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Getting under the skin: what is the potential of the transfollicular route in drug delivery?

“The rationale for drug delivery via the hair follicle is the large contact area and the large storage volume of the hair follicle.”

Keyword: hair therapy • nanomedicine • transdermal drug delivery

Dermal and transdermal delivery have gained renewed interest as possible drug administration routes; thanks to substantial progress made in drug delivery technologies [1]. Transdermal delivery of drugs is an attractive option compared with the intravenous route, because it is noninvasive, can be easily carried out by patients and allows for sustained drug delivery without dangerous high initial plasma levels. Other than the oral route, the transdermal administration route avoids drug degradation, hepatic first-pass metabolism and side effects such as gastrointestinal adverse reactions. In addition, transdermal delivery by means of patches or delivery systems enables sustained drug delivery, which is desired in those cases where constant blood levels are necessary to achieve the therapeutic effect. With regard to treatment of skin diseases, delivery by topical application increases the local therapeutic effect and helps reduce systemic toxicity. Moreover, the introduction of new drug delivery systems such as nanoparticles offers the great potential to deliver the drug selectively to specific skin areas, for example, healthy versus diseased tissue, and targeting structures at the cellular or even molecular level.

Yet, an important limit of the transdermal route is the low skin penetration of hydrophilic, high molecular weight drugs. Therefore, a wide range of methodologies have been developed and are being increasingly explored including physical means (e.g., sonophoresis, electroporation, micro-needle systems and thermal ablation) as well as chemical means (penetration enhancers or incorporation in carrier systems) [2]. In

this context, the hair follicles (HF) play a highly interesting role as penetration shunts of several types of substances, including macromolecules. Drug delivery via the transfollicular route has several advantages and applications.

Why choose the transfollicular route?

The follicular penetration route was considered a secondary route of penetration until it was shown that skin penetration of different drugs was significantly lower in hairless mice relative to hairy mice [3]. A further proof of the central role of HF for transdermal delivery is that the skin permeation of drugs depends on the site of application and is correlated with the HF density [4]. Highly relevant data were provided also by a study with healthy volunteers using blockage of HF openings [5]. The rationale for drug delivery via the HF is the large contact area and the large storage volume of the HF. When we consider the infundibular surface area as a surface available for drug permeation, the overall skin surface of hairy skin is much more extended than that of skin with low HF density [6]. Moreover, considering the volume of the infundibulum, the HF canal can be considered as a significant reservoir for penetrated substances [7,8]. The HF openings represent in average only 0.1% of skin surface, but they reach at least 13% in the forehead. Nevertheless, vellus, intermediate and terminal HF vary significantly in dimension, distribution and density. Moreover, there are gender- and age-related variations of HF type, distribution and density. All these

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variables require careful consideration as they may result in dosage variability and different uptake rates.

On the structural level, several factors contribute to the special role of HF in drug penetration. The network of capillaries around HF is well developed, especially in the anagen phase. The HF extends deep into the dermis or even in the subcutaneous fat, in case of terminal HF, which provides fast access to such deeper compartments. Last but not least, the stratum corneum appears to be less developed in the lower part of the infundibulum. Thus, once accumulated in the HF canal, substances can continuously diffuse to the surrounding epithelia, effectively reach follicular and perifollicular cells, cross the capillary walls and reach the blood system. Alternatively, drugs can be drained to the lymph nodes, from where they can reach the systemic compartment.

How to improve transfollicular drug delivery?

An elegant method to improve the transfollicular drug delivery is the targeting of drugs to the HF by means of micro- and nano-particles [9]. These carriers can transport different types of drugs, including macromolecules, high lipophilic or hydrophilic drugs, favoring their penetration in the HF infundibulum. Whereas solutes are normally washed out, particulate materials can accumulate in the infundibulum and be retained there for days [10]. Depending on particle characteristics like size, surface functionalization and flexibility/deformability, different penetration depths and drug depot effects can be achieved. Thus, micro and nanoparticles loaded with drugs can be used to achieve a sustained and preferential drug delivery via the transfollicular route [11]. Triggered controlled release taking advantage of special conditions in the HF canal, for example, lipophilic environment or pH gradient, is also an attractive possibility of transfollicular drug delivery.

“An elegant method to improve the transfollicular drug delivery is the targeting of drugs to the hair follicles by means of micro- and nano-particles.”

Even if the transfollicular route is not mentioned, in almost all studies where nanoparticles were used for transdermal drug delivery, accumulation in the HF was reported and, therefore, it is likely that the transfollicular route played a central role. The number of applications for nanoparticles in transdermal drug delivery is consistently increasing. Especially for the transdermal delivery of hydrophilic

macromolecules, like proteins and nucleic acids, the use of nanocarriers allows the preferential delivery to the HF canal and in addition protects the drugs from enzymatic degradation. Nonetheless, HF of healthy skin are normally filled with exfoliating stratum corneum, sebum as well as with bacteria or even mites, which can impede penetration. Hence, specific means of opening HF gain importance when targeted therapeutic approaches aim at exploiting the entire infundibular volume and delivering compounds to a maximum of HF in a defined skin area. Among chemical methods, hexane, ethanol or detergents have been successfully applied to open the HF orifices [12]. Also, physical means which do not require special equipment represent interesting approaches. For example, cyanoacrylate skin surface stripping has been used to remove the material occluding the HF orifices and to improve the penetration of micro and nanoparticles in the HF canal [13]. The combination of such technologies with carrier-based delivery systems are promising strategies to target large amounts of drugs to the HF canal and improve drug transdermal delivery [14]. In the last decades, there have been several concerns regarding nanoparticle toxicity after translocation across body barriers. Translocation of nanoparticles to the viable skin layers was never observed when skin barrier was intact, whereas small amounts of nanoparticles could be observed in the epidermis when skin barrier was partially disrupted. Thus, when using technology altering the skin barrier function, biodegradable or at least biocompatible nanocarriers should be utilized.

Clinical applications for the transfollicular administration route

The specific potential of the transfollicular administration route is of interest for several different therapeutic challenges:

- Dermal and transdermal delivery through intact or only mild diseased skin. Under such conditions, HF, which represent natural interruptions of the skin barrier, can be effectively used to improve drug penetration and to set drug depots;
- Effective and selective treatment of hair diseases and HF-associated disorders such as acne vulgaris. In fact, there is substantial medical need in this field especially because deep HF compartments are hard to reach by conventional dermatotherapeutics. In addition, severe cases which require systemic medication would profit from more effective topical treatments. Particulate formulations of actives to treat acne have been successfully used to improve

drug specific accumulation in the HF infundibulum and create persistent levels of drug in the sebaceous gland [15]. Also, particle-based formulations of minoxidil have been tested for the treatment of androgenetica alopecia [12];

- Cell-targeted delivery approaches such as transcutaneous immunization, where the combination of penetration enhancement and smart delivery technologies may help maximize immune cell targeting [16]. Also, the targeting of stem cells has gained increasing interest. Gene delivery could be helpful for the treatment of hair growth disorders, wound healing and inflammatory skin diseases [17].

Future perspective

Although the role of HF in drug skin permeation is widely recognized, the potential of the transfollicular delivery route has not been fully explored yet. For example, the development of patches that deliver particulate carrier systems, for the exploitation of

the follicular reservoir, hold great potential. Also, in order to improve dermal and transdermal delivery of high molecular weight drugs, HF targeting strategies can be combined to methods such as electroporation, iontophoresis or sonophoresis.

Nevertheless, the optimal transfollicular drug delivery system that will meet both the demands of the patient and the physician is one that will be safe, user-friendly and will exploit the transfollicular pathway without requiring sophisticated expensive equipment or trained personnel.

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