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Targeted delivery of a poorly water-soluble compound to hair follicles using polymeric nanoparticle suspensions

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ABSTRACT

This study explored the utility of topically applied polymeric nanoparticle suspensions to target delivery of poorly water-soluble drugs to hair follicles. Several formulations of amorphous drug/polymer nanoparticles were prepared from ethyl cellulose and UK-157,147 (systematic name (3S,4R)-[6-(3-hydroxyphenyl)sulfonyl]-2,2,3-trimethyl-4-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yloxy)-3-chromanol), a potassium channel opener, using sodium glycocholate (NaGC) as a surface stabilizer. Nanoparticle suspensions were evaluated to determine if targeted drug delivery to sebaceous glands and hair follicles could be achieved. In *in vitro* testing with rabbit ear tissue, delivery of UK-157,147 to the follicles was demonstrated with limited distribution to the surrounding dermis. Delivery to hair follicles was also demonstrated *in vivo*, based on stimulation of hair growth in tests of 100-nm nanoparticles with a C3H mouse model. The nanoparticles were well-tolerated, with no visible skin irritation. *In vivo* tests of smaller nanoparticles with a hamster ear model also indicated targeted delivery to sebaceous glands. The nanoparticles released drug rapidly in *in vitro* nonsink dissolution tests and were stable in suspension for 3 months.

The present results show selective drug delivery to the follicle by follicular transport of nanoparticles and rapid release of a poorly water-soluble drug. Thus, nanoparticles represent a promising approach for targeted topical delivery of low-solubility compounds to hair follicles.

1. Introduction

Nanoparticles represent an attractive means to achieve preferential delivery of therapeutic agents to target tissues in the human body, achieving the desired drug release profile at the site without the use of organic solvents (Moghimi et al., 2001; Yih and Al-Fandi, 2006). Nanoparticles have been successfully used to target drug delivery, improve bioavailability, sustain drug release, and increase dissolved drug levels for poorly water-soluble compounds (Singh and Lillard, 2009).

This article describes the results of studies to investigate the feasibility of using suspensions containing drug/polymer nanoparticles to achieve targeted delivery to hair follicles of UK-157,147 (systematic name (3S,4R)-[6-(3-hydroxyphenyl)sulfonyl]-2,2,3-trimethyl-4-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yloxy)-3-chromanol), a potassium channel opener with low aqueous solubility. The structure of this compound is shown in Fig. 1.

Successful drug targeting requires increasing the proportion of drug delivered to the target tissue relative to the systemic exposure (Knorr et al., 2009). For treatment of some dermatological indications, this requires delivering a higher proportion of drug to the hair follicles and sebaceous glands. Restricting the amount of drug travelling through the transepidermal pathway to systemic circulation can be important for increasing the drug's therapeutic index, particularly for drugs that require chronic use or drugs that produce significant adverse events in other locations within the body. For example, severe side effects occur when podophyllotoxin is absorbed systemically, but no such effects occur when

Abbreviations: D_{fr}, dissolved free drug; D_p, drug in nanoparticle; K_p, polymer/aqueous partition coefficient; V_p, volume fraction of ethyl cellulose in the suspension.

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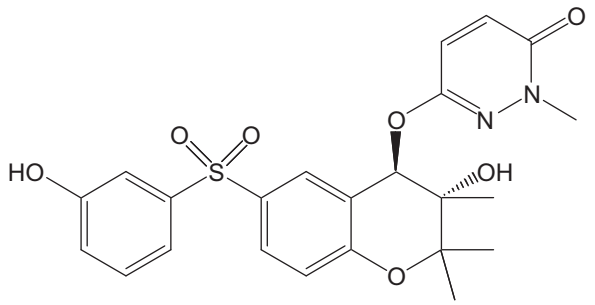

Fig. 1. Chemical structure of UK-157,147 (systematic name (3S,4R)-[6-(3-hydroxyphenyl)sulfonyl]-2,2,3-trimethyl-4-(2-methyl-3-oxo-2,3-dihydropyridazin-6-yloxy)-3-chromanol).

~75-nm solid lipid nanoparticles containing podophyllotoxin are delivered with epidermal targeting (Chen et al., 2006).

In principle, topically applied agents can reach the lower portion of the hair follicles by either the transfollicular or the transepidermal route. The former pathway involves drug diffusion through the upper reaches of the pilosebaceous gland, whereas the latter pathway involves secondary local/systemic distribution into hair follicles. The relative importance of the two routes depends on the drug and the formulation.

In many cases, delivery occurs simultaneously via both transepidermal and transfollicular pathways. For example, caffeine appears in systemic circulation within 5 min after it is topically applied as a solution, but takes 20 min to appear if the same formulation is applied to skin in which the hair follicles are blocked. These results demonstrate the importance of the transfollicular route (Otberg et al., 2008).

Significant research has been focused on drug transport via the transfollicular route using various topical dosage forms (Rolland et al., 1993; Lademann et al., 2005; Jung et al., 2006; Chourasia and Jain, 2009). Many different nanoparticle systems, including those based on metal oxides (Lekki et al., 2007), liposomes (Jung et al., 2006), and polymeric materials (Shim et al., 2004; Alvarez-Roman et al., 2004; Tsujimoto et al., 2007) have been investigated for use as follicular drug-delivery carriers.

Several studies have demonstrated that nanoparticles can reach the deep hair follicles after topical application to human and animal skin, with some research suggesting that follicular delivery is more efficient with smaller nanoparticles—generally, those less than about 300 nm in diameter—than larger nanoparticles (Chen et al., 2006; Shim et al., 2004; Alvarez-Roman et al., 2004; Vogt et al., 2006). For example, Vogt et al. (2006) found that 40-nm nanoparticles were internalized by Langerhans cells found around hair follicles of human skin, but 750-nm and 1500-nm nanoparticles were not.

Lademann et al. (2005) clearly showed the penetration of 320-nm poly(lactide-co-glycolide) (PLGA) nanoparticles into hair follicles in porcine and human skin. With massage after topical application, the nanoparticles penetrated much deeper and remained in the hair follicles much longer than a formulation that did not contain nanoparticles (Lademann et al., 2007). Similarly, Rancan et al. (2009) reported that 228-nm and 365-nm polylactic acid (PLA) nanoparticles penetrated human hair follicles and released loaded dyes into the surrounding tissues, indicating the potential of targeted drug delivery using nanoparticle systems.

Although biodegradable and nonbiodegradable nanoparticles have been reported, biodegradability may not be essential, because it is likely nanoparticles will be eliminated from the skin surface (e.g., due to hair growth, outflow of sebum, and epidermal turnover). In addition, evidence exists that nanoparticles larger than 100 nm do not pass out of the follicles into living tissue (Lademann et al., 2007). Another study suggests that polymeric nanoparticles ranging in size from approximately 30 to 100 nm did not penetrate beyond the superficial stratum corneum (Wu et al., 2009). One study showed 20-nm titanium oxide nanoparticles penetrated 400 μm into the hair follicles, but no evidence of nanoparticles in vital tissue or sebaceous glands was observed (Lekki et al., 2007).

On the other hand, a recent study in mice suggested that 40- and 200-nm polystyrene nanoparticles taken up into hair diffused into the surrounding tissue and were transported to the draining lymph nodes (Mahe et al., 2009). Additional studies would be valuable to assess the potential for transport of nanoparticles into surrounding tissue from hair follicles.

In this study, we investigated the feasibility of using a suspension of drug/polymer nanoparticles to achieve targeted delivery of UK-157,147, a low-solubility compound, to hair follicles. For this study, ethyl cellulose—which is known to solubilize a large number of hydrophobic drugs—was chosen as the matrix for the UK-157,147 nanoparticles. (It is likely that similar solubilization can be achieved using other polymeric materials, including biodegradable polymers if desired.)

The nanoparticles were characterized, and their performance was evaluated in (1) an *in vitro* test to evaluate drug distribution within the skin (using rabbit ear tissue); (2) an *in vivo* test to evaluate drug delivery to sebaceous glands (using a Golden Syrian hamster ear model); and (3) an *in vivo* test to evaluate hair-growth efficacy (using a C3H mouse model).

In this study, delivery of UK-157,147 was demonstrated to the sebaceous glands in a hamster ear model using an aqueous nanoparticle suspension. Similar formulations with larger nanoparticles also stimulated hair growth in the C3H mouse model, caused no visible skin irritation and were well-tolerated. *In vitro* imaging of rabbit ear tissue suggests that aqueous nanoparticle suspensions successfully limit distribution of small-molecule drugs to the dermis while delivering drug to the follicles.

These results suggest that nanoparticle suspensions can effectively deliver low-molecular-weight drugs to the follicles through the transfollicular route, while limiting distribution to the rest of the skin and to systemic circulation. By targeting delivery to the hair follicles, nanoparticles have the potential to improve the therapeutic index for a number of topically applied drugs.

2. Materials and methods

2.1. Materials

UK-157,147 was provided by Pfizer Inc. (Groton, CT). Ethyl cellulose (Ethocel® Viscosity 4) was a generous gift from the Dow Chemical Co. (Midland, MI). Sodium glycocholate (NaGC) (Product No. G7132), poly[methyl methacrylate-co-(fluorecein-o-methacrylate)] (PMMA)(Product No. 56,888-0), and poly[2-methoxy-b-(2-ethylhexyloxy)-1,4-phenylenevinylene] (MEH-PPV) (Product No. 541435) were purchased from Sigma Aldrich Corp. (St. Louis, MO). Methylene chloride (Product No. BDH1113) was purchased from VWR International LLC (Radnor, PA). Syringe filters (1-μm glass-microfiber membrane and 0.2-μm polyethersulfone [PES] Supor filters) were purchased from Pall Corp. (Port Washington, NY). Molecular-weight-cutoff (MWCO) filters (100 kDa, Microcon Ultracel YM-100) were purchased from Millipore Corp. (Billerica, MA).

2.2. Nanoparticle preparation methods

For the *in vitro* tests to evaluate distribution within the skin using rabbit ear tissue, 19:1:0.6 ethyl cellulose: MEH-PPV:NaGC