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Polymer conjugated retinoids for controlled transdermal delivery

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ABSTRACT

All-trans retinoic acid (ATRA), a derivative of vitamin A, is a common component in cosmetics and commercial acne creams as well as being a first-line chemotherapeutic agent. Today, formulations for the topical application of ATRA rely on creams and emulsions to incorporate the highly hydrophobic ATRA drug. These strategies, when applied to the skin, deliver ATRA as a single bolus, which is immediately taken up into the skin and contributes to many of the known adverse side effects of ATRA treatment, including skin irritation and hair loss. Herein we present a new concept in topical delivery of retinoids by covalently bonding the drug through a hydrolytically degradable ester linkage to a common hydrophilic polymer, polyvinyl alcohol (PVA), creating an amphiphilic nanomaterial that is water-soluble. This PVA bound ATRA can then act as a pro-drug and accumulate within the skin to allow for the sustained controlled delivery of active ATRA. This approach was demonstrated to release active ATRA out to 10 days *in vitro* while significantly enhancing dermal accumulation of the ATRA in explant pig skin. *In vivo* we demonstrate that the pro-drug formulation reduces application site inflammation compared to free ATRA and retains the drug at the application site at measurable quantities for up to six days.

1. Introduction

All-trans retinoic acid (ATRA), a metabolite of Vitamin A, is a key component in the topical treatment of numerous skin disorders, including: acne, psoriasis, and UV-induced photo aging [1–8]. ATRA therapy acts by reducing abnormal follicular epithelial hyper-keratinization as well as repressing UV-induced cell signaling pathways that lead to up-regulated expression of metalloproteinases [9–14]. Use of ATRA however is limited by its serious side effects such as skin irritation and hair loss as well as its poor chemical stability [15–20]. Previous investigations have looked to control these undesirable characteristics through controlled release formulations such as creams, microparticles, and emulsions [17,21–24]. These strategies, however, rely on bolus delivery of active ATRA that, in the case of creams and emulsions, can become immediately available. This rapid increase in local concentration causes a number of adverse side effects [10,25]; while on the other hand, microparticle approaches require injection across the dermis, increasing the potential for immunologic response and infection. To date, there has been limited research into polymer-conjugated forms of ATRA, with the focus on application in cancer therapies [26–28].

Poly (vinyl alcohol) (PVA) is an excipient of choice in many pharmacologic formulations and is commonly used in the preparation of biodegradable particles [29–32]. PVA is well tolerated and has demonstrated a very good safety profile *in vivo*[33–36]. Applications for PVA in drug delivery primarily focus on it as a surfactant, providing excellent drug loading while allowing control over particle size and stability [37–40]. Recent reports have highlighted the mucoadhesive nature of PVA coated particles, suggesting that the hydrogen bonding ability of PVA promotes interaction with mucosal proteins [41–44]. This adhesive nature of PVA to mucosal components suggests a broader potential use, one that can take advantage of the hydrogen bonding to increase the residence time of drugs within tissues. Conjugating the hydrophobic ATRA to the very hydrophilic PVA through a hydrolytically degradable ester linkage, creates a new approach to formulate ATRA into a controlled release nanomaterial with potentially enhanced tissue residence.

Controlling ATRA release presents many substantial improvements over the current techniques for ATRA delivery. Currently ATRA is placed as a bolus at the sight of interest, immediately activating retinoic acid receptors and generating a strong pro-inflammatory response that can cause serious pain, irritation, and damage to the dermis. Bolus

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