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# Skin Penetration Enhancement Techniques

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**ABSTRACT**

Transdermal drug delivery systems allow delivery of a drug into the systemic circulation via permeation through skin layers at a controlled rate. In addition to the currently marketed formulations, new drugs are being formulated using the transdermal system because of the inherent advantage of administration by this route. It offers a noninvasive route of drug administration, although its applications are limited by low skin permeability. Innovative research exploiting penetration-enhancing strategies, such as iontophoresis, electroporation, microneedles, and sonophoresis, holds promise for the successful use of these drugs as consumer-friendly, transdermal dosage forms in clinical practice. This review outlines promising new technologies involved in enhancing transdermal permeation.

**Key words:** Electroporation, iontophoresis, microneedles, penetration, sonophoresis, transdermal

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## INTRODUCTION

The use of the transdermal route has been well established since the1800s. The rapid increase in its market value has led to transdermal drug delivery becoming one of the fastest growing sectors within the pharmaceutical industry. There is considerable interest in the skin as a site of drug application both for local and systemic effects. The skin poses an extremely good barrier to drug penetration and it is usually necessary to employ enhancement strategies.[1] Furthermore, topical application bypasses systemic deactivation of drugs and minimizes gastrointestinal incompatibility and potential toxicological risk.[2]

Various technologies have been developed to bypass or modulate the barrier function of the skin and to allow easier passage of drugs into the dermal microcirculation; these can be categorized into physical and chemical approaches.[3]

## ADVANTAGES OF TRANSDERMAL DRUG DELIVERY

Some of the advantages of TDDS over conventional routes are as follows:

- Avoids the risk and inconvenience of intravenous therapy
- Usually provides less chance of an overdose or underdose
- Permit both local and systemic effects[4]
- Reduces dosing frequency
- Avoids hepatic first pass elimination and gastrointestinal irritation
- Noninvasive drug delivery system
- Improve physiological and pharmacological responses[5]
- Reduction of fluctuations in plasma levels of drugs
- Allow easy termination
- Utilization of drug candidates with short half-life and low therapeutic index
- Reduction of dosing frequency and patient compliance[6]

## PHYSICAL APPROACHES

### Iontophoresis

Iontophoresis is the process of enhancing the permeation of topically applied therapeutic agents through the skin by the application of electric current.[7] The drug is applied under an electrode of the same charge as the drug, and an indifferent counter electrode is positioned elsewhere on the body. The active electrode effectively repels the active substance and forces it into the skin.[8]

Increase in drug penetration by iontophoresis can be due to following mechanisms: i) The first mechanism proposes that the drug is forced across the skin by simple electronic repulsion of similar charges. Anionic drugs can cross the skin by using a negatively charged working electrode. Similarly, cationic drugs can cross the skin when a positively charged electrode is used.[9] ii) The second explanation suggests that the electric current enhances the permeation by inhibiting the skin's ability to perform its protective barrier function.[10] iii) The third states that iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum (SC) by electrosmosis.[11]

Transdermal iontophoresis would be particularly useful in the delivery of hydrophilic drugs produced by biotechnology (peptides and oligonucleotides). Iontophoretic delivery of drugs would be beneficial in the treatment of skin disorders such as skin cancer, psoriasis, dermatitis, hypertrophic scars.[12] It has been widely used to treat conditions of the eye, ear, nose, teeth, and mouth. It has been used for extraction of analytes (such as glucose) from the body.[13]

### Electroporation

Electroporation is another electrical enhancement method which involves the application of short (microsecond or millisecond), high voltage (50-1000 volts) pulses to the skin. The mechanism of penetration is the formation of transient pores due to electric pulses that subsequently allow the passage of macromolecules from the outside of the cell to the intracellular space via a combination of processes such as diffusion and electrophoresis.[14]

Larger macromolecules have also been delivered by electroporation, including insulin,[15] vaccines,[16] oligonucleotides,[17] and microparticles.[18] A few model compounds such as calcein[19] and LHRH[20] drugs have also been studied for increased transdermal absorption by electroporation.

### Microporation

Microporation involves the use of microneedles that are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. Microneedles are needles that are 10 to 200 μm in height and 10 to 50 μm in width.[21]

Microneedles do not stimulate the nerves, so the patient does not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles.[22]

### Heat

Heat enhances the skin permeation of drugs by increasing body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility, thus facilitating drug transfer to the systemic circulation. When heat is applied, the kinetic energy of drug molecules, proteins, lipids, and carbohydrates is known to increase in the cell membrane. Also, drug solubility both in the patch and within the skin may increase with a rise in temperature. The effect of temperature on *in vitro* transdermal fentanyl flux was estimated at temperatures of 32° and 37°C. Drug flux approximately doubled over this 5° range. Further studies indicated that temperature changes of approximately 5°C are necessary to cause measurable changes in cell membrane permeability. Heat may also cause changes in physiochemical properties of patches, sweating, and increased hydration of skin, thus increasing the permeation of drugs.[23]

### Needleless injection

Needleless injection involves a pain-free method of administration of drugs to the skin. This technique involves firing the liquid or solid particles at supersonic speeds through the stratum corneum.[24] The mechanism involves forcing compressed gas such as helium or nitrogen through the nozzle with the resultant drug particles entrained within the jet flow, reportedly traveling at sufficient velocity for skin penetration.[25] Problems with this technique include the high developmental cost for both the device and dosage form and the inability to program or control drug delivery to compensate for intersubject differences in skin permeability.[26]

### Medicated tattoos

Medicated tattoos are a modification of temporary tattoos which contain an active drug medicament for transdermal delivery. They are very attractive and fun to wear and are

applied by wetting with water and pressing against the skin. The tattoo contains a drug layer, a colored design layer, and an adhesive layer that binds to the skin.[13]

There is no predetermined duration of therapy. The manufacturer provides a color chart that can be compared to the color of the patient's tattoo to determine when the tattoo should be removed.[3] It gives a visual indication as the drug is absorbed into the skin. Upon absorption, the tattoo gradually fades away and is painless to remove with a simple astringent wash containing isopropyl alcohol. The drugs used in medicated tattoos prototypes include acetaminophen, vitamin C etc.[6]

**Pressure wave**

Pressure waves generated by intense laser radiation, can permeabilize the stratum corneum as well as the cell membrane. PW is only applied for a very short time (100ns-1μs). It is thought that the pressure waves form a continuous or hydrophilic pathway across the skin due to expansion of lacunae domains in the stratum corneum.

A single pressure wave is sufficient to permeabilize the stratum corneum and allow the transport of macromolecules into the epidermis and dermis. In addition, the drug delivered into the epidermis can enter the vasculature and produce a systemic effect.[27] For example; insulin delivered by pressure waves resulted in reducing the blood glucose level over many hours.[28] The application of pressure waves does not cause any pain or discomfort and the barrier function of the stratum corneum always recovers.[27] The enhancing effect of such a mechanism on caffeine permeation has been reported.[29]

**Sonophoresis**

Sonophoresis is a technique which involves the use of ultrasonic energy to enhance skin penetration of active substances.[30] Transdermal enhancement is particularly significant at low frequency regimes (20 KHz < f <100 KHz) than when induced by high frequency ultrasound.[31] Ultrasound parameters such as treatment duration, intensity, pulse length, and frequency are all known to affect percutaneous absorption with frequency being the most important.[32]

The mechanism of transdermal skin permeation involves the disruption of the stratum corneum lipids by the formation of gaseous cavities, thus allowing the drug to pass through the skin.[33] Sonophoresis of hypotensive agents and papain has been used in the treatment of eye diseases. Several antibiotics including tetracycline, biomycin, and penicillin have been sonophoretically administered for the therapy of skin diseases.[34]

**MagnetoPhoresis**

The term, "magnetophoresis" was used to indicate application of a magnetic field and acts as an external driving force to enhance drug delivery across the skin. It induces alteration in the skin's structure that could contribute to an increase in permeability.[35]

Magnetoliposomes consist of magnetic nanoparticles wrapped by a phospholipid bilayer which can be successfully applied for drug delivery systems, magnetic resonance imaging markers for cancer diagnosis, and thermal cancer therapy.[13]

**Radiofrequency**

Radiofrequency involves exposure of the skin to a high frequency alternating current of 100 KHz that results in the formation of heat-induced microchannels in the cell membrane. The drug delivery rate is controlled by the number and depth of microchannels formed, which depends on the properties of the microelectrodes in contact with the skin during treatment.[36]

Experiments in rats have shown the device to enhance the delivery of granisetron HCl. Skin delivery of testosterone and human growth hormone are in progress by use of this device.[37]

## CHEMICAL APPROACHES

**Use of permeation enhancers**

Incorporation of penetration enhancers facilitates the absorption of drugs by altering the barrier property of the stratum corneum. A permeation enhancer should be pharmacologically inert, nontoxic, nonirritating, nonallergic, odorless, tasteless, colorless, compatible with most drug and excipients, inexpensive, and have good solvent properties.[38]

Different classes of penetration enhancers including alcohols and polyols (ethanol, propylene glycol), surfactants (Tween, Span, SLS), fatty acids (Oleic acid), amines and amides (Azone, *N*-methylpyrrolidone), terpenes (limonene) sulfoxides (dimethylsulfoxide), esters (isopropylmyristate) were developed over the past two decades.[13,39]

Permeation enhancers can enhance the skin permeability by a variety of mechanisms, including interaction with intercellular lipids leading to disruption of their

organization and increasing their fluidity,[40] extraction of lipids from the stratum corneum, displacement of bound water, loosening of horny cells, delamination of stratum corneum,[41] enhancing solubility and increasing partitioning into the stratum corneum,[42] interaction with intercellular protein, and keratin denaturation.[43]

### Prodrug approach

Prodrugs are therapeutically inactive derivatives of therapeutically active drugs. A prodrug undergoes metabolism to produce the therapeutically active drug. A prodrug is more lipophilic than the parent drug and has different physicochemical properties.[44]

Different prodrugs were developed for estradiol and "Transdermal Bioactive Hormone Delivery" devices were developed based on the results. The release rate of estradiol from Transdermal Bioactive Hormone Delivery is dependent on the chain length of the ester group at the 17$^{th}$ position.[45] Alkyl ester prodrugs of ketorolac having optimum lipophilicity could improve the transdermal delivery of ketorolac.[46] Also, the prodrug approach is a very feasible way to increase the skin permeation of protein/peptide drugs.[47]

## OTHER ENHANCEMENT APPROACHES

### Supersaturation

It is a means to increase skin penetration without alteration of the stratum corneum structure. The mechanism is based on the increased thermodynamic activity of the drug. This increases the concentration gradient (Co- Ci) in Fick's law:

{(J = KD/h (Co- Ci)} and thus forces the active principle out of the stratum corneum.[21]

Several methods can be used to produce supersaturated systems:

- Heating and subsequent cooling
- Removal of a solvent
- Reaction of two or more solutes to produce a compound which is less soluble
- Addition of a substance to a solution that reduces the solubility of the solute[48]

### Water as a penetration enhancer

Hydration of the stratum corneum is one of the primary measures to increase the penetration of both hydrophilic and lipophillic permeants.[41] Free water within the tissue could alter the solubility of a permeant in the stratum corneum and hence, could modify partitioning from the permeant vehicle into the membrane.[49] Increased skin hydration may swell and open up the compact structure of the stratum corneum, leading to an increase in penetration.[2]

## FORMULATION APPROACHES

Penetration enhancement with special formulation approaches is mainly based on the usage of colloidal carriers. Submicron-sized particles are intended to transport entrapped active molecules into the skin. Such carriers include liposomes, transferosomes, ethosomes, niosomes, nanoemulsions, and solid-lipid nanoparticles.[21]

Liposomes have been promoted as another means of enhancing transdermal drug delivery. These are microscopic bilayer vesicles and are usually made of phospholipids and cholesterol. They contain both hydrophilic and lipophilic portions and can serve as carriers for both polar as well as nonpolar drugs.[50] The liposomes become trapped within the top layer of SC cells and interact with skin lipids to release their drug.[41]

Transferosomes are modified liposomes that possess an increased power of penetration through the skin.[51] They consist of phospholipids, cholesterol, and additional surfactant molecules such as sodium cholate.

The surfactant molecules act as "edge activators", conferring ultradeformability on the transferosomes which allows them to squeeze through pores of the stratum corneum that are less than one-tenth of their diameter.[52]

Transferosomes have been used as a carrier for many proteins, immunomodulators, corticosteroids, NSAIDS, anticancer drugs, etc.[53]

Ethosomes are liposomes composed mainly of phospholipids, alcohol in relatively high concentrations, sometimes glycols, and water.[54] They are capable of enhancing penetration to deep tissues and the systemic circulation.[55] It is proposed that alcohol fluidizes the ethosomal lipids and stratum corneum intercellular lipids, thus allowing the soft, flexible ethosome to penetrate the stratum corneum.[56]

They provide enhanced skin permeability for various compounds and have been reported to effectively deliver acyclovir, minoxidil, propranolol, and testosterone transdermally.[57]

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications.[58]

Another formulation approach aiming to enhance skin penetration is the preparation of microemulsions. Microemulsions consist of water, oil, and surfactant which yields a transparent thermodynamically stable liquid. Properties of microemulsions include optical transparency, thermodynamic stability, and solubility of both hydrophobic and hydrophilic components. Penetration enhancement from microemulsions is mainly due to an increase in drug concentration which provides a large concentration gradient from the vehicle to the skin.[59] Solid lipid nanoparticles have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide, and glucocorticoids.[60]

## CONCLUSION

Transdermal drug delivery system has been recognized as a potential delivery system in spite of its limitations. Essentially this drug delivery system brings ratecontrolled delivery with fewer side effects, increased efficacy, and constant delivery.

The skin has an extremely good barrier function and to improve the penetration of active ingredients, it is frequently necessary to employ enhancement strategies.

Various physical methods of enhancing transdermal drug delivery will open up the benefits of the transdermal drug delivery technology to a much broader range of therapeutic areas. Existing small molecule products have proven that transdermal drug delivery is a more patientfriendly and preferred method of administration as compared to injections, and offers the additional benefit of controlled drug delivery.

With the use of newer physical means of enhancement, these benefits can be extended to macromolecules and biopharmaceuticals as well. So overcoming the road block of low skin permeability using these approaches will be the crucial advance that lets transdermal delivery realize its great promise.

In the future, it may be possible that patients will be seen wearing transdermal systems in the form of disposable, battery operated wrist watches that will be operated and controlled by microchips to deliver the drugs at the desired rates.

Another factor that might be important for the future direction of transdermal delivery is the current surge in the interest in nanotechnology. Application of developments in nanotechnology could lead to systems where a single device could monitor drug levels by sampling through the skin and thus, provide controlled delivery of the drug. The attractiveness of the technology is obvious because of the accessibility of the device for adjustment, control, and removal.

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