Injectable Thermoresponsive Hyaluronic Acid–GelMA Composite Hydrogel Loaded with Tacrolimus and Tyrosinase-Activating Peptides for Local Immunomodulation and Melanocyte Regeneration in Vitiligo

Abstract

Vitiligo is an autoimmune skin disorder characterized by localized melanocyte loss due to immune-mediated destruction, resulting in depigmented lesions. Current therapies often lack targeted delivery and regenerative capacity. This study aims to develop a multifunctional injectable hydrogel system composed of methacrylated hyaluronic acid (HAMA) and gelatin methacrylate (GelMA), designed for localized immunomodulation and melanocyte regeneration. The composite hydrogel will be synthesized via photoinitiated free-radical polymerization using lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) as a cytocompatible photoinitiator under visible light (405 nm). This method ensures tunable crosslinking density, optimized for mechanical stiffness mimicking native dermis (~1–3 kPa). The hydrogel formulation incorporates tacrolimus encapsulated within biodegradable poly(lactic-co-glycolic acid) (PLGA) nanoparticles for sustained, pH-responsive release, and synthetic tyrosinase-activating peptides to promote melanogenic signaling. Rheological analysis will evaluate shear-thinning behavior and sol-gel transition at physiological temperature (37 °C) using oscillatory rheometry. The hydrogel's biocompatibility and functional efficacy will be assessed via in vitro 3D co-culture of primary human keratinocytes and melanocytes embedded within the hydrogel matrix, evaluating melanogenesis through melanin quantification assays and gene expression of MITF and TYR. Immunomodulatory effects will be investigated by co-culturing with activated CD8+ T-cells, measuring cytotoxicity reduction via lactate dehydrogenase release and cytokine profiling. Hydrogel degradation kinetics and tacrolimus release profiles will be characterized under simulated dermal pH (5.5) and physiological pH (7.4). We hypothesize that this HAMA–GelMA injectable hydrogel platform will provide a dual-function localized immunosuppressive and regenerative microenvironment, offering a promising strategy for vitiligo treatment. Positive outcomes will pave the way for in vivo evaluation and clinical translation.

Keywords

Vitiligo; Injectable hydrogel; Hyaluronic acid methacrylate; Gelatin methacrylate; Tacrolimus; PLGA nanoparticles; Immunomodulation; Melanocyte regeneration; Tyrosinase-activating peptides; Rheological properties; pH-responsive drug release.