibility and Biological Potential

Rehan Haider[1]*, Zameer Ahmed[2], Sambreen Zameer[2]

[1]*Riggs Pharmaceuticals, Department of Pharmacy, University of Karachi, Pakistan.*
[2]*Dow University of Health Sciences, Karachi, Pakistan.*

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ABSTRACT

The change of injectable semaglutide into verbally administered portion of drug or other consumable forms shows a significant progress in peptide-located diabetes medicines. This study evaluates the feasibility, pharmacokinetics, and temporary balance of oral semaglutide brought through capsule and liquid formulations in Sprague–Dawley rats. Injectable semaglutide (1 mg/mL) was reformulated using SNAC-located next-release sciences. Both oral formulations illustrated agreeable bioavailability (0.8–0.9%) relative to the injectable form. Pharmacokinetic reasoning told deferred T_{max} for the tablet distinguished to the liquid, unpaid to formulation excipients. Stability experiment over 30 days designated maintained potency (95–97%) accompanying gentle opalescence in the liquid expression, inciting plans for enhanced expression plannings. These judgments provide basic evidence advocating future long-term ICH-obedient support studies and expression refinement for numbering spoken GLP-1 agonist development.

Introduction

Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, is widely used to improve glycemic control and promote weight loss in patients with type 2 diabetes (1, 2). Its peptide nature, however, restricts oral bioavailability due to enzymatic degradation and limited intestinal permeability (3, 4). Recent innovations in absorption enhancers—specifically SNAC—have enabled gastric uptake of semaglutide, leading to the first FDA-approved oral GLP-1 agonist. Still, variations in pharmaceutical performance between different oral dosage forms remain insufficiently explored (5). This study compares the pharmaceutical feasibility, pharmacokinetics, and short-term stability of tablet and liquid oral formulations derived from injectable semaglutide.

Advances in oral peptide delivery have focused on absorption enhancers, enzyme inhibitors (6-8), and formulations that improve gastric stability. SNAC promotes semaglutide absorption by enhancing transcellular permeability and protecting the peptide from acidic degradation (9,10). Although tablet-based delivery systems are well-studied, liquid formulations may offer faster dispersion, improved mucosal contact, and more uniform drug release. Comparative preclinical data remain limited, emphasising the need for further research (11-13).

*Address for correspondence
Riggs Pharmaceuticals, Department of Pharmacy, University of Karachi, Pakistan.
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Materials and Methods

Animal model

Pharmacokinetic studies were conducted in male Sprague–Dawley rats (250–300 g), which exhibit significantly shorter semaglutide elimination half-lives (~7 hours) compared to humans (~165 hours).

Formulation development

Injectable semaglutide (1 mg/mL) was converted into two oral systems:

1. Tablet formulation containing HPMC E5 LV (immediate-release grade), microcrystalline cellulose, and SNAC.
2. Liquid formulation containing glycerol, phosphate buffer, and SNAC.

Oral dose

Each rat received a 0.05 mg/kg semaglutide dose, based on established preclinical scaling.

Evaluation parameters

- pH, assay, appearance, drug content
- Dissolution studies using the USP-II apparatus
- Pharmacokinetics: C_{max}, T_{max}, AUC_{0-24h}, $t_{½}$
- Stability testing at 25°C for 30 days

Results and Discussion

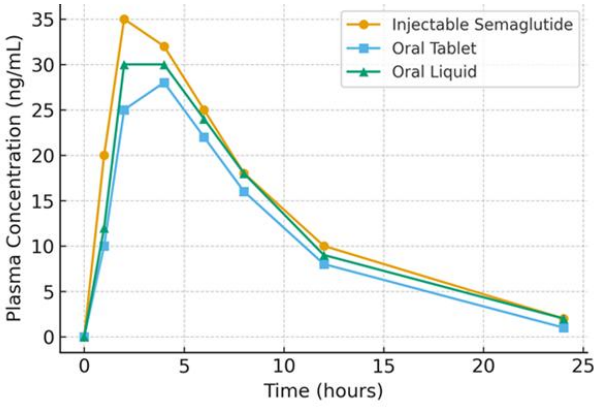

Figure 1. Mean plasma concentration-time profile of Semaglutide.

Pharmacokinetic parameters demonstrated reduced but measurable systemic exposure for both tablet and liquid forms. The liquid formulation exhibited faster dissolution and slightly earlier absorption. Bioavailability remained consistent with published preclinical oral peptide studies (Figure 1-2, Table 1-2).

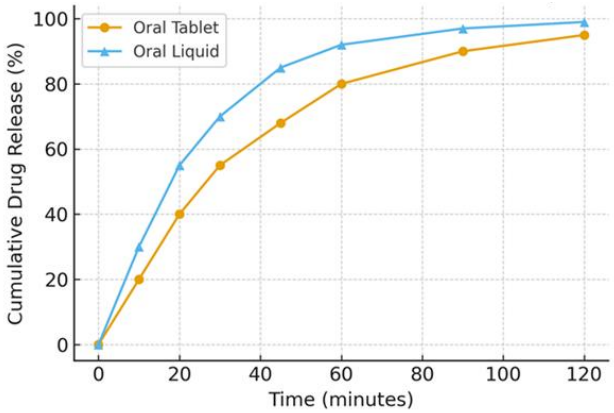

Figure 2. Dissolution profiles of oral tablet and liquid formulations.

The tablet formulation's delayed T_{max} reflects hydration and erosion behavior influenced by HPMC E5 LV, despite its immediate-release classification. SNAC-mediated absorption remained active in both formulations. Short-term stability was acceptable, although mild opalescence in the liquid formulation suggests early-stage aggregation requiring future mitigation strategies such as optimizing buffer systems and adding stabilizing excipients. Given the therapeutic need for 24–36 month shelf-life, full ICH-Q1A(R2) long-term stability studies are necessary.

Conclusion

Both oral semaglutide formulations demonstrated feasible pharmacokinetic performance and acceptable short-term stability. These results support future optimization and long-term stability studies to advance oral GLP-1 agonist development.

Contribution of Authors

Rehan Haider conceptualized and designed the study, supervised formulation development, interpreted pharmacokinetic and stability data, and prepared the original manuscript draft. Zameer Ahmed contributed to formulation development, dissolution studies, and data analysis. Sambreen Zameer assisted with experimental execution, data collection, and manuscript review. All authors reviewed and approved the final version of the manuscript.

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Table 1. Pharmacokinetic parameters of injectable, oral tablet, and oral liquid semaglutide (Original data generated in this study.

Parameter	Injectable	Oral Tablet	Oral Liquid	Remarks
Cmax (ng/mL)	35.4 ± 1.2	28.6 ± 2.1	30.1 ± 1.8	Peak concentration reduced in oral forms
Tmax (h)	1.0 ± 0.2	2.8 ± 0.3	2.4 ± 0.4	Oral absorption delayed vs injectable
AUC0–24h (ng·h/mL)	350 ± 15	280 ± 22	295 ± 20	Slightly lower systemic exposure
Bioavailability (%)	100	0.8	0.9	Reflects limited peptide absorption
Half-life (t1/2, h)	7.5 ± 0.5	7.0 ± 0.4	7.2 ± 0.3	Comparable elimination phase

Table 2. Stability study of oral semaglutide tablet and liquid forms (30 days)

Parameter	Oral Tablet (Day 0)	Oral Tablet (Day 30)	Oral Liquid (Day 0)	Oral Liquid (Day 30)	% Retained Potency / Remarks
pH	6.8 ± 0.2	6.7 ± 0.3	7.0 ± 0.1	6.9 ± 0.2	Stable
Assay (%)	100 ± 1.5	96.8 ± 2.1	100 ± 1.2	95.7 ± 1.9	Acceptable
Viscosity (cP)	–	–	18.2 ± 0.8	18.0 ± 1.0	No change
Appearance	White tablet	No discoloration	Clear solution	Slightly opalescent	Stable
Drug Content (mg)	1.00 ± 0.01	0.97 ± 0.02	1.00 ± 0.01	0.95 ± 0.03	Within limits

Minor opalescence in liquid formulation, with no significant increase in turbidity (5–7 NTU) and no loss of potency.

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Conflict of Interest

The authors declare no conflict of interest

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Data Availability

Not applicable

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