Polymer Crosslinking Regulates Local, Multimodal Drug Release to Skin

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Background and purpose: Hydrogels are an effective therapeutic platform for administering drugs to cells in the skin due to their localized delivery, biocompatibility, flexible chemistry, and mechanical similarity to living tissues. Prescribed drug release rates are necessary for certain disease states in order to target physiological processes and promote sustained therapeutic effects with a single administration. However, mechanisms governing drug release are often inextricably linked to bulk properties of the hydrogel. There remains a need for a simple transdermal delivery system that enables multimodal release of immunomodulatory drugs for a variety of skin diseases.

Methods: We describe a tissue-adhesive hydrogel embedded with microparticles to enable tunable release of encapsulated drugs in a manner independent of hydrogel properties. While many implanted drug reservoirs aim to degrade over time, this hydrogel was designed to sustainably deliver localized treatments to skin while adherent, after which it can be removed by peeling. Use of a detachable hydrogel also enables the incorporation of a range of synthetic particle types to guide drug release without dependence on particle degradability, long-term biocompatibility, repeated injections, or accumulation in tissues. The hydrogel was synthesized using a one-pot free radical polymerization to create a biocompatible and nondegradable polyacrylamide gel containing adhesive galloyl groups, capable of encasing multiple populations of particles to release drugs to cells in a multimodal manner. Embedded silicone particles with a range of crosslink densities were synthesized from varied ratios of silicon alkoxide and alkoxysilane monomers using a nucleation and growth technique. The differential drug release afforded by these engineered particles enables a high level of control over the rate at which drugs reach the skin disease site.

Results: We demonstrate multimodal drug release for skin cancer treatment by designing particles that can release resiquimod (a macrophage-stimulating drug) over several hours and palbociclib (a T-cell-stimulating drug) over several days. We show cell activation by promoting polarization of macrophages *in vitro* and *ex vivo* toward anti-tumor phenotypes, with significantly higher expression of macrophage inflammatory markers (iNOS, CD86, and MHCII) compared to free drug over five days. Furthermore, we show that that ionic liquids can transport small molecule drugs across the stratum corneum, resulting in higher drug efficacy than clinical creams. Finally, we demonstrate therapeutic efficacy of this delivery system by inhibiting melanoma spheroid growth through the combined release of FRAX486, which targets tumor-associated fibroblasts to reduce tumor stroma effects, and paclitaxel, a chemotherapy, from the hydrogel system.

Conclusions: The tunable and multimodal nature of this hydrogel system has implications in treating a variety of skin disorders and delivering vaccines transdermally at well-defined rates, reducing off-target drug effects and improving therapeutic efficacy.