Modalities to enhance the transepidermal penetration of therapeutics of topic usage

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Abstract

Transdermal drug delivery is the controlled release of drugs through the skin to obtain therapeutic levels systematically. Although the skin as a route for drug delivery can offer many advantages, the barrier nature of skin makes it difficult for most drugs to penetrate into and permeate through it. The nonviable uppermost layer of the epidermis, the stratum corneum, is an impediment to the delivery of many drugs at therapeutic levels. To overcome the skin barrier safely and reversibly while enabling the penetration of macromolecules is a fundamental problem in the field of transdermal drug delivery. Several technological advances have been made in the recent decades to overcome skin barrier properties. Examples include physical means (such as iontophoresis, sonophoresis, magnetophoresis, microneedles), chemical means using penetration enhancers, and biochemical means (such as liposomal vesicles and enzyme inhibition). This review aims to examine the modalities for promoting the transepidermal drug delivery and also trends in development of penetration enhancement.

Key words: *transdermal drug delivery, chemical penetration enhancers, liposomes, transfersomes, niosomes, ethosomes.*

Skin is an optimal interface for systemic drug administration. Transdermal drug delivery (TDD) is the controlled release of drugs through intact and/or altered skin to obtain therapeutic levels systematically and to affect specified targets. TDD has the advantages of bypassing gastrointestinal incompatibility and hepatic 'first pass' effect, reduction of side effects due to the optimization of the blood concentration-time profile, predictable and extended duration of activity, elimination of multiple dosing schedules and enhancing patient compliance and relatively large area of application compared with the mucosal surfaces. After decades of extensive study, the success of this technology remains limited, with many problems waiting to be solved.

Stratum corneum is 10-15 cell layers thick over much of the body. The intercellular spaces between corneocytes are filled with stacked sheets of lipid bilayer membranes whose organization and unique chemical composition confer a high degree of water impermeability.

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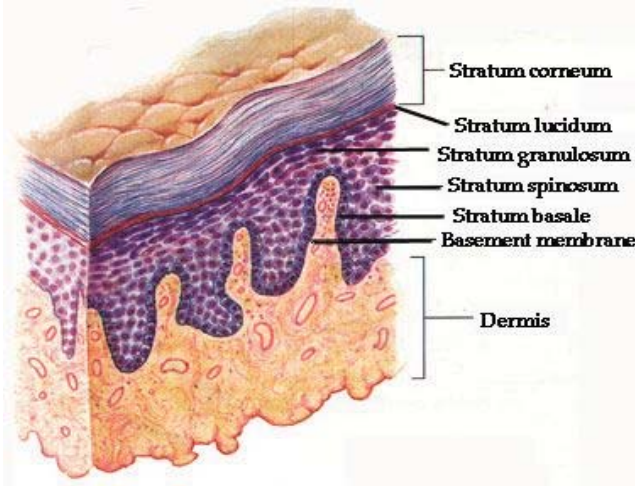

Figure 1. Epidermal structure. The uppermost layer of the epidermis is stratum corneum.

It is these lipid lamellae that constitute the epidermal permeability barrier, both to water (which permits terrestrial life) and to other penetrants.
The transport of medication across the stratum corneum is controlled by three fundamental physicochemical parameters. Primarily, these consist of the partition (*K*), diffusion (*D*), and solubility (*C*(s)) coefficients. In order to enhance the transfer of a medication across the stratum corneum, these variables need to be manipulated and targeted. Often the formulation influences more than one of these parameters.

1. HYDRATION

Hydration allows water to open up the dense structure of the horny layer of the epidermis, thereby altering the barrier functions of the stratum corneum. Although water may be a safe and effective penetration enhancer, rapid evaporation on application to the skin limits its usefulness. Nevertheless, any pharmacologically inert chemical that promotes nondamaging hydration of the horny layer of the stratum corneum may be considered as a penetration enhancer. Based on the hydration principle, transdermal drug bioavailability can be enhanced by hydrophobic ointments, moisturizers, occlusive films, and transdermal patches.

Occlusive films allows moisture to be built up underneath the films, thereby facilitating the transepidermal delivery of drugs across the stratum corneum. The occlusion technique has long been utilized in the delivery of topical steroids to inflammatory skin diseases, such as psoriasis, or connective tissue skin conditions, such as discoid lupus erythematosus. Standard adhesives may be placed at 90° angles to occlude smaller areas. Plastic food wrap or adhesive gas-permeable surgical dressings are useful for the trunk and extremities. Buccal mucosa occlusion may be performed using custom-designed dental appliances. Most recently, companies have provided semiocclusive hydrogel films to custom-fit application

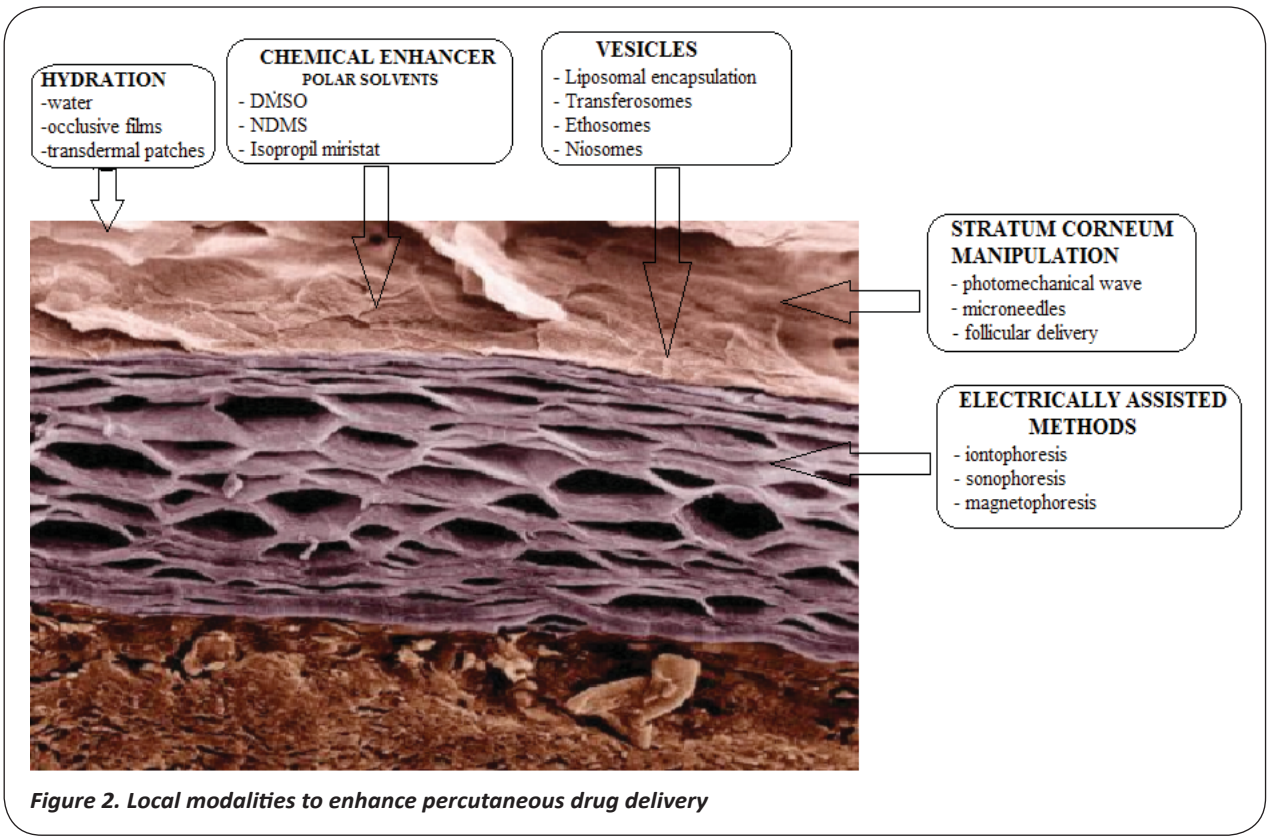

Figure 2. Local modalities to enhance percutaneous drug delivery

to almost any body contour, such as the face.
Transdermal adhesive patches are used as a drug delivery mechanism that transfers drugs through intact skin to produce a therapeutic systemic effect. Transdermal patches comprise a polymeric adhesive layer that contains a solubilized drug and/or dispersed drug. Following the placement of a transdermal patch on the skin, the drug is released from the patch at a controlled rate and the drug diffuses into the skin. Some examples of drugs that are delivered via transdermal patches are nitroglycerin, clonidine, scopolamine, nicotine, fentanyl, and estradiol.

2. CHEMICAL ENHANCERS *(POLAR SOLVENTS)*

Chemical permeation enhancers are able to reduce the diffusional resistance of the stratum corneum and increase the partition coefficient of the drug. Polar solvent vehicles, such as DMSO, ndecylmethyl sulfoxide (NDMS), and isopropyl myristate, may enhance the permeability of compounds across the skin as if there were no stratum corneum. These enhancers increase the drug's diffusion coefficient by disrupting, extracting, or causing acyl chain disorders of the lipid bilayer of the stratum corneum. Disruption leads to the formation of microcavities in the bilayer and, in turn, increases the volume available for drug diffusion. DMSO, ethanol, and micellar solutions may also act by extracting lipids, thereby forming aqueous channels, which make the horny layer more permeable to drugs. The use of DMSO is limited by its potential to induce either a nonimmunologic immediate contact urticaria or an irritant reaction, depending on the concentration and mode of application to the skin. These vehicles have been found to be beneficial in various clinical settings, for example in the delivery of topical alpha-interferon to treat genital herpes lesions. Wider use of polar solvent vehicles has been constrained by local irritation, the potential development of contact sensitization, and a lack of strict control of the rate of transdermal penetration.

3. VESICLES

Liposomal encapsulation is another potential drug carrier for a variety of drugs and therapeutic proteins. Liposomes are lipid vesicles that fully enclose an aqueous volume (Williams, 2003). Liposomes are formed by the encapsulation of a drug in lipid vesicles that are often derived from phospholipids. Major components of liposomes include lipids, water, drugs, electrolytes, antioxidants, preservatives, and viscosity-inducing agents. The drug entrapment ability of liposomes makes them more useful for the targeting of drugs to a specific site within the tissue. Several studies have reported a localizing effect of liposome vesicles to the stratum corneum or other upper layers of the skin. Many methods for preparation of liposomes are described in the literature. Most commonly, the film hydration method is used (Williams, 2003). Lipid composition, method of preparation and thermodynamic state of the bilayers of liposomes, were all shown to greatly affect skin deposition behavior of liposomes. A decrease in cholesterol content in vesicular bilayers, which increases fluidity of the bilayers, resulted also in an increase in drug transport across the stratum corneum. Other physico-chemical properties, such as size, charge and lamellarity may also influence the effectiveness of liposomes as delivery vehicles. Liposomes have also been used to target therapeutic and cosmetic agents to skin appendages, especially to the pilocebaceous units (hair follicles with their associated sebaceous glands). In most cases, classic liposomes are of little or no value as carriers for transdermal drug delivery as they do not deeply penetrate skin, but rather remain confined to upper layers of the stratum corneum. Confocal microscopy studies showed that intact liposomes were not able to penetrate into granular layers of the epidermis.
The major drawbacks of liposomal encapsulation include limited penetration across the stratum corneum, difficulty in strictly controlling the rate of penetration of the active ingredient, and the technical challenge to manufacture the liposomes with adequate physicochemical stability to be efficacious in the clinical setting.
Intensive research led to the introduction and development (Cevc and Blume, 1992), over the past 15 years, of a new class of lipid vesicles, the highly deformable (elastic or ultraflexible) liposomes, that have been named **Transfersomes**. These are ultradeformable hydrophilic lipid vesicles that cross the skin under the influence of a transepidermal water activity gradient. They are able to transport both high- and low-molecular weight molecules into the body noninvasively. These vesicles are up to 105 times more deformable than unmodified liposomes. This characteristic allows transfersomes, up to 200–300 nm in size, to squeeze through pores in the stratum corneum. These pores are less than one-tenth of a liposome's diameter. Nonoccluded conditions are best for transfersome drug delivery, as this type of delivery requires a hydration gradient for maximal penetration. Transfersomes have markedly enhanced the delivery of macromolecules, such as insulin.
They consist of phospholipids and an edge activator. An edge activator is often a single chain surfactant, having a high radius of curvature, that destabilizes lipid bilayers of the vesicles and increases deformability of

the bilayers. Sodium cholate, sodium deoxycholate, Span 60 or 80, Tween 60 or 80 and dipotassium glycyrhizinate were employed as edge activators. Most commonly, the film hydration method is used for their preparation. Reported success of deformable liposomes to deliver macromolecules and proteins such as insulin through intact human skin with efficiency comparable with subcutaneous administration led to their introduction as possible carriers for non-invasive gene delivery and transcutaneous immunization.
Two possible mechanisms by which deformable vesicles could improve skin delivery of drugs were proposed. First, vesicles can act as drug carrier systems, whereby intact vesicles enter the stratum corneum carrying vesicle-bound drug molecules into the skin. Second, vesicles can act as penetration enhancers, whereby vesicle bilayers enter the stratum corneum and subsequently modify the intercellular lipid lamellae. This will facilitate penetration of free drug molecules into and across the stratum corneum. Cevc and Blume, 1992, proposed that the driving force for the vesicles entering the skin is xerophobia (the tendency to avoid dry surroundings). It was suggested that one of the two mechanisms might predominate according to the physico-chemical properties of the drug. The rate and amount of released drug is a balance between two factors: (1) drug affinity to vesicles, and (2) drug solubility in lipids of the stratum corneum.

Ethosome is another novel lipid carrier, recently developed by Touitou, showing enhanced skin delivery. The ethosomal system is composed of a phospholipid, ethanol and water (Touitou et al., 2000). Ethanol is known to be an efficient enhancer of permeability. Experiments using fluorescent probes and ultracentrifugation have shown that ethosomal systems have a high entrapment capacity for molecules of various lipophilicities (for example acyclovir, minoxidil, and testosterone). Ethosomes are most commonly prepared as described by Touitou et al. Briefly, the lipids and the drug are dissolved in ethanol. The aqueous component is added slowly in a fine stream at constant rate in a well-sealed container with constant mixing. Mixing is then continued for additional few minutes. Ethosomes were reported to be effective at delivering molecules to and through the skin to the systemic circulation. Enhanced delivery of chemicals from the ethosomal carrier was observed in permeation experiments with fluorescent probes. Contrary to deformable liposomes, ethosomes were able to improve skin delivery of drugs both under occlusive and non-occlusive conditions (Elsayed et al., 2007).
A hypothetical model was suggested by Touitou, of how ethosomes may enhance penetration of drugs through stratum corneum lipids. Ethanol interacts with lipid molecules in the polar headgroup region of the stratum corneum lipids, increasing their fluidity. The intercalation of ethanol into the polar headgroup environment can result in an increase in the membrane permeability. In addition to the effects of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier.

Niosomes are another alternative to liposomes as a vesicular drug delivery system. Niosome vesicles have similar structure and properties to liposome vesicles. The niosome is formed by the encapsulation of drugs in a vesicle that is derived from nonionic surfactants. Studies have shown that the function of niosomes *in vivo* is similar to that of liposomes. The primary differences between the two types of vesicle include the superior chemical stability and relatively low cost of niosomes when compared with liposomes. Both of these features make the niosome more attractive for industrial manufacturing.

4. PHYSICAL MANIPULATION OF THE STRATUM CORNEUM

Photomechanical waves increase the permeability of the stratum corneum by pulsed laser irradiation, leading to disruption of the stratum corneum and enhancement of drug delivery. Prior to the application of the pulsed laser, the skin is covered with a drug solution and a black polystyrene target.

Microneedles are able to bypass the stratum corneum and enter just below it, into the permeable regions of the skin, where they are able to permit drug delivery. An advantage of this mode of drug delivery is that it does not cause pain. Microneedles are short and thin enough to avoid the stimulation of nerves that are found deeper in the tissue.

Follicular delivery uses the hair follicle as a route for localized and systemic drug delivery. The pilosebaceous unit is a complex structure that contains unique metabolic, biologic, and immunologic characteristics. It is a target for drug delivery because the sebaceous gland cells are more permeable than corneocytes and there is a rich blood supply, which increases absorption of the drug.

5. ELECTRICALLY ASSISTED METHODS

There are several nonvehicle-based modalities that have emerged as efficacious methods for the delivery of drugs across the stratum corneum with good control of the penetration rate and minimal risk of contact

sensitization. Individually, each of these methods has been shown to enhance transdermal drug transport via an electrically assisted modality.

Iontophoresis uses an electromotive force to facilitate percutaneous absorption of a drug. It enhances percutaneous drug delivery by three mechanisms: the electrical current increases skin permeability, electro-osmosis produces bulk motion of the solvent which carries ions or neutral particles, and the ion-electric field interaction provides additional force that drives ions across the skin. Iontophoresis is thought to induce the charged substance to travel across the stratum corneum via disorganization of the lipid bilayer. The electric potential gradient may alter the permeability of the stratum corneum by altering the arrangement of the lipid bilayer. The efficacy of transport is primarily dependent on polarity, electrical duty cycles, formulation components, and the valency and mobility of the charged species. Studies suggest a strong association between cationic drug delivery via electromigration and molecular size.

Sonophoresis or phonophoresis is based on the piezoelectric effect, in which the application of an alternating current causes a crystal to produce ultrasonic pressure waves which, in turn, are transferred through a coupling medium (a pharmacologic agent) to maximize the energy transmission to tissues. Ultrasound is thought to enhance drug delivery via the induction of thermal, chemical, and/or mechanical alterations in the stratum corneum. The enhancement of sonophoresis varies linearly with the ultrasound intensity and exposure time.

Magnetophoresis is a novel approach to enhance transdermal drug delivery by allowing magnetic fields to move diamagnetic materials through the skin. Drug diffusion is influenced by the magnetic field strength, and is increased with increasing applied field strength. This approach to transdermal drug delivery is in an early stage of development.

CONCLUSIONS

The described modalities offer ways to deliver therapeutics of topic usage (that cannot efficiently penetrate the stratum corneum via passive diffusion). Some of these techniques may allow for the strict control of transdermal penetration rates. It may be reasonable to combine more than one of the above modalities to maximize permeability. Indeed, when various enhancers are combined (iontophoresis, chemicals, ultrasound, and electroporation), they have often been found to enhance transdermal transport to a greater extent than when utilized individually. Epicutaneous drug carriers provide a possible solution to such problems. Amongst the many different colloidal systems proposed to improve transdermal drug delivery only the most energetic or deformable really overcome the skin barrier. The reason is not only narrowness of prevailing transepidermal conduits but also the inevitably large number of epicutaneously administered carriers, which exceeds the maximum possible number of pathways across skin. A special kind of ultra-adaptable carriers (transfersome vesicles) can be applied on skin without a device, exploiting the tendency of such carriers to avoid dehydration on skin surface and thus to penetrate spontaneously the stratum corneum.

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