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Transdermal Drug Delivery: A Novel Approach to Skin Permeation

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ABSTRACT

Transdermal therapeutic systems, or transdermal patches, facilitate controlled release of active ingredients through the skin and into the systemic circulation. Drugs administered through such systems escape first pass metabolism and steady state is maintained similar to a continuous intravenous infusion for up to several days.The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route. Few pharmacologically active substances can currently be administered through transdermal patches and production is technically demanding. Research is ongoing to improve the systems and expand the indications. This article gives a brief overview over principles behind transdermal drug delivery, as well as the advantages and disadvantages of transdermal therapeutic systems and the recent innovations in the field of transdermal drug delivery.

Keywords: Transdermal, skin, permeability.

INTRODUCTION

The transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of fixed dose at regular intervals due to which drug concentration in the body follow a peak and trough profile leading to a greater chance of adverse effects or therapeutic failure, large amount of drug is lost in vicinity of target organ and close attention is required to monitor therapy to avoid overdosing. The negatives of oral route can be overcome, and benefits of intravenous drug infusion such as to bypass hepatic "first-pass" elimination (HEPE) to maintain constant prolong and therapeutic effective drug level in the body can be closely duplicated, without its potential hazards, by transdermal drug administration through intact skin.

Although the skin represents a suitable target for drug delivery, as mentioned above, the functional properties that enable it to act as an excellent barrier also serve to limit the access of drugs into and across the epidermis. Whereas an initial consideration of the skin structure might suggest a simple barrier, a closer examination reveals a complex combination of a range of cell types. The outer layer, the stratum corneum, is a membrane ~20 µm thick, which represents the main contributor to the skin's impermeability. Much effort has been devoted to understanding the reasons for this impermeability as it is widely recognized that therein resides the answer to developing more efficient TDD products[1-5].

ADVANTAGES OF TDDS

It offers therapeutic benefits such as

- Sustained delivery of drugs to provide a steady plasma profile, particularly for drugs with short half-lives, control input kinetics and hence reduced systemic side effects
- Reducing the typical dosing schedule to once daily or even once weekly
- Potential for improved patient compliance
- Avoidance of the first-pass metabolism effect for drugs with poor oral bioavailability
- Convenient, patient-friendly option for drug delivery with the potential for flexibility, easily allowing dose changes according to patient needs and the capacity for self-regulation of dosing by the patient
- TDD can be used in situations requiring minimal patient cooperation, that is, in situations involving administration of drugs by someone other than the patient
- The non-invasive character of TDD makes it accessible to a wide range of patient populations and a highly acceptable option for drug dosing

LIMITATIONS FOR DRUG CANDIDATES

- Higher molecular weight candidates (>500Da) fail to penetrate the stratum corneum.
- Drugs with very low or high partition coefficient fail to reach systemic circulation.
- High melting drugs, due to their low solubility both in water and fat.
- Barrier function of the stratum corneum [1-8].

THE SKIN AS DELIVERY TARGET

The objective of transdermal drug delivery system is to achieve systemic medication through topical application on intact skin application. For this, three important factors, which are involved in pharmacokinetics of topical application of the drug, are essential to consider. These three factors are:

- The skin, as a target for efficacy and tolerance.

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- The drug, in its optimum formulation for specific disease.
- The rest of the body, which in general has to be considered from the point of view of safety.

Functions of the Skin

- The mechanical function - to contain body fluids and tissues.
- The protective or barrier function - to protect from potentially harmful external stimuli (a) microorganisms; (b) chemicals; (c) radiations; (d) heat; (e) electrical barrier; or (f) mechanical shock.
- To receive external stimuli, i.e., to mediate sensation (a) tactile (pressure); (b) pain; or (c) heat.
- To regulate body temperature.
- To synthesize and to metabolize compounds.
- To dispose of chemical wastes (glandular secretions).
- To provide identification by skin variations.
- To regulate blood pressure.

Human skin comprises a series of layers penetrated by hair shafts and gland ducts (Fig. 1). The major skin layers, from inside to outside, comprise the fatty subcutaneous layer (hypodermis), the dermis of connective tissue and the stratified avascular, cellular epidermis.

The dermis, at 3–5mm thick, is composed of fibrous proteins (collagen and elastin) and an interfibrillar gel of glycosaminoglycans, salts and water. Blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands are embedded within the dermis. The hair follicles and sweat ducts open directly into the environment at the skin surface and provide the so-called appendageal route of skin permeation. The epidermis contains no blood vessels so nutrients and waste products must diffuse across the dermal–epidermal junction to maintain its vitality. The epidermis consists of five layers, which from inside to outside are the stratum germinativum (basal layer), stratum spinosum (spinous layer), stratum granulosum (granular layer), stratum lucidum and stratum corneum (SC). Because the SC cells are dead, the epidermis without the SC is usually termed the viable epidermis. The SC is considered as the rate limiting barrier in transdermal

permeation of most molecules. The SC comprises 15–20 layers of corneocytes and when dry it has a thickness of 10–15µm. Upon hydration, the SC swells and its thickness can reach 40µm. The structure of the SC is often depicted in the so-called bricks and mortar arrangement, where the keratin-rich corneocytes (bricks) are embedded in the intercellular lipid-rich matrix (mortar).

ROUTES OF PENETRATION

For any molecules applied to the skin, two main routes of skin permeation have been defined; the transappendageal and transepidermal pathways (fig. 2). The transappendageal routes are also known as the shunt routes and include permeation through the sweat glands and across the hair follicles with their associated sebaceous glands. Recent studies have re-examined the long held assumption that the follicles occupy approximately 0.1% of the surface area of human skin. Otberg et al. showed that follicular number, opening diameter and follicular volume are important considerations in drug delivery through these appendages and indeed the forehead provides 13.7mm^2/cm^2 as the follicular infundibula, i.e. approximately 13.7% of the surface area of the forehead is available as follicles. Interestingly, the same study also showed that the historically held view of the follicles providing approximately 0.1% of the surface area of the stratum corneum appears to be valid for forearm skin.

The transepidermal pathway can be defined as the pathway where compounds permeate across the intact, unbroken stratum corneum. This pathway contains two micropathways. First, the intercellular route, which is a continuous but tortuous way through the intercellular lipid domains and secondly, the transcellular pathway through the keratinocytes, then across the intercellular lipids. The transcellular pathway requires not only partitioning into and diffusion through the keratin bricks but also into and across the intercellular lipids. Thus, the intercellular lipids play a major role in the barrier nature of the SC [9-11].

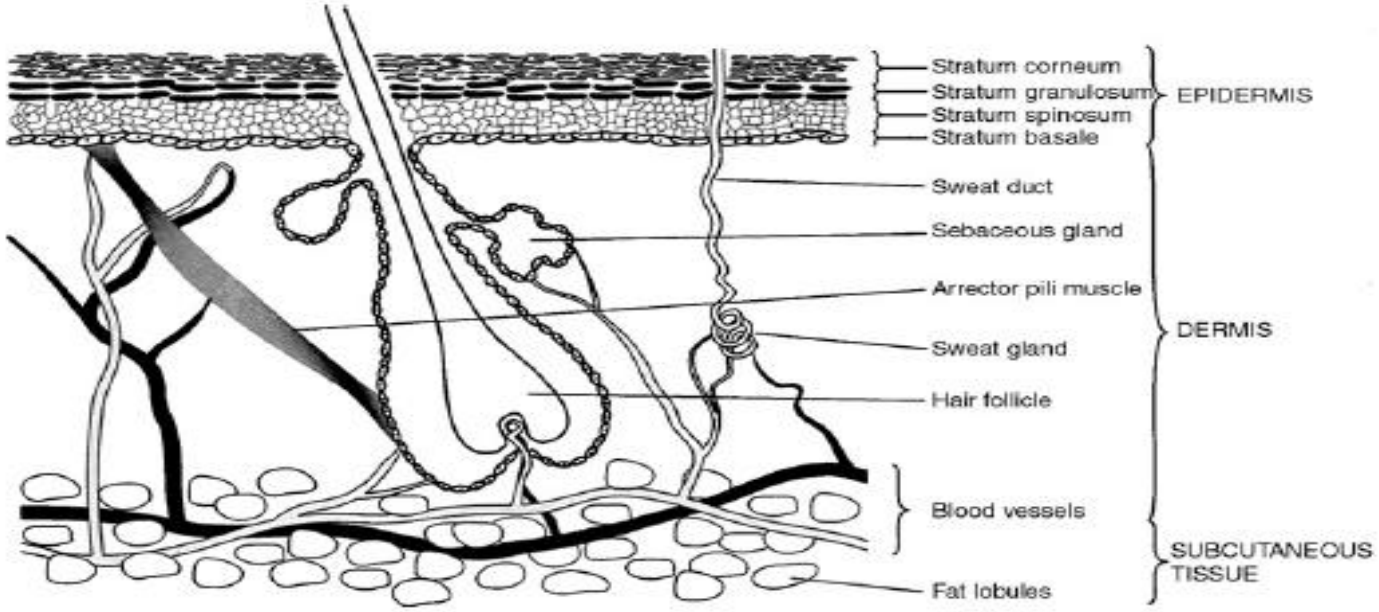

Fig1. Cross-section view of human skin showing different cell layers and appandages (taken from El Maghraby GM, 2008).

Different Modes of Solute Diffusion

Four different modes of solute diffusion across the SC are considered. The first mode include diffusion through lipid bilayers by hopping between free volume pockets. This mode is particularly important for transport of low molecular weight hydrophobic solutes (M_W < 400 Da). The second mode includes solute motion due to lateral diffusion of lipid molecules. This mode will be shown to be important for high molecular weight solutes (M_W < 400 Da) that partition preferentially in lipid bilayers but possess low diffusion coefficients due to their large size. The third mode includes solute diffusion through pores and the fourth mode includes solute diffusion through shunt pathways. The last two pathways will be shown to be important for hydrophilic solutes. The relative contribution of each pathway varies from drug to drug. Solute permeation through four possible routes in the stratum corneum, including free-volume permeability through lipid bilayers (K_p^{fv}) lateral permeability along lipid bilayers ($K_p^{lateral}$), permeability through pores (K_p^{pore}) and permeability through shunts (K_p^{shunt}). Mathematically, skin permeability of hydrophobic or hydrophilic solutes is described by following equation.

$$K_p = K_p^{fv} + K_p^{lateral} + K_p^{pore} + K_p^{shunt} \quad \text{Eq 1}$$

Where K_p^{fv} shows permeability associated with free-volume type of diffusion through lipid bilayers, $K_p^{lateral}$ corresponds to permeability of hydrophobic solutes due to lateral diffusion of lipids, K_p^{pore} corresponds to solute permeability through pores, and K_p^{shunt} corresponds to solute permeability through shunts (hair follicles and sweat ducts). Hydrophilic solutes permeate the skin through imperfections in the lipid bilayers, modelled as pores [12-13].

Representation of drug transport process from the formulation and absorption into systemic circulation [14]

Formulation
Drug release from
The formulation into SC
Controlled by thermodynamic activity

Stratum Corneum
(main barrier)
Drug diffusion across
SC via intercellular lipid pathway
Determined by diffusivity

Viable epidermis
(Aqueous milieu)
Drug partitioning from lipidic
SC into aqueous epidermis followed
By diffusion

Dermis
Entry into systemic
Circulation

Capillary network

PHYSICOCHEMICAL BASIS OF TRANSDERMAL DRUG DELIVERY

Drug Lipophilicity

Essentially, the SC barrier is lipophilic, with the intercellular lipid lamellae forming a conduit through which drugs must diffuse in order to reach the underlying vascular infrastructure and to ultimately access the systemic circulation. For this reason, lipophilic molecules are better accepted by the SC. A molecule must first be liberated from the formulation and partition into the uppermost SC layer, before diffusing through the entire thickness, and must then repartition into the more aqueous viable epidermis beneath. Ideally, a drug must possess both lipoidal and aqueous solubilities: in case of low log*P*, or to hydrophilic, the molecule will be unable to transfer into the SC because permeability is low since partitioning into skin lipids is low. However partitioning into stratum corneum can be improved by increasing the thermodynamic activity of the drug in transdermal formulation (push), by the use of permeation enhancer (pull) or physical enhancement strategies such as iontophoresis, sonophoresis, electroporation, microfabricated microneedles. Despite good partitioning into the stratum corneum lipids, the permeability of highly lipophilic molecule is low. This is probably due to accumulation of lipophilic drugs in the stratum corneum.

Diffusivity

The chemical structure of the drug also influences the diffusivity due to interactions between the polar head groups of the intercellular lipids with hydrogen-bond forming functional groups present in the drug structure.

Occlusion

To improve the efficiency of TDD systems, traditional TDD products relied mainly on their occlusive nature to increase the permeability of the drug candidates. Although the mechanism by which occlusion increases the diffusivity of many drugs is not known, some of the effects of occlusion that might be important include: water accumulation within the skin leading to increased water content and swelling of the corneocytes and increased water content of the intercellular matrix; increase in skin temperature and decreased evaporative loss of cosolvents. However, occlusion often causes an increased propensity for skin irritation at the application site that could be due to the affects of the accumulated water or to trapped sweat. This represents a major hurdle to the patient acceptance of occlusive TDD systems and recent efforts have focused on the development of newer generation products with less potential for this reaction. Occlusive systems can also provide an environment for microbial proliferation [1].

ANATOMY OF TRANSDERMAL PATCH

1. **Peel of Layer/Release Liner**
   During storage patch is covered by a protective liner that is removed and discarded before application of patch to the skin. It carries very a thin release coating and provides low energy surface for ease of removal.
2. **Backing**
   Backing laminate is used to provide flexibility, appearance and need for occlusion. It must be compatible with formulation and printable. Examples of backing are polyester film, polyethylene film, aluminium and polyolefin film.
3. **Rate Controlling Membrane**
   It governs the drug release from the patch to control the availability of the drug or limits the passage of drug. Examples of rate controlling membrane are Ethylene vinyl acetate (EVA) copolymer, Microporous polypropylene and

polyethylene

4. **Chemical Penetration Enhancers**

Penetration enhancers can act on the stratum corneum intracellular keratin, influence desmosomes, modify intercellular domains, or alter the solvent nature of the stratum corneum, which results in a decrease of the skin barrier resistance.

Penetration enhancers are chemical compounds which are themselves pharmacologically inactive, but can partition into and interact with the SC constituents when incorporated into a transdermal formulation, thereby reducing the resistance of the skin to drug diffusion.

Ideal Properties of penetration enhancers

- They should be non-toxic, non-irritating and nonallergenic.
- They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body—i.e. should not bind to receptor sites.
- The penetration enhancers should work unidirectionally, i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- When removed from the skin, barrier properties should return both rapidly and fully.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin 'feel'.

Chemical Classification of Enhancer

Because there are so many chemical classes of enhancers available, the following section will review some recent data for a selected group of enhancers. In general, the data suggest that enhancers may be placed into several groups depending on their activity.

- Those compounds that enhance drug concentrations across the skin (transdermally) and into the skin (locally)
- Those that enhance the permeation of drugs transdermally
- Those that increase local skin-drug concentrations, but which do not produce significant transdermal enhancements
- Those that act as retardants, producing low local-drug concentrations and low transdermal fluxes (often significantly lower than controls)

5. **Pressure Sensitive Adhesives (PSAs)**

PSAs are the material that adhere to a substrate by application of light force and leave no residue when removed, they form interatomic and intermolecular attractive forces established at the interface, provided that intimate contact is formed. The properties of the PSA layer in a TDDS depend on the incorporated drug, the components of the TDDS (eg. backing film), the excipients (eg, penetration enhancers, solubilizers), and the chemical composition of the PSA. Widely used PSA polymers in TDDS are polyisobutylene (PIB)-based adhesives, hydrocarbon resins, rosin esters, acrylics and silicone based PSAs [8, 15-21].

EVALUATION PARAMETERS FOR TRANSDERMAL PATCHES[22-26]

1. **Folding Endurance**

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance

2. **Moisture Content**

The film was weighed and kept in a desiccator containing calcium chloride at 40^0C in a drier for at least 24 h or more until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content.

3. **Moisture Uptake**

A weighed film kept in desiccators at 40^0C for 24 h was taken out and exposed to two different relative humidity of 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) in two different desiccators, respectively, at room temperature. Then the weights were measured periodically to constant weights.

4. **Percentage Moisture Absorption**

The films were weighed accurately and placed in the desiccator containing 100mL of saturated solution of aluminum chloride, which maintains 79.50% RH. After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula

Percentage moisture absorption

$$= \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

5. **Percentage Moisture Loss**

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula

Percentage moisture loss

$$= \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

6. **Moisture Vapour Transmission (MVT)**

MVT is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass cells were filled with 2 g of anhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 h.

7. **Flatness**

Longitudinal strips were cut out from the prepared medicated patches and the lengths of each strip were measured and then the variation in the lengths due to the non uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flat-

ness.

Constriction (%) = $\frac{(l_1-l_2) \times 100}{l_2}$

Where l_1, initial length of each strip; l_2, final length.

8. **Determination of Drug Content**
   A film of size 2 cm^2 was cut into small pieces and put in a 100ml buffer (pH-7.4). this was shaken on mechanical shaker for 2 hr to get homogeneous solution and filtered. The drug was determined spectroscopically at particular wavelength.
9. **In vitro drug release**
   Drug release testing was performed using a Franz diffusion cell for transdermal delivery systems. Testing was conducted at a rotating speed of 50 rpm. The dissolution medium was purified water maintained at 32^0C. A sample was taken through a 0.8µm filter at predetermined sampling times and replaced with an equal volume of purified water. Drug released was analyzed by a HPLC/UV method.

NEWER TRENDS IN TDDS [3,7,27,36]

Skin Permeation Enhancement/optimization Techniques

Drug/Vehicle Based	Stratum Corneum Modification
Prodrugs & Ion pairs	Hydration
Drug-Vehicle interaction	Lipid Fluidisation
Chemical potential of drug	Bypass/removal
Eutetic System	Electrical methods
Complexes	
Liposomes	
Vessicles & particles	

Prodrug & Ion pairs

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients. The prodrug design strategy generally involves addition of a promoiety to increase partition coefficient and hence solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimising solubility in the aqueous epidermis.

Charged drug molecules do not readily permeate through the human skin. Formation of lipophilic ion pairs has been made to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug which can diffuse within the epidermal and dermal tissues [7,36].

Ideal properties of a molecule penetrating stratum corneum well. These are

Aqueous solubility	> 1mg ml^{-1}
Lipophilicity	$10 < K_{o/w} < 1000$
Molecular weight	< 500 Daltons
Melting Point	< 200ºC
pH of saturated aqueous solution	pH 5-9

Abbreviation: $K_{o/w}$, oil-water partition coefficient [1,3,7,36].

Saturated and Supersaturated Solutions

The maximum skin penetration rate is obtained by increasing the thermodynamic activity of the drug substance in the formulation. According to Higuchi, the flux of a drug is directly proportional to its thermodynamic activity in the formulation. In conventional systems this theorems is exploited by using saturated systems where the undissolved drug (the thermodynamic activity of which is equal to that of pure solute and hence, at its maximum value) is in equilibrium with the molecule in solution. Because supersaturated solution leads to an increased thermodynamic activity of the drug substance in the vehicle compared with subsaturated or saturated solutions, a correspondingly higher flux can be expected [14,19, 28-29].

Eutectic Systems

The melting point of a drug influences solubility and hence skin penetration. According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture: a mixture of two components which, at a certain ratio, inhibit the crystalline process of each other, such that the melting point of the two components in the mixture is less than that of each component alone [7,19,36].

Complexes

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (a-, ß-, ?-cyclodextrin) bound in a 1, 4- configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Derivatives of ß-cyclodextrin with increased water solubility (e.g. hydroxypropyl-ß- cyclodextrin HP-ß-CD) are most commonly used in pharmaceutical formulation [19,30,36].

Liposomes and Vesicles

Liposomes are colloidal particles formed as concentric biomolecular layers that are capable of encapsulating drugs. Five potential mechanisms of action of these liposomes were assessed

- A free drug process-drug releases from vesicle and independently permeates skin
- Enhancement due to release of lipids from vesicles and interactions with skin lipids
- Improved drug uptake by skin
- That different entrapment efficiencies of the liposomes controlled drug input
- Penetration of stratum corneum by intact liposomes

Transfersomes are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant (such as sodium cholate) and 3-10% ethanol. The surfactant molecules act as “edge activators”, conferring ultradeformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome. According to their inventors, where liposomes are too large to pass through pores of less than 50 nm in size, transfersomes up to 500 nm can squeeze through to penetrate the stratum corneum barrier spontaneously. Conventional liposomes remain near the skin surface, dehy-

drate and fuse, whilst deformable transfersomes penetrate via the pores in the stratum corneum and follow the hydration gradient. Extraordinary claims are made for the penetration enhancement ability of transfersomes, such as skin transport of 50-80% of the applied dose of transferosome-associated insulin. Ethosomes are liposomes with a high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation. It is proposed that the alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate. Niosomes are vesicles composed of non-ionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. This area continues to develop with further evaluation of current formulations and reports of other vesicle forming materials [3,7,10,19,31-34,36].

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) have been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. It is thought their enhanced skin penetration is primarily due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN. A 31% increase in skin hydration has been reported following 4 weeks application of SLN-enriched cream [19].

PENETRATION ENHANCEMENT BY STRATUM CORNEUM MODIFICATION

The activity of penetration enhancers may be expressed in terms of an enhancement ratio (ER):

ER = Drug permeability coefficient after enhancer treatment

Drug permeability coefficient before enhancer treatment

Barry and co workers devised the lipid-protein partitioning (LPP) theory to describe the mechanisms by which enhancers effect skin permeability:

- Disruption of the intercellular bilayer lipid structure
- Interaction with the intracellular proteins of the stratum corneum
- Improvement of partitioning of a drug, coenhancer, or cosolvent into the stratum corneum

Hydration

Water is the most widely used and safest method to increase skin penetration of both hydrophilic and lipophilic permeants. The water content of the stratum corneum is around 15 to 20% of the dry weight but can vary according to humidity of the external environment. Additional water within the stratum corneum could alter permeant solubility and thereby modify partitioning from the vehicle into the membrane. In addition, increased skin hydration may swell and open the structure of the stratum corneum leading to an increase in penetration, although this has yet to be demonstrated experimentally. For example, Scheuplein and Blank showed that the diffusion coefficients of alcohols in hydrated skin were ten times that observed in dry skin. Hydration can be increased by occlusion with plastic films; paraffins, oils, waxes as components of ointments and water-in-oil emulsions that prevent transepidermal water loss; and oil-in-water emulsions that donate water. Of these, occlusive films of plastic or oily vehicle have the most profound effect on hydration and penetration rate [7,19,35,36].

Lipid Disruption/Fluidisation by Chemical Penetration Enhancers

Many enhancers, such as Azone, DMSO, alcohols, fatty acids and terpenes, have been shown to increase permeability by disordering or 'fluidising' the lipid structure of the stratum corneum. The diffusion coefficient of a drug is increased as the enhancer molecules form microcavities within the lipid bilayers hence increasing the free volume fraction. In some cases the enhancers penetrate into and mix homogeneously with the lipids. However, others such as oleic acid and terpenes, particularly at high concentration, pool within the lipid domains to create permeable 'pores' that provide less resistance for polar molecules [1,2,4,7,8,11,15,19,20,36]

Iontophoresis

The most evolved of these technologies, iontophoresis, uses a small electrical current (usually <500 microamperes cm^{-2}) to facilitate the transfer of drugs across the skin. Charged species are repelled into and through the skin as a result of an electrical potential across the membrane; the efficiency of this process is dependent on the polarity, valency and ionic mobility of the permeant as well as on the composition of the delivery formulation and the current profile. Typically, two electrolyte chambers containing electrodes (one of which contains the ionized therapeutic molecule of similar polarity, i.e. cationic drug in anodal chamber) are placed on the skin surface and driven by a constant current source. The magnitude of current determines the amount of charge generated in the circuit and, in turn, the number of ions transported across the skin; this ensures a controlled and efficient method of drug delivery because the amount of compound delivered is directly proportional to the quantity of charge passed [1,3,4,7,10,11,36-38]

Electroporation

Electroporation, uses high-voltage short duration pulses is thought to create localized regions of membrane permeabilization by producing aqueous pathways in lipid membrane bilayers. This routine tool for destabilizing and hence permeabilizing nuclear membranes to effect DNA transfer has been the subject of increasing focus as a means to enhance transdermal transport. Electroporation of the SC *in vitro* is typically performed using square wave or exponential voltage pulses that generate a transmembrane potential of up to 1 kV and that last for periods of 10 ms–500 ms. Although this mode of electrical transdermal enhancement has been shown to be more effective (at least, quantitatively) relative to iontophoresis for several molecules *in vitro*, and to produce significantly elevated levels of transport compared with passive delivery, the limited data from *in vivo* and skin toxicological studies means that its clinical value remains to be established [1,3,4,7,10,11,19,27,36.]

Ultrasound

It is defined as sound of frequency greater than 20 kHz, to compromise the skin's barrier function has also received considerable attention. Frequencies ranging from 20 kHz to 10 MHz with intensities of up to 3W cm^{-2} have been used in an effort to increase transdermal drug delivery. It is suggested that low frequency ultrasound (~20 kHz) induces a greater perturbation of the skin barrier than conventional, therapeutic ultrasound (~1 MHz) resulting in up to a 1000-fold difference in the level of enhancement. Sonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue [1,3,4,7,11,19,27,36,39].

Conclusion

Percutaneous absorption is inevitable because of the permeability of the skin, albeit limited to a number of compounds with specific characteristics and simultaneous penetration of drug by transcellular and intercellular pathways, as well as movement of drug between these two pathways. The deeper knowledge of the skin structure and physiology will create applications to add and improve the protection capacity of the skin against challenges. It will also help the development of formulations or devices for transdermal drug delivery as an advantageous method compared with the more common oral and parenteral deliveries. The future will show which of these methods will succeed in achieving the goal without provoking new problems for the skin and related tissues.

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