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Skin Penetration Enhancement Techniques – Physical Approaches

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Abstract

Transdermal delivery represents an attractive alternative to oral delivery of drugs and is poised to provide an alternative to hypodermic injection too. Transdermal drug delivery system which can deliver medicines via the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentration over a prolonged period of time. To date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin. Improvement in physical permeation-enhancement technologies has led to renewed interest in transdermal drug delivery. Some of these novel advanced transdermal permeation enhancement technologies include: iontophoresis, electroporation, ultrasound, microporation, radiofrequency and microneedles to open up the skin. This review focus on some existing and novel physical approaches intended for skin penetration enhancement of drugs.

Keywords: transdermal; skin penetration, iontophoresis; microneedle.

1. Introduction

Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desire therapeutic effect and undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of adsorption of drug at the site of action.[1] To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for a medication. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent.[2]

The old age theory that imparted the status of "dead impermeable barrier devoid of biological activity" to skin had already been challenged by the development of pioneering transdermal products. But a less than impressive commercial growth in this sector had raised some doubts about the feasibility of this route as an effective device of drug delivery. The journey of transdermal research had commenced with a lot of enthusiasm, as it heralded the promise of noninvasive cutaneous application.[3]

Transdermal delivery represents an attractive alternative to oral delivery of drugs and is poised to provide an alternative to hypodermic injection too. For thousands of years, people have placed substances on the skin for therapeutic effects and, in the modern era, a variety of topical formulations have been developed to treat local indications. The first transdermal system for systemic delivery—a three-day patch that delivers scopolamine to treat motion sickness—was approved for use in the United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the public in general. Between 1979 and 2002, a new patch was approved on average every 2.2 years. Over the past 5 years (2003–2007), that rate has more than tripled to a new transdermal delivery system every 7.5 months. It is estimated that more than one billion transdermal patches are currently manufactured each year.[4]

Transdermal drug delivery system which can deliver medicines via the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentration over a prolonged period of time. To date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin. These are termed 'Novel' due to recent development with satisfactory results in the field of drug delivery.[5]

Improvement in physical permeation-enhancement technologies has led to renewed interest in

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transdermal drug delivery. Some of these novel advanced transdermal permeation enhancement technologies include: iontophoresis, electroporation, ultrasound, microporation, radiofrequency and microneedles to open up the skin.[6,7,8]

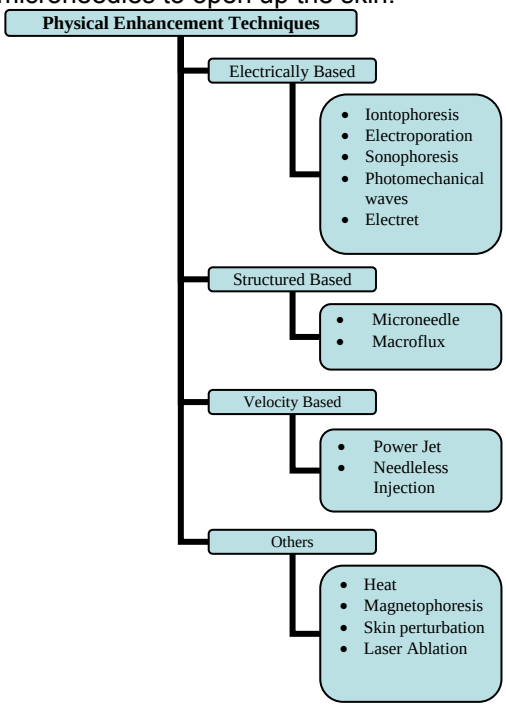

Figure1. Classification of Physical Enhancement Technique meant for Skin Permeation.

2. Physical Enhancement Techniques

2.1 Iontophoresis

Iontophoresis is an electrically facilitating methodology to deliver a precise dosage of drugs into the body through skin and control its plasma level in the circulation at the specific site to the required therapeutical level. Iontophoresis enhances transdermal drug delivery by three mechanisms[9] :

- The ion electrical field interaction provides the directional force which drives ions through the skin.
- Flow of electric current increase the permeability of the skin.
- Electrophoresis produces bulk motion of the solvent itself that carries ions or neutral species, with the solvent 'stems'.[10]

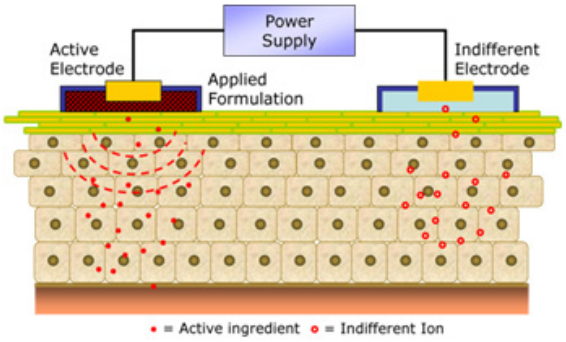

Figure 2. Schematic Expression of Drug Administration Facilitated By Iontophoresis.[11]

A number of factors influence the iontophoretic transport of drug.

a) *The pH of the medium:* As the ionization of the drugs is controlled by pH, transport is optimum in the pH range in which the drug is fully ionized although uncharged species can be carried by the electro osmotic solvent flow[12,13,14]

b) The nature of the other ions in the formulation, which compete for transport of the current.[15]

c) *The current density:* The drug flux is proportional to the current density, but the allowable density is limited by safety and patient tolerance to about 0.5 mA cm^{-2} [16,17,18]

d) *Molecular weight:* Larger drug have lower transport number and so are delivered less effectively. As the drug size increases, the importance of ionic transport decreases and the drug becomes predominantly carried by the electro-osmotic solvent flow.[19]

e) *Concentration of drug in the delivery system:* As the drug concentration at the donar site is increased, the flux across the skin increases.[20]

f) *Physiological variations:* A major advantage of iontophoresis is that relatively low level of variation is observed. This is probably due to the fact that the applied voltage is adjusted to achieve a specific current, and this will take amount of much variability

between the subjects due to site, age and color of skin.[21]

g) *Wavelength of applied current:* A number of authors have studied the effect of using AC voltages instead of a steady DC voltage, which can reduce efficiency due to polarization of the skin.

Products have already reached the US market using iontophoresis. One example is Iomed's Iontocaine (Numby Stuff- Lidocaine HCL and epinephrine in the Phoresor iontophoresis system), which is marketed for local dermal analgesia.[22] Similarly, Vyteris is awaiting approval for its iontophoretic system, which also delivers Lidocaine for dermal anesthesia in children.Several other companies have completed various stages of clinical iontophoresis studies, most notableamong them being ALZA with its E-TRANS system using fentanyl for the management of postoperative pain.[23]

Fan et. al.[24] have reported the application of a porous polyaniline membrane as a conducting polymeric membrane as well as an electrode in an iontophoretic transdermal drug delivery system. In conventional iontophoresis with Ag|AgCl electrodes, the Ag electrode is the anode; the AgCl electrode acts as the cathode. The Ag electrode is easily oxidized and is therefore known to be unstable; the Ag|AgCl system is also quite costly. The Ag anode can be reused only by an intense cleaning process both before and after usage to prevent oxidation and damage. To overcome such limitations, a novel conducting polymeric membrane made of polyaniline can be use as an electrode replacing the Ag electrode in iontophoresis.[25]

2.2 Electroporation

Electroporation is the creation of aqueous pores in the lipid bilayer by the application of short electrical pulses of approximately 100-1000 V/cm. Flux increases of upto 10,000 folds have been obtained for charged molecules. The efficacy of transport depends on the electrical parameters and the physicochemical properties of drugs. The in vivo application of high voltage pulses is well tolerated but muscle contractions are usually induced. The electrode and patch design is an important issue to reduce the discomfort of the electrical treatment in humans.[26] A number of studies have demonstrated that electroporation-mediated transdermal delivery of peptides, polysaccharides, oligonucleotides and genes.[27]

There are numbers of work reported that shows increase flux by elctoporation effect.[28] However greater enhancement can be achieved by combining skin electroporation with iontophoresis, ultrasound, and macromolecules.[29] Electroporation may combine with iontophoresis to enhance the permeation of peptides such as vasopressin, LHRH, neurotensin and calcitonin.[30,31]

Electoporation enhancement can be use for transdermal delivery of macromolecules of at least 40kDa.[32] Although DNA introduction is the most common use for electrophoresis, it has been used on isolated cells for introduction of enzyme, antibodies and viruses and more recently, tissue electroporation has begun to be explored, with potential application including enhanced cancer tumor chemotherapy, gene therapy and transdermal drug delivery.[26,33]

2.3 Sonophoresis

Another technique beside electroporation attempting to overcome the challenges of transdermal drug delivery involves the usage of high or low frequency ultrasound waves. The enhancement may result from enhanced diffusion due to ultrasound-induced skin alteration and/or from forced convection. Tang et al have a theory describing the transdermal transport of hydrophilic permeants in the presence of ultrasound. Ultrasound alters the skin porous pathways by two mechanisms: (1) enlarging the skin effective pore radii, or (2) creating more pores and/or making the pores less tortuous.[34] Conical microscopy indicates that cavitations occur in the keratinocytes of the stratum corneum upon ultrasound exposure.[35] Recent studies have shown that ultrasound can increase up to 5,000 times the ability of protein the size of insulin to penetrate the skin. Using a transdermal patch design in conjunction with ultrasound may provide an improved method for Insulin delivery.[36,37]

Frequency of ultra sound wave is also an important factor. Prolonged exposures at high frequencies, however, can alter epidermal morphology.[38] Menon et al had reported that permeability enhancement by high frequency sonophoresis is due to disruption the compact organization of SC bilayersv[39] Bommanan et al have also reported that enhancing effect of sonophoresis is due to a direct effect of ultrasound on (presumably) the stratum corneum.[40] It was reported that desired permeability enhancement can be achieved regardless of choice of frequency, although the necessary energy density is higher at higher frequencies.[41] Low-frequency ultrasound did not induce a long-term loss of the barrier properties of the skin (in vitro) or damage to living skin of hairless rats.[42]

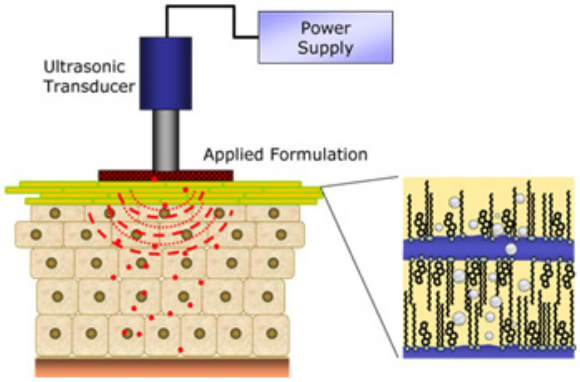

Figure 3. Schematic Expression of Drug Administration Facilitated By Sonophoresis.[11]

2.4 Photomechanical Waves

Photomechanical waves are also known as laser generated stress waves. Photomechanical waves are the pressure pulses produced by ablation of a material target (polystyrene) by Q-switched or mode-locked lasers.[43] A single photomechanical wave modulates barrier function of human stratum corneum in vivo without adversely affecting viability of and structure of epidermis and dermis.[44] Photomechanical waves are able to make the stratum corneum more permeable to macromolecules via a possible transient permeabilisation effect due to the formation of transient channels. The application of pressure waves does not cause any pain or discomfort and the barrier function of the SC always recovers.[45] The largest molecule that has been reported to be delivered through the rat skin to date has a molecular weight of 40,000Da. Suggestions have been made that many clinically important proteins such as insulin (6000 Da) and hematoprotien (48000 Da) are within or close to the delivery capability range of PW's. However; this relatively new technique does not yet seem to have produced any human clinical data.[46, 47]
The PW delivery of insulin through the skin of diabetic rats was shown to cause reductions in blood glucose of around 80±3%, and was maintained below 200mg/dl for more than 3 hours.[48]

2.5 Electret Enhances TDDS[49]

Electret is an electrically charged Teflon®disk that carries semi permanent electric charge. It is characterized by the surface potential in volts. These provide surfacepotentials from 500 to 3000V, easily measurable using an electret reader. Electrets and the electret readers used in this study are commercially available under the brand name E-PERM® (Rad Elec Inc., Frederick, MD, U.S.A.). The active surface of the electret is about 12 cm^2. These are widely used as components of electret ion chambers used for measuring radon and radiation. Electret was found to enhance the penetration of hydrophilic drugs (but not lipophilic drugs) across the skin. However, the electret effect disappears when moisture content in the formulation increases. The electrets seem to work well with the topical bases which do not have moisture in them. The surface voltage of electret was not affected significantly by the presence of white petroleum jelly coating on the E-PERM® electrets. It is also possible to use a thin layer of removable uncharged Teflon® to cover the surface of the electret. This allows electric field to go through and at the same time protects the electret surface from getting contaminated. Cui et al. have reported the effect of electret on the skin permeability of methyl salicylate.[50 51]

2.6 Microfabrication Microneedles Technology

The microfabricated microneedles technology employs micron-sized needles made from silicon.[52] Microneedles have been fabricated with different range of size, shape and materials. These microneedle arrays after insertion into the skin create conduits for transport of drug across the stratum corneum. Microneedles inserted into the skin of human subjects were reported as painless. Drug delivery by microneedle increase skin permeability for a broad range of molecules and nanoparticles.[53 54]
Past research on drug delivery suggest that microfabricated microneedles are a promising technology to deliver therapeutic compounds like insulin into the skin. Martanto and co author has reported that Solid metal microneedles are capable of increasing transdermal insulin delivery and lowering blood glucose levels by as much as 80% in diabetic hairless rats in vivo. Microneedles increased skin permeability to insulin, which rapidly and steadily reduced blood glucose levels to an extent similar to 0.05-0.5 U insulin injected subcutaneously.[55]

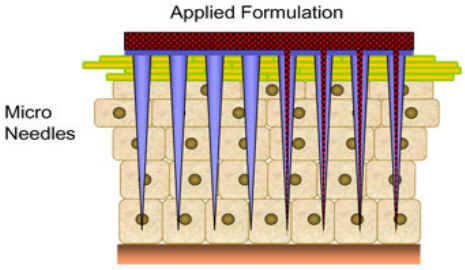

Figure 4. Schematic Expression of Drug Administration Facilitated By Microneedles.[11]

Current technologies have combined these needles with pressurized reservoirs, creating a transdermal

insulin pump. The incorporation of microprobes **(**biosensors**)**, channels, and further modification of needle dimension will allow for more optimal, self-regulating insulin delivery platforms.[56 57 58]

Microneedles may create microconduits sufficiently large to deliver drug-loaded liposomes into the skin. The combination of elastic liposomes and microneedles may provide higher and more stable transdermal delivery rates of drugs without the constraints of traditional diffusion-based transdermal devices, such as molecular size and solubility.[59]

2.7 Macroflux

Technology is another novel transdermal drug delivery system that ALZA Corporation has developed to deliver biopharmaceutical drugs in a controlled reproducible manner that optimizes bioavailability and efficacy without significant discomfort for the patient.

The system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer to allow transportation of therapeutic proteins and vaccines or access to the interstitial fluids for sampling. Macroflux has an area of up to 8cm and contains as many as 300 microprojection per cm2 with individual micro projection length being < 200µm. The maximal adhesive patch size is 10 cm2. A coating process is used to apply drug to the tip of each microprojection in the array. When the patch is applied to the skin, the drug-coated microprojections penetrate through the skin barrier layer into the epidermis. The microcapillaries for systemic distribution absorb the drug. The rate of absorption is promoted by the high local drug concentration around the microprojections and the large surface area provided by the patch array.

Three types of Macroflux® have been designed and tested in preclinical studies. They include,

Dry-Coated Macroflux®

System for short duration administration that consists of a drug coated microprojection array adhered to a flexible polymeric adhesive backing.

D-TRANS®

Macroflux® system for short duration administration that consist of a microprojection array coupled with a drug reservoir.

E-TRANS

Macroflux® system for pulsatile or on demand delivery that include a microprojection array coupled with an electrotransport system.

Therapeutic peptides, proteins and vaccines such as desmopressin, human growth hormone (HGH), TH 9507 (a human growth hormone releasing factor analog), ovalbumin(45000 Da protein) are in the developmental stage for transdermal delivery by Macroflux.

2.8 Jet Propelled Particles

The core technology involves the high velocity injection of particle formulated drugs and vaccines into any physically accessible tissue. These may be for therapy or prevention of disease and may be small molecules, peptides, proteins and genes. [60] However microparticles would be unsuitable for the delivery of drugs into the skin because of their non-biodegradable nature and subsequent accumulation in the body, therefore powders and larger biodegradable particles (75-100µm) have been investigated for this application.[61]

The use of compressed gas to force solid drug particle through a convergent divergent nozzle was reported by Bellhouse et al. using compressed helium. High-velocity powder injection is a promising new drug-delivery technique that provides needle- and pain-free delivery of traditional drugs, drugs from biotechnology such as proteins, peptides, and oligonucleotides as well as traditional and genetic vaccines. The energy of a transient helium gas jet accelerates fine drug particles of 20 µm−100 µm diameter to high velocities and delivers them into skin or mucosal sites. Particle velocity is controlled within the device by three parameters namely nozzle geometry, membrane burst strength and gas pressure.[62] Preclinical and clinical results that best characterize the technology and introduce its potential as a drug-delivery platform.[63]

The Powderject system involves the propulsion of solid drug particles into the skin by means of high-speed gas flow. This needle-free method is painless and causes no bleeding and damage to the skin. Drug particle velocities of up to 800 m/s were obtained at the nozzle exit. Adjusting the momentum density of the particles within the gas flow optimizes the depth of penetration of the drug particles. . Powderject system consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. At the release, virtually instantaneous rupture of both membranes causes the gas to expand rapidly, forming a strong shock wave that travels down the nozzle at speed of 600–900 m/s. Insulin has been one of the first molecules to appear in the clinical literature relating to the use of jet injectors, with early studies in the mid to late 1980's reporting better absorption rates than traditional needle injection.[64, 65]

Jet propelled particle device has been reported to successfully deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin.[47]

2.9 Needleless Injection

Liquid jet injections employ a high-speed jet to puncture the skin and deliver drugs without the use of a needle. Research on jet injectors began in the early 1930s with Arnold Sutermesiter, an engineer who noticed accidental injections of diesel oil into the hands of workers when small leaks occurred in high-pressure lines.[66] Since then, two main classes of liquid jet injectors have been developed. These are single-dose jet injectors, known as DCJIs (Disposable Cartridge Jet Injectors) and MUNJIs (Multi-Use-Nozzle Jet Injectors)[67]

The highest value, least developed and most technically challenging group of needle-free technologies is prefilled, disposable injectors. The development of such technologies is primarily driven by the demand for a convenient, non-invasive alternative to the conventional needle and syringe injection. Some of the needle free injectors under development are:

Intra-Ject

One of the prefilled disposable injectors, intraject, under development, is designed to use the nitrogen propelled device which has a blank drug capsule. The patient snaps off the tip, tears off the safety end and plenus the nozzle against the skin pressurized gas, and then pushes the liquid formulation through a narrow orifice into the skin.

Implaject

Implaject first pushes a tiny, potential “Pioneer tip” thorough the skin ahead of the drug. The tip pierces the tissue, creating a channel through which the therapeutic agent follows immediately

Jet Syringe

The Jet Syringe can be configured with either an adjustable dose “fill and shoot” ampoule or a proprietary pre-filled ampoule for fixed dose applications. Dose volume of delivery is up to 0.5 ml. It is suitable for short-term infrequent injection therapies

Mini-Ject™

The Mini-Ject™ can deliver a wide range of drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous, or intramuscular depending on the therapeutic need.

The Mini-Ject™ system utilizes a glass drug cartridge to accommodate for long term drug storage and stability; a polycarbonate syringe, to accommodate for a wide range of pressure profiles; and a proprietary multiphase energy system that can deliver a specific pressure profile to ensure that the entire drug is delivered comfortably.

Crossject

The gas generating technology used in Crossject injectors produces pressure profiles that are particularly well suited to the needle-free injection of drugs. It comprises three modules. The gas generator contains the chemical energy source and is triggered by the impact of a syringe, the drug container and the third module, nozzle, of polycarbonate with one or more orifices depending on the quantity of the formulation.

2.10 Heat-enhanced transdermal delivery[68]

Heat is expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility. According to Kligman,[69] diffusion through the skin, as elsewhere, is a temperature-dependent process, so raising the skin temperature should add thermodynamic drive. Heat is known to increase the kinetic energy of the drug molecules and the proteins, lipids, and carbohydrates in the cell membrane. Heating prior to or during topical application of a drug will dilate penetration pathways in the skin, increase kinetic energy and the movement of particles in the treated area, and facilitate drug absorption. Heating the skin after the topical application of a drug will increase drug absorption into the vascular network, enhancing the systemic delivery but decreasing the local delivery as the drug molecules are carried away from the local delivery site.

2.11 Magnetophoresis

Magnetophoresis is a novel approach in enhancing drug delivery across biological barriers. The influence of magnetic field strength on diffusion flux was determined and was found to increase with increasing applied field strength.[70] Murthy and hiremath had also reported that magnetic field enhanced transdermal delivery of terbutaline sulphate.[71]

2.12 Mechanical perturbation

Microstructured Transdermal Systems enables the disruption of the outermost layer of the skin, the stratum corneum, without causing pain. MTS expands the range of drugs that can be delivered transdermally and potentially reduces variation in transdermal drug delivery caused by different skin types and application sites. It is suited for vaccines, protein or peptide based drugs.[72]

Recent research and development efforts have been channelized into the development of new high technology based analytical probes. Electron microscopy is used for quantitative ultrastructural studies in the skin, and to detect many changes in the various layers and organelles of the skin after treatment with a penetration enhancer. ATR-FTIR is a powerful in-vivo technique for studying the

biophysics of skin functions. Thermal analysis techniques such as DTA and DSC are used to investigate the physical properties of stratum corneum and the measurement of lipid and protein thermodynamic behavior in model and biological membranes.[73]

2.13 Laser Ablation

The use of lasers to remove the stratum corneum barrier by controlled ablation has also been investigated as a means of enhancing topical drug delivery.[74]

This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

It has been also reported that laser ablation of stratum corneum enhanced the permeation of both hydrocortisone and interferon.[75]

A handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia) that has been approved by the U.S. and Australian regulatory bodies for the administration of a topically applied anaesthetic. However, the structural changes caused by this technique still need to be assessed for safety and reversibility, particularly at the higher intensities that may be needed to enhance the penetration of large molecular weight solutes where evidence of deeper level ablation effects exist.

Er:YAG laser can be effective for transdermal delivery of macromolecules and hydrophilic permeants such as peptides and protein-based drugs.[76]

Lee WR et al. has reported that the stratum corneum (SC) layer in the skin was partly ablated by an erbium:YAG laser, resulting in a greater enhancement effect on skin permeation of 5-FU.[77]

Use of an erbium:YAG laser is a good method for enhancing transdermal absorption of both lipophilic and hydrophilic drugs.[78]

It was demonstrated for the first time that laser treatment with no adjuvant or penetration enhancer significantly enhanced the production of antibodies in the serum by 3-fold.[79]

3. Conclusion

Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. In past delivery of large size drug molecules through skin was challenge. However to date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin. Improvement in physical permeation enhancement technologies has led to renewed interest in transdermal drug delivery.

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