Dermal drug delivery: Revisited

Sateesh Khandavilli, Ramesh Panchagnula*

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, Mohali, Punjab 160062, India.

ABSTRACT: The unique histological and molecular organization of skin poses a formidable barrier to drug delivery into and across skin. Due to the severe restrictions on molecular transport, only potent and lipophilic drug candidates have been able to successfully enter the market. New drug discovery programs based on high-throughput screening and combinatorial chemistry have lead to synthesis of potent but highly lipophilic molecules, and yet these molecules are difficult to deliver by conventional routes of administration. (trans)dermal delivery offers an attractive route of administration for these lipophilic molecules. Further, the diverse opportunities offered by genomics and proteomics cannot be effectively utilized without an equally diverse delivery approach. Skin offers a convenient and effective route for those genes and proteins due to the presence of the stem cell compartment in the epidermis.

Keywords: Dermal, Localized delivery, Penetration, Body burden

The recent advances in formulation and drug discovery programs have brought an increased number of molecules within the purview of (trans)dermal delivery. This review critically analyzes the challenges and opportunities offered by (trans)dermal drug delivery for the delivery of lipophilic molecules and genes as well as polypeptides. It also addresses the issue of skin localization of drugs with respect to systemic delivery, where systemic escape of a drug is not desirable. Finally, a survey of clinical trials on psoriasis and melanoma therapy by localized administration of drugs is presented as an example of the recent enhanced interest in (trans)dermal delivery.

1. Skin: an efficient barrier

In order to physically protect an organism from the rigors of its environment and to maintain its water homeostasis, nature has molded skin into an excellent barrier with a unique histological and molecular organization (1). It is equally adept in limiting molecular transport both from and into the body. Overcoming this barrier, for the purpose of (trans)dermal drug delivery, has been a challenge for the pharmaceutical scientist (2). Various approaches such as chemical penetration enhancers (3,4), iontophoresis (5,6), electroporation (7,8), and sonophoresis (9) have been tried in order to overcome the skin barrier. Apart from these widely reported approaches, various novel formulation methodologies such as microspheres (10,11), nanoparticles (12,13), hydrogels (14,15), liposomes (16-18), and nanoemulsions (19-21) were also employed to enhance the transdermal or dermal delivery of drugs.

1.1. Dermal delivery vis-à-vis oral delivery

From the drug delivery point of view, skin differs from the gastro-intestinal tract (GIT) both structurally and functionally. It imposes a formidable challenge in the form of a very impermeable, lipophilic, and highly tortuous barrier, unlike GIT, which is much more permeable. Research has now established that the main barrier to cutaneous penetration lies in the outermost layer of skin, the stratum corneum (SC). The SC, consists of flat, hexagonal corneocytes which are tightly packed by intercellular cement consisting of primarily ceramides, and is approximately 0.3 μm thick (22). Immediately below the SC lies the viable dermis, followed by the dermis. The confluence of the lipidic epidermis and predominantly aqueous dermis makes the drug delivery of molecules at both extremes in terms of their lipophilicity index difficult. While the lipidic SC determines the rate of permeation of hydrophilic solutes, the dermis limits the transdermal transport of lipophilic molecules. Furthermore, immunogenicity of the organ, by virtue of its status as the first line of immunological defense, will limit the deliverability of proteins and peptides. On the other hand, skin also provides drug delivery scientists with distinctive opportunities. It is the only organ, apart from oral route, which has been found to provide zero-order delivery for up to a week (2). In addition, the skin has been widely explored
for the delivery of potent molecules with high hepatic extraction due to its relatively subtle enzymatic activity. Moreover, formulation of delivery systems should be easier given the vast repertoire of excipients approved for topical or transdermal use. Quite uniquely, the existence of the stem cell compartment in the epidermis (23,24) has provided an exclusive opportunity for delivery of genes and anti-sense nucleotides. Further, lipophilic molecules that are otherwise potent but are orally non-deliverable due to poor aqueous solubility (anti-fungals, anti-psoriatics, anti-neoplastics, etc.) can be delivered to their site of action inside skin layers and thereby considerably reduce the systemic drug burden. Moreover, up to 95% of pathogens cross epithelial barriers, so attempts to manipulate specific immune responses at inductive sites (25) such as skin could lead to development of new vaccines against established and emerging diseases.

1.2. Dermal delivery is as difficult as transdermal delivery

Primary objective of transdermal delivery is to deliver a drug into systemic circulation while minimizing the local drug concentration in the skin. However, the objective of dermal delivery is to maximize the drug concentration in the desired skin layer with a minimal net drug transport across the skin into the blood, or in other words, to minimize 'systemic escape' of the drug. More often than not, in many pathological situations involving skin the target skin layer is not known and, furthermore, the target within the skin layer is seldom known (26). Therefore, contrary to general belief, the development of dermal products is more complex than that for transdermal products. Apart from the uncertainty in target location, the required local concentrations in the biophase at the tissue level is seldom known, mainly because required local drug concentrations can vary with the state of a disease. In the case of transdermal delivery, drug pharmacokinetics is modeled based on systemic drug concentrations by compartment or non-compartment-based modeling. In localized delivery, though, systemic drug pharmacokinetics are limited only to assessment of drug leakage from the target site. However, some recent attempts were made to model regional pharmacokinetics of drug absorption into various skin layers using multi-compartment models (27-29). Unlike the enhanced permeation and retention effect observed in tumors as facilitates local targeting, such phenomena do not prevail in the case of non-malignant diseases such as psoriasis. Bucks et al. have proposed that specific interaction with skin components may be required for long-term skin reservoir formation (30). Hence, the delivery technologies must mature far beyond their current level in order to enhance the local targeting of drugs to skin layers with greater reproducibility and reliability. Delivery is further complicated by the lack of knowledge on how a drug redistributes amongst different layers of skin and then into blood.

Contrary to accepted beliefs, blood supply to the dermis is not capable of resorbing certain drugs proportionate to their penetration through the epidermis. High lipophilicity, and molecular weight (MW), together with a slow rate of dissolution, or a rapid intake by dermatological tissues such as keratinocytes could be responsible for this preferential distribution of drug into these high-perfusion tissues. Due to this restricted systemic distribution of drugs applied dermally via systemic circulation (27-29,31), new avenues have opened up in the area of localized drug delivery via the skin. Therapeutically, localized dermal delivery can achieve two goals: delivery to superficial skin layers, i.e., the SC and epidermis, and delivery to deeper layers such as the dermis, subcutaneous tissue, and finally into muscles directly beneath the area of application.

1.3. Factors affecting molecular transport across skin

Although the histological and molecular organization of skin is highly complex and heterogeneous, the transport of molecules across this barrier is surprisingly Fickian (32). The passive flux (J) of a drug across the skin is a function of diffusivity (D), its partition coefficient (K), and the concentration gradient (C/h) prevailing across the barrier with a diffusion path length (h) and is governed by equation 1.

\[ J = \frac{DKC}{h} \quad \text{Equation 1} \]

Thus, the permeability of drugs can be enhanced by altering K, D and C of a drug with an appropriate choice of a solvent system, penetration enhancers, or by means of super saturation of a vehicle with the drug. According to lipid-protein-partitioning (LPP) theory (33), the penetration enhancers act by alteration of intercellular lipids or intracellular protein domains or by enhancing partitioning of a drug into the skin. Thus, permeation of drugs within the lipid bilayer can be enhanced by targeting the hydrophilic head groups or lipophilic fatty acyl chains of the lipid bilayer or by enhancing the partitioning of the drug into the aqueous space between the polar heads by the appropriate choice of a vehicle. At the current point in time, bilayer disruption by azone (34,35), terpenes (36-39), and fatty acids (40-42) has been reported to increase the flux of hydrophilic and lipophilic drugs of different MW varying from 200 to 500 Da. However, few studies reported using permeants with MWs above 500 Da and instead used chemical penetration enhancement such as insulin (5,43,44) and FITC-dextran (45,46). As the MW exceeds 500 Da, the penetration characteristics of normal skin decrease significantly (47). According
to free volume theory for molecular transport across a membrane (48), there exists an inverse relationship between the diffusion coefficient (D) and MW, and D of a molecule decreases exponentially with MW (Equation 2)

\[ D = D_0 \cdot \exp(-\beta \cdot MW) \]  

where, \( D_0 \rightarrow \) Diffusivity of molecule at zero molecular volume; \( \beta \rightarrow \) Constant

Similar to other biological lipid membranes, in the SC diffusivity also decreases exponentially with increasing MW (49). Further, the skin permeation of molecules is also dependent on lipophilicity along with MW; based on these physicochemical properties, a model was proposed to predict the skin permeability of molecules (50).

**1.4. Penetration-permeation balance**

Many predictive approaches were tried to describe molecular transport across the skin (27-29,50,51) based on the various physicochemical properties of solutes, such as octanol-water partition coefficient (log P), MW, melting point, and concentration of unbound drug in the skin. Despite the variety of approaches employed, they shared an emphasis on the importance of lipophilicity and MW as the primary determinants of solute transport across skin.

A generally accepted precept is the larger the MW, the lesser drug permeation due to the slower diffusion coefficient. However, based on permeation data obtained from a series of alkanols, Behl et al. proposed that lipophilicity may play a larger role than MW (26). In the current authors’ opinion, this trend may be valid for molecules less than 500 Da, upon which the analysis

\[ D = D_0 \cdot \exp(-\beta \cdot MW) \]  

where, \( D_0 \rightarrow \) Diffusivity of molecule at zero molecular volume; \( \beta \rightarrow \) Constant

Although several studies have dealt with the influence of penetration enhancers on transdermal delivery, few have actually focused on dermatological drug localization in skin. In the case of dermal penetration enhancers, a desirable trait would be to promote penetration, and thus drug localization, while decreasing drug permeation. Chemical substances that break the SC barrier may enhance both events simultaneously while those enhancers that act purely by enhancing the partitioning of the drug into the SC subsequent to the alteration of the microenvironment may help in maximizing penetration and form a depot of the drug.

In transdermal delivery literature, the terms "penetration" and "permeation" are often used interchangeably. However, these are two distinct events, essentially separated at the level of the main barrier to molecular transport, the SC. "Penetration" specifically describes the entry of molecules into the SC, and "permeation" describes the mass transfer from the SC across different layers of skin into the systemic circulation. However, since these events overlap during permeation studies, they may not be quantified separately, but dermal and transdermal delivery can be delineated by the penetration/permeation balance, which in turn is a complex function of the MW and the lipophilicity of a drug and is further influenced by the extent of enhancement provided by a formulation strategy (Figure 1). If a drug is hydrophilic (log P < 1) and its MW < 500 Da, it can be made to penetrate into skin using a penetration enhancer, as in the case of zidovudine (52), but its localization in vivo is difficult due to the hydrophilic environment existing after the dermo-epidermal junction. In contrast, a lipophilic molecule with a lower MW, such as naloxone, can easily be made to penetrate as well as permeate, thus enabling transdermal delivery (53,54). However, a permeation retardant or depot former such as propylene glycol is needed for retention in the skin (55). In contrast, a hydrophilic molecule with a high MW, such as insulin, can be made to penetrate with a high degree of penetration enhancement (5,43,44) but is very difficult to localize inside the skin. Similarly, a lipophilic molecule with a high MW, such as paclitaxel (PCL), can be made to penetrate using formulation strategies (3); due to its high lipophilicity, it would not require any permeation retardant for its localization, and therapeutically effective concentrations could be built up in the biophase (56).

Rapid advances in drug discovery with the advent of combinatorial chemistry and receptor-based drug design, enabled by high-throughput screening methodologies and further accelerated by genomics and proteomics, have lead to discovery of millions of molecules that have been pharmacodynamically optimized. However, drug optimization is not complete
Figure 1. Schematic representation of penetration-permeation balance and its correlation with physicochemical properties. Dermal and transdermal delivery can be delineated by the penetration/permeation balance, which in turn is a complex function of lipophilicity and MW. A small hydrophilic molecule like zidovudine can be made to penetrate the skin easily using penetration enhancers, and from there it quickly permeates to produce systemic levels due to its small MW and the aqueous environment in deeper skin layers. A small lipophilic molecule like naloxone can be made to localize in skin using a skin depot former like propylene glycol or systemic therapeutic concentrations can be effected using oleic acid as a penetration enhancer. However, delivery of a hydrophilic macromolecule such as insulin would be difficult since it has trouble penetrating the lipophilic SC despite enhancement by iontophoresis and/or penetration enhancers. Further, a lipophilic drug with a high molecular weight such as paclitaxel can penetrate into deeper skin layers and form a depot through use of a proper formulation strategy.

Although genomics have opened up many avenues for therapeutic intervention, the full potential of these therapies cannot be realized until an understanding of the choice of vector and delivery strategies has matured (59). There is currently no practical method, either viral or non-viral, available to allow safe and efficient delivery in most clinical situations. Broad applicability of gene therapy will invariably require diversity in formulation and routes of administration. Although the oral route of delivery has been explored (60,61), significant success has yet to be achieved. Skin, by virtue of its ready accessibility and non-invasiveness, is an obvious target for both systemic and local delivery. Advances in delivery methods are increasing the feasibility of this delivery route (62). Dermal formulations can modulate gene expression within the skin, an application that would be useful for the inhibition of viral genes in skin lesions or inhibition of genes associated with ongoing pathology in the skin. Further, transdermal delivery for systemic administration can provide reliable sustained release, reduced enzymatic and first-pass metabolism, and improved patient compliance. Moreover, skin is the anatomical site where most exogenous antigens are encountered first, so in vivo transfection of epidermal or dermal cells by DNA would be expected to provide an efficient route to gene immunization that mimics a physiological response to an infection (63).

ANs mainly permeate through intra-appendageal route through hair follicles. Approximately 0.5% of the applied dose of a 22-25-base oligomer was observed to be delivered to the hair bulbs and deeper strata (64). Keratinocytes are particularly sensitive to ANs and provide an excellent target for dermal administration. These cells can internalize ANs very rapidly in 30-60 min after exposure (65), and uptake of these molecules proceeds without cell surface accumulation or endosomal sequestration (66). Internalization of ANs is dependent upon molecular size and sequence (67). Furthermore, uptake is also influenced by concentration, exposure time, and temperature (68). Once a drug passes through viable epidermis, it reaches the vascular and lymphatic systems for potential systemic availability. However, this systemic escape is preceded by keratinocyte internalization, and an inverse relation between transdermal permeation of phosphorothioate ANs and internalization by keratinocytes has been observed. This presents the possibility that ANs may be designed to treat skin diseases with little systemic availability, and conversely that ANs may also be designed for systemic treatment with little local interaction in the skin. Vlassov et al. were the first to report the transdermal permeation of ANs (69), in which they described systemic availability of a 32P-labelled oligonucleotide following application of a lotion of AN to mouse ear helices. Further, they reported the iontophoretic delivery of oligonucleotides and noted accumulation of intact AN in mouse tumors (70). Other

2. Dermal delivery of genes and antisense nucleotides (ANs)
physical enhancement strategies like electroporation (71), gold micro projectiles (72), gene guns (73), and microprojection patches (74) have also been explored to deliver genes into the skin.

Gillardon et al. reported a complete blockade of c-fos gene expression in a UV-irradiated rat upon topical application of an AN to c-fos to tape-striped skin and further suggested its applicability to intact skin (75). The ability of an AN to TGF-β1 to control the healing of incisional wounds in mice was tested by applying an AN to the site, and the AN was observed to decrease scarring (76). A chimeric AN (TYR-A) designed to correct a point mutation in the tyrosinase gene was able to restore melanin synthesis by topical and intradermal administrations for at least 3 months after application (77). Topical delivery of a cream consisting of AN to intercellular adhesion molecule-1 (ICAM-1) effectively inhibited 66% mRNA synthesis in the skin of human skin-transplanted immunodeficient mice. Upon topical administration, local concentrations were 3 times as high in the epidermis and 2 times as high in the dermis than with intravenous (i.v.) administration. AN metabolism was also considerably lower upon topical administration (78). However, few studies have been performed to study the in vivo efficacy of chemical enhancement as a means to achieve transdermal delivery. Brand et al. have reported a modified backbone AN transdermal delivery in rats using propylene glycol and linoleic acid as enhancers (79). Zhang et al. reported the application of pressure-mediated electroporation to deliver a LacZ reporter gene in vivo into hairless mouse skin, and gene expression was observed up to a depth of 370 μm (80).

3. Dermal delivery of class II and IV drugs

Dermal delivery is an attractive option for the molecules of classes II and IV of the Biopharmaceutic Classification System (BCS) as they are otherwise very difficult to deliver orally (Figure 1). By virtue of their high lipophilicity, they will readily partition into and permeate through skin, rendering themselves deliverable by this route. Delivery across and into skin would be the more natural route for drugs that are intended to act in the skin, such as anti-psoriasis, anti-fungals, anti-neoplastic, anti-leishmanials, and antibiotics. This would give the delivery strategy an element of passive targeting together with a reduction in non-target organ toxicity (Figure 2).

Methotrexate, which is normally given systemically by i.v. or orally, has been developed for topical application for the treatment of psoriasis. Alvarez-Figueroa et al. reported on the topical delivery of methotrexate by both iontophoresis and passive delivery using microemulsions (21,81). Enhanced transdermal delivery of methotrexate was also reported using penetration enhancers (82). PCL, an effective antineoplastic agent given by i.v., is being explored for use in psoriasis therapy via dermal application (3,56,83). 5-Fluorouracil via dermal application has been used to treat epidermal dysplasia (84) and pre-malignant actinic keratoses (85). Topical therapy using paromomycin ointment was reported to be effective against cutaneous leishmaniasis without any local or systemic side effects (86). Amphotericin B, an antibiotic with several systemic side effects, was delivered effectively to the skin in order to treat cutaneous leishmaniasis. Vardy et al. reported the effectiveness of a lipidic formulation of amphotericin B for cutaneous leishmaniasis in a prospective placebo-controlled clinical study (87). Topical and transdermal delivery of cyclosporin is being explored as a therapy for various inflammatory skin diseases such as psoriasis, atopic dermatitis, and diseases of hair follicles like alopecia areata (88,89). Tacrolimus, a cyclosporine-like inhibitor of T-cell activation, is currently available for the treatment

![Figure 2](image-url)
of atopic dermatitis (90). Steroids and non-steroidal anti-inflammatory drugs (NSAIDs) by far comprise the largest group of topical medications. The dermal delivery of triamcinolone acetonide was found to improve upon administration as transfersomes in comparison to its gel formulations (91). NSAIDS such as diclofenac (92,93), piroxicam (94), ketoprofen (95), and flurbiprofen (96) are actively being studied for use in in vivo dermal delivery.

4. Dermal delivery systems in clinical trials

The past few years have witnessed a dramatic increase in therapies aimed at the treatment of many dermatological disorders, with special emphasis on psoriasis and melanoma. Unlike previous approaches that were mainly symptomatic, recent therapies have essentially focused on the cause of the disease.

4.1. Psoriasis

Psoriasis is a chronic, hyperproliferative, inflammatory disease of the skin that affects 1-3% of the world's population. The annual cost of psoriasis outpatient care in the US is estimated to be between US$1.6 billion and US$3.2 billion (www.angiotech.com accessed on 23.08.2005). A comprehensive survey of various treatments for psoriasis and psoriatic arthritis in the development stage or late development stage (updated until May 2005) can be found at http://www.psoriasis.org/research/pipeline/.

Since the disease's pathogenesis involves a complex series of molecular events, various molecular targets are being targeted to treat psoriasis. The delivery approaches are mainly concentrating on localized dermal delivery in comparison to oral and other systemic routes.

Vitamin D analogs were found to be efficacious in the treatment of psoriasis, but their therapy is limited by the development of hypocalcaemia. Bexacalcidiol, a vitamin D analog without this adverse effect, has recently completed phase IIB clinical trials for the topical treatment of mild to moderate psoriasis (www.quatrX.com). Ligands of nuclear hormone receptors such as glucocorticoids, retinoids, and vitamin D are useful antipsoriatic drugs. Peroxisome proliferator-activated receptors (PPARs), which also belong to the nuclear hormone receptor super family, were also reported to be effective in vitro against psoriasis. However, a pilot in vivo study found their efficacy to be inadequate (97). The marketed PPAR-γ agonist rosiglitazone was found not to be efficacious against psoriasis in phase III clinical trials (http://science.gsk.com/pipeline/index.htm). A novel class of drugs called Retinoic Acid Metabolism Blocking Agents (RAMBA) uses the body's own endogenous retinoic acid to provide a therapeutic effect against ichthyosis, psoriasis, and acne. RAMBAs have been shown to be safer than retinoids. Rambazole, a second generation RAMBA, has completed early Phase II testing in topical clinical studies (http://khandekar.com accessed on 22.08.2005).

Stimulation of epidermal keratinocytes by insulin-like growth factor I (IGF-I) is essential for cell division, and increased sensitivity to IGF-I occurs in psoriasis. A second-generation antisense drug (ATL1101) was designed by Antisense Therapeutics to silence or suppress the gene for the insulin-like growth factor-I receptor (IGF-1r). IGF-1r's pivotal role in the regulation of cell over-growth in psoriasis was previously established (98-100). ATL1101 is being developed by Antisense Therapeutics as a cream for treatment of mild-to-moderate cases of psoriasis. In a novel extension to its established activity as antineoplastic, paclitaxel is being developed as an anti-psoriatic by Angiotech Pharmaceuticals (www.angiotech.com). The topical gel has completed phase I clinical trials for mild to moderate psoriasis. Micellar paclitaxel for treatment of rheumatoid arthritis and severe psoriasis is in phase II clinical trials. Selectins are the cell surface proteins involved in the recruitment of leucocytes during inflammation. A new topical formulation of the small molecule pan-selectin antagonist bimosiamose was recently found to be effective in the treatment of psoriasis during a phase IIa clinical trial (101). Tacrolimus and pimecrolimus, immunosuppressant calcineurin inhibitors, are approved in the US for the treatment of atopic dermatitis and severe psoriasis. (101). Various innovative approaches are being explored for the treatment of melanoma including gene therapy, immunological intervention using vaccines, and molecular targeting-based therapies.

Applicative of the skin's function as a barrier, many clinical trials involving macromolecules such as vaccines oligonucleotides, genes, and large proteins have been performed using either an intradermal or subcutaneous route. Vaccine-based preparations were mainly prepared as emulsions in montanide ISA-51 (mannide oleate), which itself can act as an immuno adjuvant. However, delivery approaches must still mature in order to harness the full therapeutic potential of these novel molecules.

Recently, the National Cancer Institute (NCI) started a phase II clinical trial on vaccine therapy using melanoma peptides for cytotoxic T cells and helper T
cells by a dermal/subcutaneous route. In another phase I/II clinical trial, the multiple synthetic melanoma peptide sargramostim is being evaluated for stage III/IV melanoma involving the eye. The biological response modifier imiquimod is also being tried in a phase I clinical trial as an adjuvant to enhance the response of transdermal vaccines consisting of multi-epitope melanoma peptides. Subcutaneous Interferon-β is in a phase II clinical trial for the treatment of metastatic cutaneous melanoma or ocular melanoma.

5. Conclusion

Despite the toughness and complexity of the skin barrier, (trans)dermal delivery remains an innovative and successful route of drug administration. Recent developments in drug discovery technologies coupled with high-throughput screening have lead to discovery of highly lipophilic and poorly permeating drugs. Further, biopharmaceuticals arising from genomics and proteomics research may not be amenable to oral delivery due to the abundance of enzymes in GIT. Due to the poor peroral bioavailability of such poorly soluble and permeating molecules and given the unique advantages offered by skin with respect to localized delivery, this route has received renewed attention. With the likelihood of an imminent increase in biopharmaceuticals and vaccines, (trans)dermal delivery has come into its own.

References

60. Beck GR, Irwin WJ, Nicklin PL, Akhtar S. Interactions

www.ddtjournal.com


94. Curdy C, Kalia YN, Naik A, Guy RH. Piroxicam


(Received March 8, 2008; Revised March 27, 2008; Accepted April 7, 2008)