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In Situ Forming Biodegradable Triblock Polymeric Depots for 90-Day Sustained Delivery of Tirzepatide: A Pharmacokinetic and In Vitro Release Study

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Abstract

Tirzepatide—a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor co-agonist—has demonstrated unprecedented efficacy in glycemic control and weight reduction in patients with Type 2 diabetes and obesity. However, current commercial therapy requires weekly subcutaneous injections, leading to compliance erosion during chronic multi-year treatment. In this study, we engineered an injectable, thermo-responsive, biodegradable triblock copolymer hydrogel platform (PLGA-PEG-PLGA, Mw 1,500-1,000-1,500 Da) combined with sucrose acetate isobutyrate (SAIB) to achieve zero-order sustained release of tirzepatide over 90 days. Four distinct polymer-depot formulations (Formulations F1 through F4, varying in copolymer concentration from 20% to 35% w/v and SAIB additive ratios) were prepared and evaluated for sol-gel phase transition temperature, syringeability (27G needle), in vitro release kinetics in biorelevant phosphate buffer (pH 7.4, 37°C), and in vivo pharmacokinetic profiles in Sprague-Dawley rats (N = 6 per group). Formulation F3 (30% w/v PLGA-PEG-PLGA with 10% SAIB) exhibited an optimal low-viscosity liquid state at 20°C (viscosity 18.4 mPa·s) that rapidly transformed into a semi-solid gel depot within 45 seconds upon exposure to 37°C physiological temperature. In vitro, F3 virtually eliminated the initial burst release (only 3.8 ± 0.6% in the first 24 hours) and maintained steady zero-order daily peptide release (0.95 ± 0.08 mg/day) over 90 consecutive days. In vivo pharmacokinetic evaluation confirmed sustained therapeutic plasma tirzepatide levels (mean C_ss: 42.6 ± 5.2 ng/mL) for 90 days following a single subcutaneous injection, without local tissue necrosis or granuloma formation. This in situ forming depot system provides a scalable, patient-centric delivery platform to transition peptide co-agonists from weekly injections to quarterly long-acting administration.

Keywords: Tirzepatide; GLP-1/GIP Co-Agonist; In Situ Gelling; Triblock Copolymer; PLGA-PEG-PLGA; Long-Acting Injectables; Sustained Drug Delivery; Obesity Pharmacotherapy

Abbreviation

GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; PLGA: Poly(lactic-co-glycolic acid); PEG: Polyethylene Glycol; SAIB: Sucrose Acetate Isobutyrate; AUC: Area Under the Curve; HPLC: High-Performance Liquid Chromatography.

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Introduction & Study Rationale

Tirzepatide is a first-in-class dual GIP and GLP-1 receptor agonist peptide that achieves superior HbA1c reduction and profound body weight loss (>20%) in clinical trials [1,2]. However, the requirement for lifelong weekly subcutaneous self-injections results in long-term treatment discontinuation rates exceeding 40% within the first year of therapy [2,3].

Developing long-acting injectable (LAI) depot systems for peptide therapeutics is notoriously challenging due to peptide aggregation, chemical instability during microencapsulation, and catastrophic initial burst release [3,4]. In this study, we investigated an aqueous, thermo-sensitive PLGA-PEG-PLGA triblock copolymer system engineered with sucrose acetate isobutyrate (SAIB) to formulate a quarterly (90-day) sustained-release tirzepatide depot (Figure 1).

Materials & Experimental Methods

PLGA-PEG-PLGA triblock copolymers (lactide:glycolide ratio 3:1, molecular weight 1,500-1,000-1,500 Da) were synthesized via ring-opening polymerization [5]. Tirzepatide (purity > 98.5% by HPLC) was dissolved with zinc acetate (1:2 molar ratio) into aqueous copolymer solutions (20% to 35% w/v) containing varying ratios of SAIB (0% to 15% w/w) to create Formulations F1 through F4 [6].

Sol-gel phase transitions were quantified using rheological oscillation. In vitro release was monitored in isotonic PBS (pH 7.4, 37°C with 0.02% sodium azide) using validated UPLC-UV. In vivo pharmacokinetics and depot biodegradability were evaluated in male Sprague-Dawley rats (n = 6 per group; 15 mg/kg single subcutaneous injection) over 90 days [7,8].

Results: Elimination of Burst Release and 90-Day Sustained In Vivo Profile

Formulation F3 (30% copolymer + 10% SAIB) demonstrated ideal rheological behavior: a freely flowing solution at room temperature (18.4 mPa·s, easily injected via a standard 27-gauge needle) that solidified into a firm, cohesive hydrogel depot within 45 seconds at 37°C [8].

In vitro dissolution demonstrated that the hydrophobic SAIB additive effectively sealed matrix micropores, suppressing the 24-hour initial burst release to just 3.8 ± 0.6%, compared to 24.2 ± 3.1% in the SAIB-free formulation F1 (Table 1) [8,9]. F3 maintained linear zero-order release ($R^2 = 0.994$) through Day 90. In vivo PK in rats demonstrated steady-state therapeutic plasma tirzepatide concentrations (mean $C_{ss} = 42.6 \pm 5.2 \text{ ng/mL}$) for 90 days with complete macroscopic polymer bioresorption observed at Day 105 without fibrous encapsulation [9,10].

Conclusion & Translational Significance

The engineered PLGA-PEG-PLGA/SAIB in situ forming depot provides a robust, clinically viable platform for the 90-day sustained delivery of tirzepatide. This formulation successfully eliminates burst release, protects peptide integrity, and offers a compelling strategy to replace burdensome weekly injections with quarterly outpatient administration.

Formulation Code	Copolymer / SAIB Composition	Sol-Gel Transition Temp (°C)	Initial 24-h Burst Release (%)	Cumulative 90-Day Release (%)	In Vivo Half-Life / Duration (Days)	Mean Plasma C_ss (ng/mL)
Formulation F1	20% PLGA-PEG-PLGA (0% SAIB)	31.2 ± 0.8 °C	24.2 ± 3.1%	98.4 ± 2.2% (at Day 45)	42.0 ± 4.5 days	18.2 ± 3.4 ng/mL
Formulation F2	25% PLGA-PEG-PLGA (5% SAIB)	33.5 ± 0.6 °C	11.4 ± 1.5%	95.1 ± 3.4% (at Day 65)	60.4 ± 5.2 days	31.5 ± 4.1 ng/mL
Formulation F3 (Optimized)	30% PLGA-PEG-PLGA (10% SAIB)	35.1 ± 0.4 °C	3.8 ± 0.6%	91.8 ± 2.8% (at Day 90)	90.2 ± 6.4 days	42.6 ± 5.2 ng/mL
Formulation F4	35% PLGA-PEG-PLGA (15% SAIB)	36.8 ± 0.5 °C	2.1 ± 0.4%	74.5 ± 4.1% (Incomplete)	98.5 ± 7.1 days	24.8 ± 3.8 ng/mL

Table 1: In Vitro Release Kinetics, Initial Burst Percentage, and In Vivo Pharmacokinetic Parameters of In Situ Gelling Tirzepatide Depots (N = 6 per formulation).

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