Cutaneous Drug Delivery: An Update

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Cutaneous delivery of therapeutics represents a proven and attractive option for treating a variety of dermatologic conditions with minimal systemic side effects. Although there have been many innovations in drug delivery systems, the number of effective cutaneous drugs remains small, primarily because of the stratum corneum permeability barrier. Overcoming this barrier safely and reversibly to deliver large hydrophilic drugs cutaneously is one of the major challenges in the field of dermatologic therapy.

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A topically applied substance has basically three possibilities to penetrate into the skin: transcellular, intercellular, and follicular. The transfollicular path has been largely ignored because hair follicles constitute only 0.1% of the total skin. Nonetheless, this method has great potential for skin treatment by providing a deeper penetration and absorption of compounds than transcellular route, and also can affect adnexal structures. Increased accumulation of drugs in the pilosebaceous unit could potentially treat alopecia, acne, and other skin diseases more efficiently. Here, we present a summary of the latest technologies used to increase cutaneous delivery through the three different routes outlined above, delineating various chemical and physical methods as well as reviewing various drug delivery systems, including liposomes, microspheres, and nanoparticles.

Skin, the largest organ of the human body, offers a painless and compliant interface for cutaneous drug administration. As compared with injections and oral delivery routes, cutaneous drug delivery increases patient compliance, avoids metabolism by the liver, provides sustained and controlled delivery over long time periods, concentrates the active agents at the site of disease, and prevents systemic side effects. Recent advances in biotechnology have laid the groundwork for very promising, potent, and highly specific molecular targeting therapies. Although innovations in drug delivery systems have enabled the successful clinical use of some of these novel pharmaceuticals, the number of effective cutaneous drugs remains small. And yet, after nearly four decades of extensive study, the success of this technology remains limited, with only a few transdermal products available, all of them based on low-molecular-weight lipophilic drugs (Bos and Meinardi, 2000). Currently, drugs administered across the skin share three constraining characteristics: low molecular mass (<500 Da), high lipophilicity (oil soluble), and small required dose (mg) (Prausnitz *et al.*, 2004). This is because the stratum corneum (SC), which evolved to protect the body from toxins, is nearly impermeable to the movement of foreign molecules across it (Scheuplein and Blank, 1971). Overcoming this barrier safely and reversibly to deliver large hydrophilic drugs cutaneously is one of the major challenges in the field of dermatologic therapy.

A topically applied substance has basically three possibilities to penetrate into the skin: transcellular (through the cell), intercellular (in between the cells), and follicular (through hair follicles) (Geusens *et al.*, 2011). Intercellular penetration requires transport through extracellular lipid matrix as well as internalization into the cell. Given the SC is highly impermeable to most molecules on the basis of size, hydrophilicity, lipophilicity, and charge, it is necessary to alter temporarily the barrier properties of skin for effective delivery of the desired drugs. Strategies to improve drug delivery can be broadly subdivided into chemical, biochemical, and physical approaches (Figure 1). Chemical strategies have included the development of novel chemical enhancers, which alter the lipid structure of the SC, including solvents (propylene glycol, DMSO), fatty acid esters (oleic acid), and surfactants (SDS) (Karande *et al.*, 2005). Chemical enhancers increase skin permeability by several mechanisms: (1) disrupting the SC lipid organization, making it permeable (many enhancers operate mainly in this way such as azone, terpenes, fatty acids, DMSO, and alcohols); (2) extracting lipids, making the horny layer more permeable through forming aqueous channels (DMSO, ethanol); (3) interacting with keratin in corneocytes, opening up the dense protein structure, making it more permeable (e.g. DMSO, ionic surfactants). Biochemical approaches include intracellular delivery peptides for gene delivery for small interfering RNAs (Deshayes *et al.*, 2008; Gooding *et al.*, 2012) and the development of nanodelivery vehicles that can deliver their payload to the deeper layers of the skin. These vehicles include nanoparticles (nanosized colloidal structures composed of synthetic or semisynthetic polymers, lipids, metals, and ceramics), liposomes (colloidal particles, typically consisting of lipid molecules form concentric layers that may entrap and deliver drugs to the

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Abbreviation: SC, stratum corneum

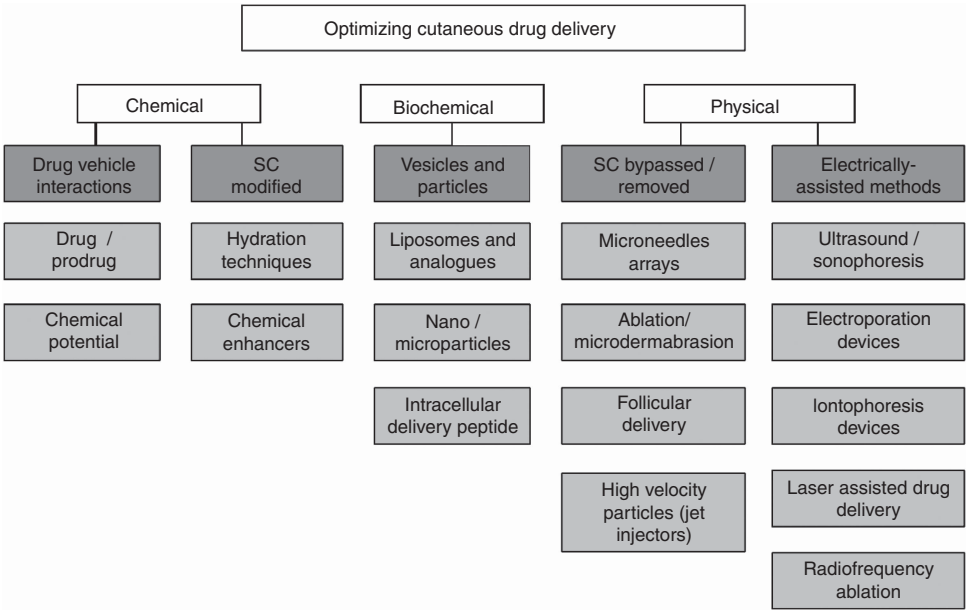

Figure 1. Summary of methods for optimizing cutaneous drug delivery.

skin), microspheres (free-flowing powders consisting of proteins or synthetic polymers, biodegradable in nature, $<200\,\mu m$) (Papakostas *et al.*, 2011; DeLouise, 2012), etc. These particles can be functionalized with a variety of moieties, including DNA and other nucleic acids, polyethylene glycol (PEG), protein, magnetic resonance imaging active agent, photosensitizer, polymeric coating, and targeting agents (Vatansever *et al.*, 2012). The unique kinetics and ability to functionalize these particles have made these particles very attractive for drug delivery applications. Physical methods include the use of external forces such as high-frequency sound waves in ultrasound or electric currents in iontophoresis to create gaps in the SC (Mitragotri *et al.*, 1995; Banga *et al.*, 1999), physical disruption of the SC via minimally invasive microneedles (van der Maaden *et al.*, 2012), the use of ablative laser therapy for dermal delivery (Gomez *et al.*, 2012; Bloom *et al.*, 2013), and chemical depilation–induced anagen for hair follicles (Domashenko *et al.*, 2000), etc. Recently, various laser therapies such as fractional and ablative lasers have been explored to create temporary barrier impairment, including channels for transport and/or ablating the SC and allowing for enhanced drug delivery (Lee *et al.*, 2001; Hædersdal *et al.*, 2010; Lee *et al.*, 2011).

The transfollicular path has been largely ignored because hair follicles constitute only 0.1% of the total skin. Nonetheless, the optimization of drug delivery to and via the hair follicles is gaining more and more importance as it has been recognized that the hair follicles are an interesting target site for topical applications. Drug delivery to hair follicles is likely dependent on the physicochemical properties of the drugs, the vehicles used in the formulation, as well as on the activity status, size, and density of the hair follicle. The available targets included surrounding capillaries and antigen-presenting cells, sebaceous glands, and stem cells in the bulge region of the hair follicle (Patzelt and Lademann, 2013). Transfollicular delivery has great potential for skin treatment by providing a deeper penetration and absorption of compounds than transcellular route, and also can affect sweat glands or the pilosebaceous unit (Teichmann *et al.*, 2005; Blume-Peytavi and Vogt, 2011). Many studies suggest that the follicular pathway, in contrast to the conventional transdermal pathway, is especially favorable for highly hydrophilic and high-molecular-weight substances (Mitragotri, 2003), as well as particle-based drug delivery systems (Alvarez-Roman *et al.*, 2004). Methods for follicular delivery include penetration enhancement via liposomal delivery of drug (Verma *et al.*, 2004; Jung *et al.*, 2006), the use of drug-loaded microspheres (Alvarez-Roman *et al.*, 2004), or transdermal delivery of particles that will interact with follicular cell targets (Chourasia and Jain, 2009). Challenges for follicular delivery include the inner and outer root sheets, the flow of sebum into the hair follicle, the interaction between the drug and the sebum, as well as the physicochemical properties of the vehicle (Illel, 1997; Chourasia and Jain, 2009). Nonetheless, studies concerning nanoparticles that can reach deeper parts of the follicles after a short time prove that the penetration process overcomes sebum flow (Lademann *et al.*, 2006).

An area that is gaining importance in follicular drug delivery is the use of particulate drug delivery systems (such as nanoparticles and microparticles) as they increase drug penetration into the hair follicle openings and can act as depots for sustained drug release within the hair follicle (Papakostas *et al.*, 2011). Nanoparticle formulations are gaining more preference over aqueous alcohol solutions used so far for the treatment of hair disorders such as androgenetic alopecia and alopecia areata. Indeed, encapsulating hair-growing ingredients in PLGA (poly(D,L-lactide-co-glycolide)) particles

increased their permeation within hair follicle regions 2.0- to 2.5-fold more than in the case of the control aqueous solutions (Tsujimoto *et al.*, 2007). The follicular penetration of nano- and microparticles depends on the sizes of the particle; therefore, particle-based delivery systems can be used to target specific regions of the follicular duct. In addition, nanoparticles or nanoparticulate delivery systems can also incorporate immunomodulatory agents, allowing for topical administrations of medications that could otherwise have severe adverse systemic side effects. For example, liposomal formulations of cyclosporin A induced visible hair regrowth in rats, thus showing a potential for new topical treatments of alopecia areata in humans (Vogt *et al.*, 2006). Gene therapy has also been recently demonstrated using small interfering RNA encapsulated in biodegradable cationized gelatin microspheres injected in a murine model of disease, resulting in remission of the alopecia areata (Nakamura *et al.*, 2008). Challenges, however, remain in topical application of large molecules such as small interfering RNAs and more study are needed. Promising concepts to optimize hair follicle delivery include the application of external or internal stimuli for controlled drug release from the particles such as the cocomitant application with protease or the usage of gold nanoparticles in combination with near-infrared irradiation (Patzelt and Lademann, 2013). Novel particle-based drug delivery system may provide promising active follicular targeting of disease-related cell populations in the hair follicle. Increased accumulation of drugs in the pilosebaceous unit could potentially treat alopecia, acne, and other skin diseases more efficiently. Ultimately, as technology leads to improved therapeutic options, we may see more successful treatments for alopecia areata, a disease that can be both challenging and frustrating for patients and physicians.

CONFLICT OF INTEREST

The author states no conflict of interest.

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