ISSN: 0975-766X
CODEN: IJPTFI
Available through Online
Review Article
www.ijptonline.com

PHYSICAL ENHANCEMENT TECHNIQUES FOR TRANSDERMAL DELIVERY SYSTEM: A REVIEW

Ukawala Ravikumar D*[1], Jaybharati Vasava[2]
[1]Dept. Of Pharmacy, BITS-Pilani, Rajasthan, India.
[2] S K Patel College of Pharmaceutical Education and Research, Ganpat University, Gujarat, India.
Email: r.d.ukawala@gmail.com

Received on 24-07-2012 *Accepted on 08-08-2012*

Abstract

Transdermal delivery represents an attractive alternative to oral delivery of drugs and is poised to provide an alternative to hypodermic injection too. Transdermal delivery has a variety of advantages compared with the other routes. In particular, it is used when there is a significant first-pass effect of the liver that can prematurely metabolize drugs. Transdermal delivery also has advantages over hypodermic injections, which are painful. In addition, transdermal systems are non-invasive and can be self-administered. Perhaps the greatest challenge for transdermal delivery is the only a limited number of drugs are amenable to administration by this route. It has been difficult to exploit the transdermal route to deliver hydrophilic drugs, peptides and macromolecules, including new genetic treatment employing DNA or small-interfering RNA (siRNA), has posed particular challenges. Another area of great interest is the delivery of vaccines. In addition to avoiding hypodermic needles, transdermal vaccine delivery could improve immune responses. Given the external placement and patient control over patches, it might also be possible to develop modulated or pulsatile delivery, which could involve feedback control. Microneedles, skin ablation, sonoporation etc. like physical methods for enhancement of transdermal delivery are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone and influenza vaccine. Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections.

Key words: Jet injector, Iontophoresis, Sonophoresis, Microneedle, Skin Ablation

Introduction: 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. Now a day, numbers of

drug formulations are available in oral dosage forms like tablets, capsules, solution, suspension, emulsion, lozenges etc. But for oral dosage forms bright as well as dark sides are also there like; first pass metabolism (Metabolism in liver), degradation in GIT, irritation to GIT mucosa, less bioavailability and many more.

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. Because transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms.[1] Besides these all benefits, transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing. They offer improved patient compliance.[2]

Since the first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more than 35 transdermal patch products, spanning around 13 molecules like fentanyl, nitroglycerin, estradiol, ethinyl estradiol, norethindrone acetate, testosterone, clonidine, nicotine, lidocaine, prilocaine, and scopolamine.(Orange Book) Certainly, transdermal drug delivery is not suited nor clinically justified for all drugs. And the skin barrier limits the number of drugs that can be delivered by passive diffusion from an adhesive patch.

Skin as Barrier

One of the major limitations to successful transdermal drug delivery from the skin is itself, an excellent physical barrier. Transdermal patches, passive or physically assisted techniques are limited by the dense tissue to deliver molecules of a certain molecular size and methods that circumvent the skin barrier (i.e. ablative methods, jet injectors or microneedles). Nevertheless, the barrier property of the skin poses a challenge for these methods as well; less from an intercellular or chemical point of view, but instead from a mechanical perspective.

The mechanical and structural properties of the skin vary significantly with age, skin type, hydration, body location, and between individuals[3,4]. Hence, general quantitative descriptions of the skin are very difficult to obtain. Stratum corneum is generally regarded as the main physical barrier of the skin. The layer is relatively stiff compared to underlying tissues.

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum.

The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 μm in the dry state to 40 μm when hydrated[5,6]. It comprises a multi-layered "brick and mortar" like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters[7].

Limitations of Conventional Dosage Forms

Oral solid and liquid dosage form have many limitations in its performance like; Inadequate Absorption, Degradation of the drug, less bioavailability, Extensive First pass metabolism, GI irritation, Sustained action is not available. For SR tablets the sustained action is achieved but the first pass metabolism, bioavailability is the problems that remain as they are.

Macromolecules such as Insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen, and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity.[8]

Nitroglycerine is available in the market in form of patches, SR tablets and buccal films are available. But the advantages of the patches are numerous due to which it is used vary widely. Sustained action is provided by the patch that can't be provided by the SR tablets without first pass metabolism as well as the degradation due to the acidic conditions in the GI environments. Study shows that the patch has provided good bioavailability and sustainable effect than the SR release tablets.

Injections and infusions have major disadvantages such as painful, high risk of infection, if not done properly, potentially fatal air boluses (bubbles) can occur.

Classification of Transdermal Delivery Systems

There are mainly 3 generations of the Transdermal Delivery System. The first generation of systems produces many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rate with little or no enhancement. The second generation has yielded additional advances for small molecule delivery by increasing skin permeability and driving forces for transdermal transport. The third generation that will enable transdermal delivery of small molecule drugs, macromolecules (including proteins and DNA) and virus based/ other vaccines through targeted permeability of the skin's stratum corneum.[9]

Generally systems for transdermal delivery are divided in 3 categories which are Structure based, Electronic based, and Velocity based. For each category underlying systems are shown below.[10]

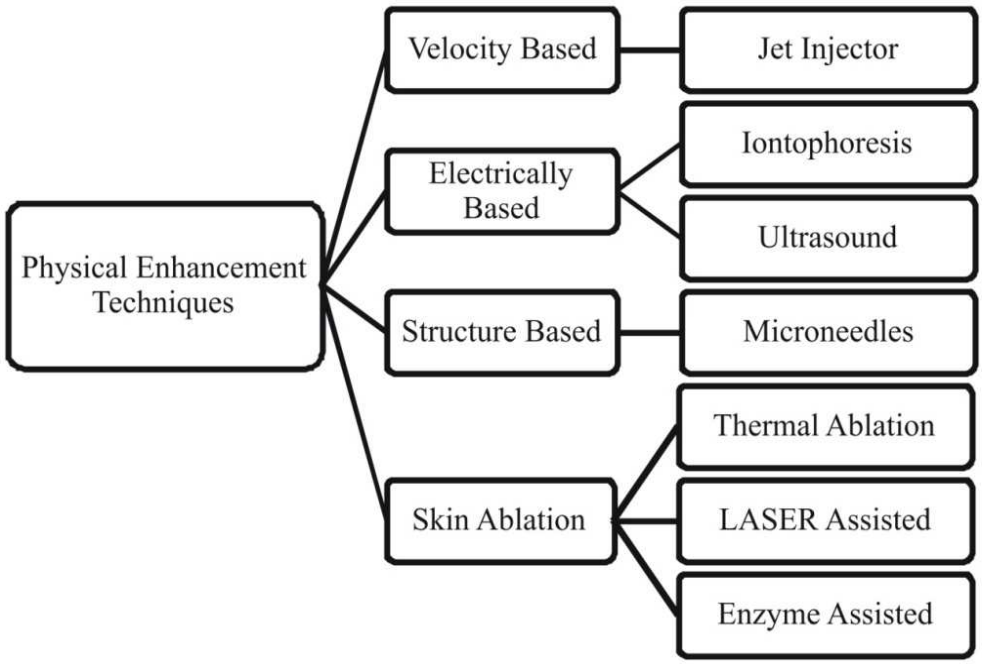

Fig-1: Classification of Physical Enhancement Techniques for Transdermal Delivery System

Jet Injectors

The concept of skin-penetrating jet injectors dates back over 50 years.[11] The advancement on this technology was slow at first, perhaps because of reports of unreliability of the jet injection in the form of occasional pooling of drug on the skin's surface and reports of bruising.[12] However, more recent research on the helium-driven particle accelerators developed for transdermal delivery today appears to have stemmed from the gunpower-based acceleration device (gene gun] developed by Sanford's group in the late 1980's for the delivery of genes into plant cells.[13]

The transdermal jet-injectors propel drug molecules into the skin by production of a high-velocity jet (>100m/s) of compressed gas (usually helium) or spring that accelerate drug particles through the nozzle of the injector device. [Figure-2] Accelerated particles then penetrate the skin at a speed and distance determined by physical properties of the device and particle size, velocity of the carrier gas and discharge pressure.[14] 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[15].

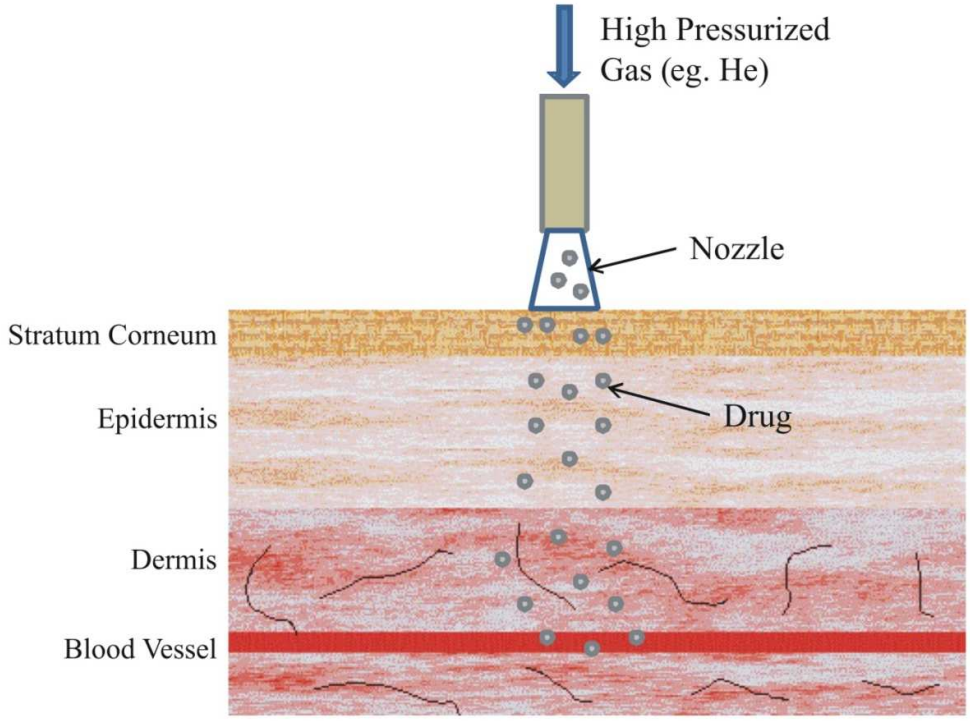

Fig-2: Jet Injector

Jet injector employs a piezoelectric actuator to accelerate a micron-scale stream of fluid (40–130 μm diameter) to velocities sufficient for skin penetration and drug delivery (50–160 m/s). Electronic control of the actuator expansion rate offers more precise injections. Further, the injection parameters including expelled volume, jet pressure, and penetration depth in soft materials vary with actuator expansion rate, but are highly coupled. Electronically-controlled jet injectors may enable the decoupling of injection parameters such as penetration depth and dose, improving the reliability of needle-free transdermal drug delivery.[16] Lorentz-force actuated needle-free injector to deliver a blend of bacterial collagenases to the skin has been reported by Hogan et al.[17]

A study of the jet injector delivery system has been performed by Schramm et al. which covered five areas i.e. Pharmacokinetics (insulin and radioisotope markers), Tissue penetration and reaction, Pain and compliance issues (alone and in comparison to traditional needle injections), General safety considerations, New clinical applications (including combination with iontophoresis for the delivery of diclofenac and angiotensin).[14]

Powder vaccine delivery by jet injectors is also in its very early stages. It is difficult to induce cellular immune responses of vaccines unless they are delivered into the cytosol of target cells. For this reason, powder vaccines are prepared that are capable of being targeted to produce better pre-clinical and clinical results. For intracellular

administration, particles are generally kept in the 1-3μm size range and plasmid DNA or protein particles precipitated onto gold or tungsten beads, whereas for intercellular targeting of protein based vaccine antigens, agents are usually formulated into powder-like particles with sugar excipients to produce particles on the 20-70μm size range The clinical testing of jet DNA vaccination is still in it's early days. These studies were reported to indicate considerable potential for the further development of the technology. However, in mice, epidermal jet injection with influenza vaccine powder (with and without adjuvants) resulted in the production of significant levels of antibodies.[18]

But in delivery by jet injector necrosis, hair loss, and minimal bruising were observed at drug injected sites.[17] Poor reliability as well as painful bruising and bleeding characterized old devices, due to the high and constant jet velocity with which drugs are delivered. Toward improved reliability and reduced pain, Stachowiak et al. have developed a jet injector capable of dynamic control of jet velocity during a single injection pulse by adjusting time at high velocity, and delivered dose.[19]

From the above information we can conclude that jet injection administration of macromolecules is possible, and that clinical results are indeed promising, but need obviously over the next few years needs further refinement. Since 1930, different types of jet injectors have been developed and used in clinical applications viz. immunization with vaccines, insulin delivery, growth hormone delivery, local anaesthesia and even tattooing. Jet injectors were and are still widely used in large vaccination campaigns, especially by the US War Department during the deployment of the American army in countries at risk. The most important usage was probably in the WHO vaccination campaign against smallpox. The feasibility of 600 or more subcutaneous injections per hour makes this the fastest immunization system.

Jet Injectors Vs Other Conventional Methods

Agerso et al. has studied pharmacokinetics and pharmacodynamics of a new formulation of recombinant human growth hormone (Zomacton®) administered by ZomaJet 2 Vision, a new needle-free device in comparison with subcutaneous administration using a conventional syringe. The study was performed according to a randomized, controlled, three-period crossover design. No withdrawal of subject was taken place due to adverse events. The local tolerance assessment (assessed by inspection) revealed no differences between ZomaJet2 Vision application and conventional injections by syringe. When using the ZomaJet 2 Vision, the absorption of hGH was faster, resulting in

higher C(max) values. Comparison of the pharmacodynamic profiles of Insulin like growth factor-1 (IGF-1) and Free Fatty Acids (FFA) demonstrated bioequieffectiveness. These results support the use of jet injectors as a viable alternative to the traditional injections.[20]

Iontophoresis

Iontophoresis was initially developed to facilitate the delivery of ionised solutes, with inherently low partition coefficients due to their charged state, across tissue membranes. The technique involves the application of a small electric current (usually 0.5mA/cm^2) to a drug reservoir on the surface of the skin with the same charged electrode as the solute of interest placed together to produce a repulsion effect that effectively drives solute molecules away from the electrode and into the skin.[15]

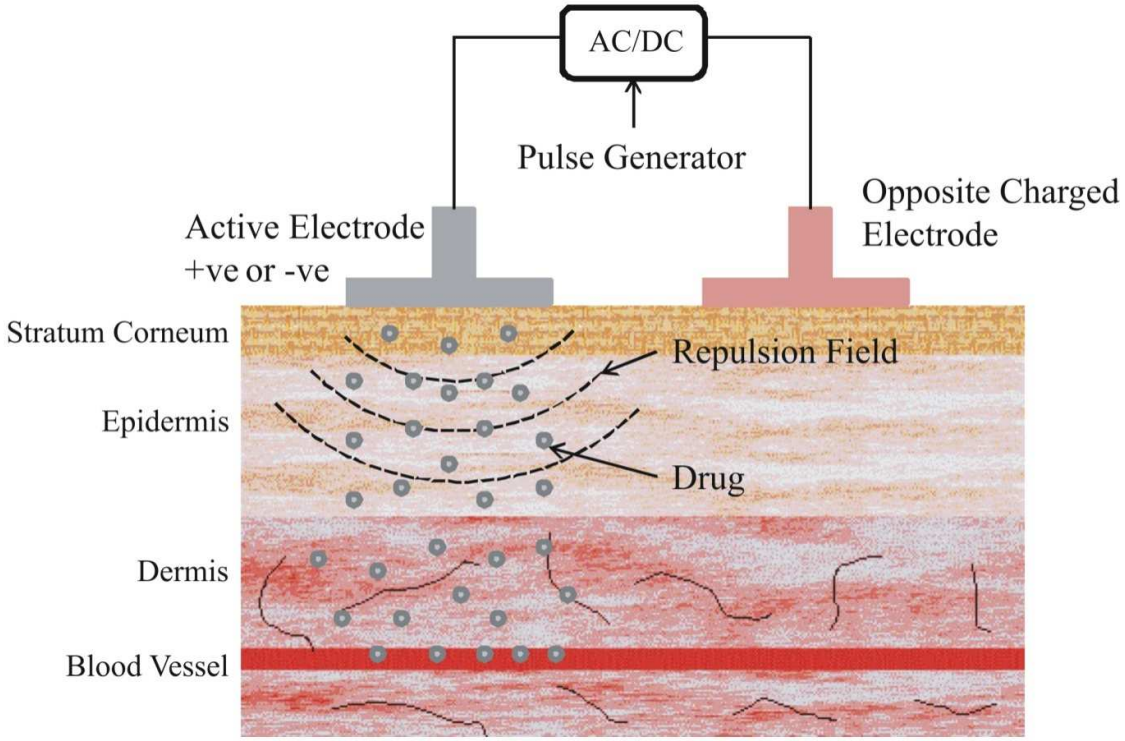

Fig-3: Iontophoresis

Iontophoresis generators produce continuous direct current which assures unidirectional flow of ions. The effect of simple electrorepulsion is known to be one of the main mechanisms by which iontophoresis produces it's enhancement effects, though other factors including the possibility of increasing the permeability of the stratum corneum in the presence of a flow of an electric current and electroosmosis of uncharged and larger water soluble molecules. [21] Many drugs have been studied for delivery by iontophoresis. Some of them are Buprenorphine,

Piroxicam, Chlorhexidine dihydrochloride, Gentamycin, Thiocolchicoside, Salbutamol, Timolol maleate, Dextran sulphate, Diclofenac, Rotigotine, Leuprolide, Nalbuphine & its prodrugs, Vasopressin, Atenolol hydrochloride.[22]

Many types of iontophoretic systems are available in market like;

1. Iontophoresis (IP) and electroporation (EP) combination.

Iontophoresis has also been used along with other skin penetration enhancing techniques like electroporation, which involves the application of high voltage (> 100 V) pulses for short duration (μs-ms) to increase the permeability through the skin.[23] Electroporation is usually applied before iontophoresis, which causes the creation of increased permeability skin due to exposure to high voltage pulses. Iontophoresis thus, when applied after electroporation helps in extending the permeability state of the skin resulting in the rapid onset (which is not possible with iontophoresis alone) and sometimes increased flux. Optimum time for electroporation is desired since if it is not applied for proper time, it may not reduce the lag time sufficiently to produce the desired permeability of skin which would otherwise facilitate the flux of the drug.[24] The increased transport by electroporation has been found due to creation of electropores as well as local field induced electrophoretic drift.[25] Fang et al. studied the effect of electroporation on the delivery of buprenorphine. They showed that application of 300 V or 500 V pulses increased the buprenorphine flux by several folds over passive transport. Despite the pulsing time of 10 min, the cumulative amount of buprenorphine in the receptor compartment increased constantly till the end of 8 h.[24] This suggested that a drug reservoir was created within the skin from where the drug was able to permeate to receptor site after 10 min of application, at a constant rate. Iontophoresis and electroporation have been used in combination for administration of drugs such as Salmon calcitonin (SCT) and PTH combination, Buprenorphine, Tacrine Hydrochloride.[22]

2. Pulsatile/switching iontophoresis.

Many studies have been conducted where instead of using constant DC iontophoresis; DC in the form of short pulses has been used. Drugs those can be given by pulsatile iontophoresis and for that the study has been performed are Human Para thyroid hormone, Glibenclamide, Phthalic acid (PA), benzoic acid (BA), Verapamil (VR), LHRH and Nafereline, Ketorolac, Salmon calcitonin (SCT) and PTH combination, Buprenorphine, Tacrine Hydrochloride.[22]

3. Reverse iontophoresis.

Reverse iontophoresis, a technique in which low electric current is applied to draw body fluid through the skin, is widely applied now a days in devices meant for diagnostic application. This provides a convenient and non-invasive

method for sampling of body fluids so as to permit simultaneous measurement of the desired substance in the body fluid and thus to monitor them efficiently e.g., devices like Glucowatch® uses the reverse iontophoretic process to continuously monitor the glucose level in the blood. It provides a needleless means of monitoring blood glucose levels in diabetic patients. GlucoWatch® is approved for use in children and adults. The technique provides a feasible method for rapid, linear extraction of phenylalanine and for easy detection and monitoring diseases like phenylketonuria.[26] Caffeine, Theophyline, Lithium, Phenytoin are the drugs that can be delivered by reverse iontophoresis.[22]

The degree of variability, safety and acceptability of iontophoresis has been addressed in only a few recent studies, with older studies tending to report only the most dramatic effects of burns resulting from electrode contact with skin. Local erythema under electrode application sites is a common reaction to iontophoresis and is thought to be due to either microscopic cellular damage at sites of high current density leading to cytokine and prostaglandin release and local vasodilatation, some form of direct stimulation or via provocation and release of substance-P and calcitonin gene-related peptide at nerve endings in the dermis.[21] Singh et al. reported regional variations in both skin irritation and barrier function following iontophoretic application of saline in humans. Erythema scores and skin reactions were noticed to be greater at the chest than the abdomen or upper arm. Following iontophoresis of unbuffered solutions in human volunteers, however the current applied in this study resulting in these effects (80mA/min) was higher than would be recommended for normal iontophoretic treatment.[27]

There have been numerous research applications of iontophoresis in topical drug delivery for lower molecular weight solutes (<500 Da). For macromolecules and protein and peptide structures there have also been a number of studies including: calcitonin (salmon)[8], corticotrophin-releasing hormone[28], delta sleep-inducing peptide[29], dextran sulphate, inulin, insulin, gonadotropinreleasing hormone, growth hormone-releasing factor, leuprolide acetate, leutenising hormonereleasing hormone, neutral thyrotrophin-releasing hormone, oligonucleotides, parathyroid hormone and vasopressin.[22]

In macromolecule delivery by iontophoresis, insulin (5808 units) has been investigated by Kanikkannan et al.[30] However, basal rates of insulin needed by diabetics is 0.5– 1 mg/day and even this low basal drug input exceeds the theoretical flux predicted for iontophoretically delivered monomeric insulin on a 10 cm^2 area.[31] Although the flux enhancement of ions during iontophoresis is due principally to the electrical potential gradient, secondary effects

such as convective solvent flow contribute also to flux enhancement of peptide delivery. This effect is dependent of physicochemical conditions of formulation.

Sonophoresis

Ultrasound has been used since the 70's to enhance penetration through the skin, and in the mid 1990's, extensive research was conducted to find attractive alternative delivery systems to injections and oral Medications.

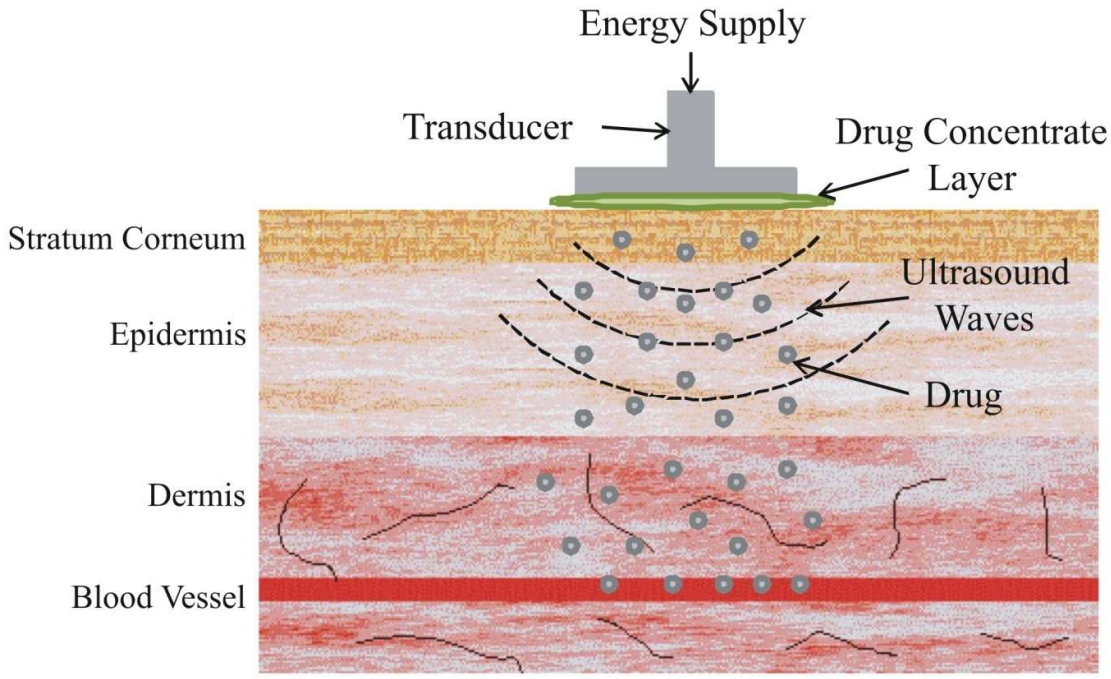

Fig-4: Sonophoresis

A number of these studies focused on facilitating transdermal permeability of various medicinal substances (e.g., insulin) by low frequency (20-25Khz) sonophoresis (LFS). During clinical evaluation of the effectiveness of sonophoresis, experiments demonstrated that a significant fraction (~30%) of the intercellular lipids of the stratum corneum, were displaced or removed during the application of low-frequency sonophoresis, increasing the skins permeability by up to 800%. It was this initial research that provided the data for the sonic frequency, safe power output levels and the design of the sonicator heads to develop the devices currently used. It is the method to move drugs across the skin barrier where skin is made permeable under influence of ultrasonic waves. The technique has been used frequently for over half a century, e.g. with hydrocortisone in combination with physical therapy of joint-related complications (arthritis).[32]

Traditionally, frequencies above 1 MHz have been used in order to reach and simultaneously stimulate tissues (joints and muscles) below the skin. However, during the past decade a considerable amount of research has been directed

towards low-frequency sonophoresis (<100 kHz) shown to interact with the superficial skin tissue and increasing transdermal transport by orders of magnitude.[33,34]

Thermal, chemical and mechanical alterations in the skin are considered to be the main transport enhancing mechanism in sonophoresis. For low-frequency sonophoresis, the formation and collapse of bubbles within the cells (cavitation) causes disruption of the skin tissue and is believed to be the predominant effect by which the method works.[35] Administration of many different drugs, e.g. insulin, low-molecular weight heparin, and vaccine, have been demonstrated feasible with low-frequency sonophoresis[33]. Typical acoustic intensities range from 0.25–1 W/cm^2.

In 2004, Sontra Medical Corp. (a spin off from R. Langer's lab at MIT) received FDA approval for the first sonophoretic transdermal delivery system. The system, SonoPrep®, is aimed for lidocaine administration (pain relief) and consists of a portable base unit connected to an ultrasonic horn that is pressed onto the area of skin to be treated.[36]

Yuh et al. has performed the study of determination of the delivery of systemic liposomal doxorubicin to tumors treated with pulsed high-intensity focused ultrasound in a murine model which has focused that doxorubicin concentration in the tumors was significantly higher than those were not treated with high intensity focused ultrasound. This study has shown the potential of the pulsed high-intensity focused ultrasound as an effective method of targeting systemic drug delivery to tumor tissue.[37]

Low-frequency ultrasound was shown to increase the permeability of human skin to many drugs, including high molecular weight proteins, by several orders of magnitude, thus making transdermal administration of these molecules potentially feasible. It was possible to deliver and control therapeutic doses of proteins such as insulin, interferon gamma, and erythropoeitin across human skin.

Ultrasound-mediated gene transfer technique has been used to produce growth factor like vascular endothelial growth factor (VEGF)[38,39], and also macromolecules delivery like ß-galactosidase[40], neuroepithelial transforming protein 1 (NET-1) siRNAs[41], angiopoietin (Ang)-1[39], microRNA (miRNA)[42], β-adrenergic receptor kinase (βARKct) gene[43], plasmid DNA encoding human neprilysin (hNEP)[44], anti-angiogenic genes, endostatin or calreticulin[45], Smad7 gene for type-2 diabetes[46], pBDNF-EGFP[47], DNA plasmids encoding for Gaussia luciferase, β-galactosidase[48,49], miR-21-knockdown plasmid[50], cell transfection with plasmid vector pEGFP-N3[51],

chemokine stromal cell-derived factor-1 (SDF-1)[52], and also for delivery to the nervous system like dorsal root ganglion[53] to transfect neuronal cells, muscle, cardiac cells, solid tumours, liver, kidney and for transdermal delivery.[38_-51]

Ultrasound is easily approved for clinical use (delivery of chemotherapeutic, thrombolytic and gene-based drugs) because of the low energy delivered and because it is non-invasive. Ultrasound has other advantages: it has good penetration through soft tissue, does not damage cells or tissues (at appropriate intensities), and does not affect DNA integrity. One limitation of this technique is that it can cause the breakdown of the cytoskeleton, thus altering, among other mechanisms, the DNA trafficking inside the cells.[54]

Ultrasound application is a mechanical way to permeabilize cells, to be compared with electroporation, an electrical way to cause cell permeabilization. Combination of sonoporation with the application of an electric field called electrosonoporation. Greater efficiency was achieved when electrical pulses were applied in the middle of the ultrasound wave delivery. Low-frequency ultrasound is thus a potential noninvasive substitute for traditional methods of drug delivery, such as injections.

Microneedles

In recent years, attention has been drawn to a new type of delivery method where arrays of miniaturized needles are used to penetrate the skin layer. Since the needles are short, they do not reach the nerve-rich regions of the lower parts of the skin. As a consequence, the stimulus caused by microneedle insertion into the skin is weak and perceived as painless[55,56] A microneedle is a needle with representative parts (e.g. diameter, length) on the micron scale. However, this definition is rather bold as it includes most of the standard hypodermic needles used in medical practice. Microneedles are significantly smaller than ordinary needles, especially concerning the length. They have length of the needle shorter than 1 mm. Microneedle for the transdermal transportation of the active molecules is the newer concept stated as the THIRD GENERATION CONCEPT. This third generation concept includes thermal ablation, microdermabration etc.[9] By combining microneedles with a patch-like structure, a system can be realized which essentially has all the favourable properties of a traditional transdermal patch, i.e. continuous release, ease-of-use, unobtrusiveness and painlessness.[57]

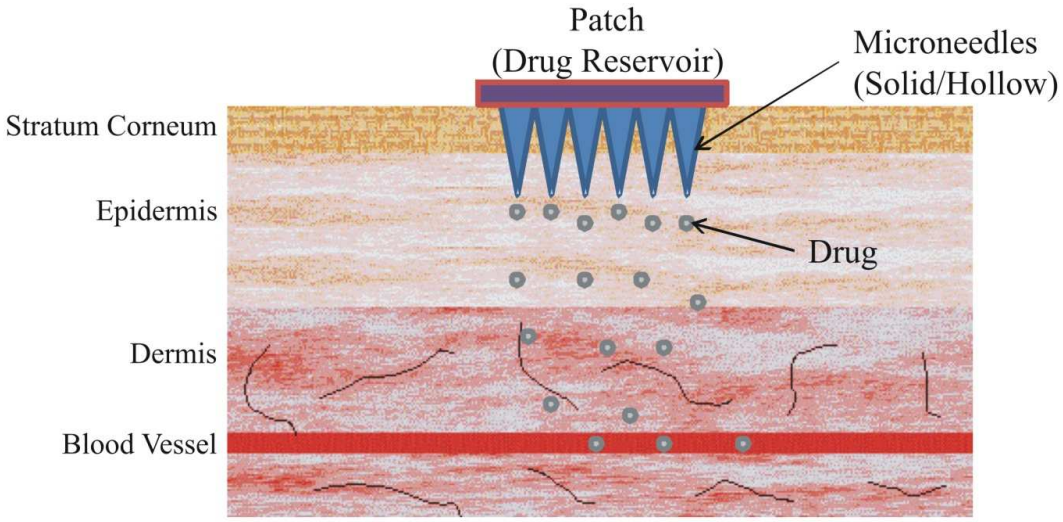

Fig-5: Microneedle

To insert microneedle arrays with a large number of needles into the skin without using a special insertion tool (e.g. a high-velocity plunger), the insertion force needed to pierce the tissue has to be minimized. To increase the permeability of the stratum corneum, it must be penetrated with very short needles as the easiest way. From many decades, microneedles are developed and used to inject the drugs into the skin in a minimally invasive manner within the epidermal layer where the drug delivered can diffuse in systemic circulation very easily.[58,59]

Microneedles: Types and Its Applications

A classification for microneedles usually used in literature is based on the fabrication process: in-plane or out-of-plane microneedles. In-plane microneedles are fabricated with the shaft being parallel to substrate surface. The advantage of this arrangement is that the length of the needle can be very accurately controlled. A disadvantage is that it is difficult to fabricate two-dimensional arrays. Out-of-plane microneedles on the other hand, protrude from the substrate and are straightforward to fabricate in arrays.[60] The extremely slender needles were used as electrical electrodes and designed to stimulate the visual cortex of the brain in order to regain sight. Related to this application, in-plane, microneedle probes have been used for activity recording and cellular chemostimuli of brain tissue.[61, 62] Solid, out of plane, microneedles have been used to penetrate the stratum corneum to facilitate EEG (Electroencephalogram) measurements for anaesthesia monitoring.[63]

Microneedles have been used in many other different applications, ranging from neurostimulation to gene delivery into individual cells. A common goal is to create a pathway to an object by physically circumventing some kind of

barrier. In most applications this barrier is the skin. The rationale of using microneedles, as opposed to macro-scale devices, is motivated either by the size of the target or the benefit of piercing in a minimally invasive manner.

The concept of an array of miniaturized needles for drug delivery purposes essentially dates back to 1976. Although the concept of miniaturized needles for drug delivery was presented earlier, it was not until the 1990s that the technique was tested experimentally. A reason for this was microfabrication techniques which were under development at that time, enabled these micrometer-sized needles to be precisely fabricated in a potentially cost-effective manner. The first reported study on microneedles for transdermal drug delivery came in 1998.[64]

Given the governing goal to deliver a substance across the skin for subsequent systemic distribution, by the means of microneedles, several possible strategies can be employed to accomplish this. The simplest way, is to perforate the skin with microneedles and then apply the drug onto the skin for subsequent diffusive spread into the body. The drug can be applied to the skin surface as a gel or through a medicated patch to achieve prolonged release. Another way is to precoat the microneedles with the drug before they are inserted into the skin. A third option is to fabricate the microneedles in a biodegradable material that incorporates the drug. When the needles are inserted into the skin, the needles dissolve and the drug is subsequently released.

If the microneedles are hollow, the drug can be actively injected into the tissue. Hollow needles can also be used with passive, diffusion-driven, delivery. In that case, the needles merely functions as controlled and sustained paths (channels) into the body. For moderately sized microneedle arrays, it is difficult to embed more than 1 mg. This may be sufficient for certain highly potent drugs (e.g. vaccines). Higher delivery rates can be achieved with hollow microneedles.

To maximize the delivery rate, a rational strategy for all the mentioned methods is to distribute the delivery over several microneedles. That is, by using an array of needles over a larger skin area, it exposes a larger area of the drug which promotes further diffusion to the capillaries. In-plane microneedles are difficult to fabricate in two-dimensional arrays and are therefore less suited for general drug delivery applications.

As per the another classification microneedles have mainly 3 types; solid, solid with drug coated on outside of needles and hollow to facilitate fluidic transport through needles and into lower epidermis. Solid microneedles penetrate the skin to increase skin permeability for a variety of small molecules, proteins and nanoparticles and other macromolecules from an extended-release patch. Alternatively, drug formulations have been coated on or

encapsulated within microneedles for rapid or controlled release of peptides and vaccines in the skin. Hollow microneedles have been used to deliver insulin and vaccines by infusion.[65]

Microneedles may be coated with the compound to be delivered including small molecules, proteins, DNA, and virus particles.[65,66] Microneedles have been made up of water-soluble polymers that encapsulate various compounds within the needle matrix.[67] These microneedles dissolve in the skin over a timescale of minutes and thereby leave no sharp medical waste after use.

Advancements

Many advances are reported in the delivery to humans using microneedles. Wermeling and his colleagues have studied the delivery of active molecule, naltrexone. Naltrexone was administered to healthy volunteers by penetration of skin with microneedles. After applying a microneedle patch, blood levels of naltrexone reached the therapeutic range. Transdermal delivery without microneedle have showed the level of naltrexone below detection.[68]

Transdermal delivery by microneedles offers new direction to improve vaccine administration. These microneedles increase skin permeability to drugs and particles.[69,70] Invivo experiments of animal studies show the delivery of macromolecules like insulin, [71,72] oligonucleotides, inactive viruses(like anthrax vaccines), DNA[73], human growth hormone[74], etc. Microneedle patches were reported to be painless by the volunteers and was generally well tolerated. Other studies have showed the effective delivery of parathyroid hormone from coated microneedles, which have advanced from animal studies through clinical trials.[9] Animal studies have showed delivery of live attenuated virus, inactivated virus, protein sub-unit, and DNA vaccines against influenza, hepatitis B, yellow fever, Japanese encephalitis and anthrax using microneedles.[75] The administration of influenza vaccine by the microneedles is about to complete in phase-3 clinical trials and filing for registration in Europe by Sanofi Pasteur (Paris) and Becton Dickinson (Franklin Lakes, NJ, USA) for their microneedle-based influenza vaccine.

Vaccine delivery by the route of the skin is targeting the potent epidermal Langerhans and dermal dendritic cells that can produce a strong immune response at very low doses than deeper injection.[76] The smallpox vaccine was administered via the skin with the help of a small needle device to cross the stratum corneum barrier. This administration has not provided good control over delivery yet it was effective. This delivery has opened the doors for the development of new delivery systems.[77] The scenario of today's world is that where at least 1.3 million

people were killed by the reuse of needles used for the vaccine delivery per year from hepatitis B and AIDS[78]. So the new delivery technique can improve this scenario because of being the needle free and once only use. Since usage of patch is very easy, any patient can use it and it gives more compliance to patients. The immune response can also be increased by employing chemical adjuvant.[77]

The sMTS (Solid Microstructured Transdermal System) technology has been tested with a range of antigens and has shown to produce an equivalent immune response to intramuscular injection with up to a 10-fold reduction in dose. 3M's sMTS system has the ability to deliver a range of biopharmaceuticals and vaccines, systemically or intradermally. sMTS enhances the efficacy of vaccines by targeting the antigen to key antigenpresenting cells (APC) within the skin, thereby improving delivery efficiency and reducing dose requirements. sMTS arrays of 3M are optimized for the depth of penetration into the skin and simplified systems of application required for placement of the arrays.[79]

Major investments for transdermal vaccine patch are made and a number of academic and industrial laboratories engaging in this field of research are continuously increasing.

Skin Ablation

The outermost layer of the skin, the main physical barrier of the skin, consists of dead keratinized cells. A straightforward approach to increase transdermal transport is therefore to simply remove this layer or make pores to cross that keratinized layer. A common approach among dermatologists and other professionals working with the skin is to use adhesive tape to remove or weaken the layer.[80] As an example, it has been determined that a doubling of the TEWL (Trans-Epidermal Water Loss), a measure of the skin permeability, occurs after approximately eleven successive tape strips with standard surgical tape.[81]

Other techniques to remove the outermost skin layer include microjets of particles that cut through the layer and thermal ablation methods making micro-conduits by burning away small micrometer-sized areas.[82] Since ablation only occurs on the superficial layer of the skin, these methods are reported to be painless. Of the thermal methods, different strategies are used to facilitate ablation, e.g. pulsed laser, arc discharge or short-duration resistive heating.[83]

Prausnitz and their colleagues have shown that heating at very high temperature for very short time has marked effect on skin permeability. Experiments were performed on porcine skin. Increase in permeability of the skin is not

dependant upon duration of heating which was shown in this experiment. Increment of permeability was upto 760 folds depending upon temperature and nature of molecule (eg. lipophilic). Reason for this increment was due to lipid melting in stratum corneum layer.[84] The study has suggested that the mechanism may involve decomposition and vaporization of the stratum corneum, which removes tissue to generate micron-scale holes. Where as iontophoresis and ultrasonic enhancement of transdermal transports, which each involve structural rearrangements of stratum corneum on the molecular or nanometer scale.[10] It also differs from microneedles, which similarly make micron-scale holes in the skin. [64]

This short duration resistive heating technique is commercialized by Altea Therapeutics Corp. Their Passport patch system resembles a classical transdermal patch but has integrated heater elements that are in contact with the skin. A separate handheld "applicator" activates the delivery by inducing a current into the patch's heaters. The company is developing the system for analgesics, insulin and vaccines alike the other transdermal methods mentioned.[83]

The other method for transdermal penetration enhancement is Laser ablation. Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. [Figure-6] As an evidence, Kalia et al. have shown the effect of laser as a skin penetration enhancer for delivery of diclofenac across the skin. P.L.E.A.S.E.® technology(Painless Laser Epidermal System) has been used to create micron size pores in skin to facilitate transport of the drug. This experiment has shown the significant increase in permeation of the drug with use of P.L.E.A.S.E.® technology.[85] Stratum corneum ablation with low intensity Er:YAG laser (light emission at 2940 nm) increased the permeability of both lipophilic and hydrophilic drugs through nude mouse skin in-vitro.[86] Penetration enhancement of the transdermal delivery of three narcotic drugs, including morphine, nalbuphine, and buprenorphine, with an erbium:yttrium-aluminum-garnet (Er:YAG) laser pretreatment has shown by Lee et al. [87]

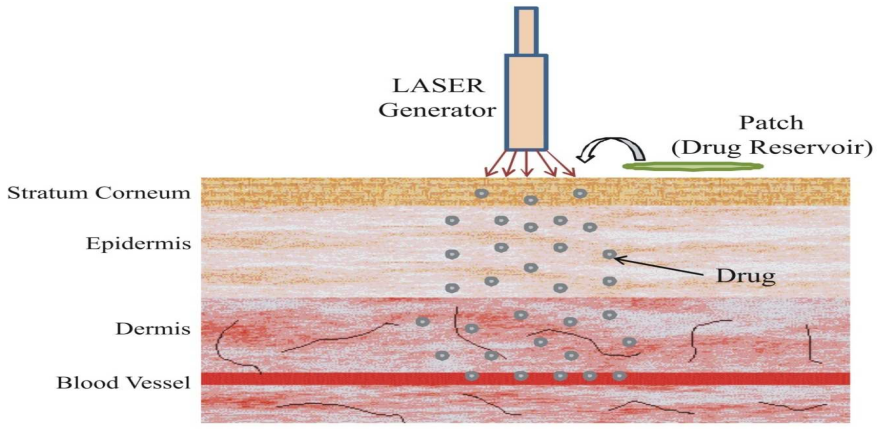

Fig-6: Skin Ablation by employing LASER

This laser assisted Transdermal delivery enhances not only low molecular weight molecule delivery but also macromolecules. There are numbers of studies performed for the evidence of macromolecule delivery across the skin with use of laser ablation. 5-aminolevulinic acid (ALA) permeation enhancement has been shown with two laser sources i.e. Er:YAG laser (Key III Plus KaVo) and a Q-switched neodymium(Nd):YAG laser (Lotis TII SL-2132) on Pinna skin of the inner side of rabbit ear by Gomez et al.[88] Laser ablation of stratum corneum (SC) enhances transdermal delivery of hydrophilic drugs. The influence of the infrared (IR) (lambda = 1,064 nm), visible (lambda = 532 nm), and ultraviolet (UV) (lambda = 355 nm) radiations of a Nd:YAG laser on transdermal delivery of 5-Fluorouracil (5-Fu) across skin was studied in vitro and has shown enhanced and controlled delivery of the drug.[89]

The laser-assisted delivery of Antithymocyte globulin (ATG) and Basiliximab has been investigated by Yu et al. In vitro delivery experiments were performed using dermatomed porcine ear and human abdominal skins. Er:YAG fractional laser ablation has used to facilitate the penetration of ATG and basiliximab. In the experiment, ATG concentration achieved in the laser-porated human skin was in the therapeutic range for providing local immunosuppression.[90] Hsiao et al. have shown the penetrability of vitamin C and its derivatives with two types of lasers viz. Er:YAG and CO(2) on balb/c nude mouce. They have shown greater penetration of vit-C and its derivatives from laser treated skin than that of untreated normal skin.[91] In the same way Fang et al. have shown increment of Fluorescein isothiocyanate (FITC)-labeled dextran (FD) (77kDa) penetration across the skin by Er:YAG laser. [92] Insulin was also studied for skin penetration by the laser ablation. Q-switched ruby laser was used for the skin poration in a streptozotocin-diabetic rat model. Decreased blood glucose level by around 80% has given evidence of significant penetration of insulin across the skin.[93] Mid-infrared laser ablation by erbium:yttrium scandium gallium garnet laser (lambda = 2.79 microns; 250 microseconds pulse width) of pig stratum corneum enhanced the permeation of both hydrocortisone and gamma-interferon.[94] Bioavailability and bioactivity of human growth hormone (hGH) delivered transdermally through microchannels (MCs) in the skin created by radio-frequency (RF) ablation on rat or guinea pig (GP) skin have been evaluated by Levin and his colleagues. The study has shown increment of 75% (rats) or 33% (Guinea Pigs) bioavailability relative to subcutaneous (s.c.).[95]

These studies have provided the evidences for the delivery of macromolecules across the skin using laser poration technique. However, the structural changes caused by this technique are still needed to be assessed for safety and reversibility where evidence of deeper level ablation effects exists.

For more than 50 years, proteolytic enzymes have been extensively used in laboratory settings for the purposes of in vitro epidermal separation and keratinocyte isolation. Previous therapeutic applications for topically applied proteases have been limited to wound debridement. But this study has given the extension of the proteolytic enzymes to skin ablation. Proteases such as subtilisin, trypsin, and dispase have been studied for the skin ablation and shown effective ablation of the hairless mouse and human skin.[96] This approach can be used for the transdermal drug delivery. But it is essential requirement that drug has no evidential stability problem with these enzymes.

Conclusion

The scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for increasingly widespread impact on medicine. Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs; the pain and inconvenience of injections; and the limited controlled release options of both.

References

1. Chong S, Fung HL. Transdermal drug delivery systems, pharmacokinetics, clinical efficacy, and tolerance development. In: Hadgraft J, Guy RH, editors. Transdermal Drug Delivery, Developmental Issues and Research Initiatives. New York: Marcel Dekker; 1989. p. 135.
2. Audet MC, Moreau M, Koltun WD, Waldbaum AS, Shangold G, Fisher AC, et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs. an oral contraceptive, a randomized controlled trial. JAMA 2001;285(18):2347-54.
3. Haut RC, Biomechanics of soft tissue. 2nd ed. New York: Springer; 2002. ch. 11, p. 228–53.
4. Reihsner R, Balogh B, Menzel EJ. Two-dimensional elastic properties of human skin in terms of an incremental model at the in vivo configuration. Med Eng Phys 1995; 17:304–13.

5. Scheuplein RJ. Mechanism of percutaneous absorption. II. Transient diffusion and the relative importance of various routes of skin penetration. J. Invest Dermatol 1967; 48(1):79-88.
6. Anderson RL, Cassidy JM. Variation in physical dimensions and chemical composition of human stratum corneum. J. Invest Dermatol.1973;61(1):30-2.
7. Hadgraft J, Guy RH. Feasibility Assessment in Topical and Transdermal Delivery: Mathematical Models and In Vitro Studies. In: Hadgraft J, Guy RH, editors. Transdermal drug delivery, developmental issues and research iniatives. New York: Marcel Dekker Inc.; 2003. p. 1-22.
8. Nakamura K, Katagai K, Mori K, Higo N, Sato S, Yamamoto K. Transdermal administration of salmon calcitonin by pulse depolarization-iontophoresis in rats. Int J Pharm 2001;218:93-102.
9. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol 2008;26(11):1261–68.
10. Cross SE, Roberts MS. Physical enhancement of transdermal drug application: is delivery technology keeping up with phamaceutical development? Curr Drug Deliv 2004;1:81–92.
11. Figge FJH, Barnett DJ. Anatomic evaluation of a jet injection instrument designed to minimize pain and inconvenience of parenteral therapy. Am Practicioner 1948;3: 197-206.
12. Schneider U, Birnbacher R, Schober E. Painfulness of needle and jet injection in children with diabetes mellitus. Eur J Pediatr 1994;153(6):409-10.
13. Klein TM, Wolf ED, Wu R, Sanford JC. High-velocity microprojectiles for delivering nucleic acids into living cells. Nature 1987; 327:70-73.
14. Schramm J, Mitragotri S. Transdermal drug delivery by jet injectors, energetics of jet formation and penetration. Pharm Res 2002;19:1673-79.
15 Consoli A, Capani F, La Nava G, Nicolucci A, Prosperini GP, santeusanio G, et al. Administration of semisynthetic human insulin by a spray injector. Boll Soc Ital Biol Sper 1984;60(10):1859-62.
16 Stachowiak JC, von Muhlen MG, Li TH, Jalilian L, Parekh SH, Fletcher DA. Piezoelectric control of needle-free transdermal drug delivery. J Control Release 2007;124(1-2):88-97.
17 Hogan NC, Hemond BD, Wendell DM, Taberner AJ, Hunter IW. Delivery of active collagenase to skin using a lorentz-force actuated needle-free injector. Conf Proc IEEE Eng Med Biol Soc 2006;1:5611-6.

18 Dean HJ, Fuller D, Osorio JE. Powder and particle-mediated approaches for delivery of DNA and protein vaccines into the epidermis. Comp Immunol Microbiol Infect Dis 2003;26: 373-88.

19 Stachowiak JC, Li TH, Arora A, Mitragotri S, Fletcher DA. Dynamic control of needle-free jet injection. J Control Release 2009;135(2):104-12.

20 Agersø H, Møller-Pedersen J, Cappi S, Thomann P, Jesussek B, Senderovitz T. Pharmacokinetics and pharmacodynamics of a new formulation of recombinant human growth hormone administered by ZomaJet 2 Vision, a new needle-free device, compared to subcutaneous administration using a conventional syringe. J Clin Pharmacol 2002;42(11):1262-8.

21 Kerum G, Profozic M, Skrabalo G, Skrabalo Z. Blood glucose and free insulin levels after the administration of insulin by conventional syringe or jet injector in insulin treated type 2 diabetics. Horm Metab Res 1987;19:422-25.

22 Dixit N, Bali V, Baboota S, Ahuja A, Ali J. Iontophoresis - An Approach for Controlled Drug Delivery: A Review. Current Drug Delivery 2007;4:1-10.

23 Banga AK, Bose S, Ghosh TK. Iontophoresis and electroporation: comparisons and contrasts. Int J Pharm 1999;179(1):1-19.

24 Sung KC, Fang JY, Hu OYP. Delivery of nalbuphine and its prodrugs across skin by passive diffusion and iontophoresis. J Control Release 2000;67 (1):1-8.

25 Prausnitz MR. Do high-voltage pulses cause changes in skin structure? J Control Release 1996;40(3):321-26.

26 Merino V, López A, Hochstrasser D, Guy R H. Transdermal alniditan delivery by skin electroporation. J Control Release 1999;61(1-2):65-69.

27 Singh P, Anliker M, Smith G, Zavortimk D, Maibach H. Transdermal iontophoresis and solute penetration across excised human skin. J Pharm Sci 1995;84:1342-46.

28 Clifton VL, Crompton R, Smith R, Wright IM. Microvascular effects of CRH in human skin vary in relation to gender. J Clin Endocrinol Metab 2002;87:267-70.

29 Chiang CH, Shao CH, Chen JL. Effects of pH, electric current, and enzyme inhibitors on iontophoresis of delta sleep-inducing peptide. Drug Deliv Ind Pharm 1998;24:431-38.

30 Kanikkannan N, Singh J, Ramarao P. Transdermal iontophoretic delivery of bovine insulin and monomeric human insulin analogue. J Cont Rel 1999;59(1):99–105.

31 Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. Adv Drug Deliv Rev 2004;56(5):619–658.

32 Martanto W, Davis SP, Holiday NR, Wang J, Gill HS, Prausnitz MR. Transdermal delivery of insulin using microneedles in vivo. Pharm Res 2004;21:947–52.

33 Mitragotri S, Kost J. Low-frequency sonophoresis, a review. Adv Drug Deliv Rev 2004;56(5):589–601.

34 Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. Science 1995;269(5225):850–53.

35 Naik A, Kalia YN, Guy RH. Transdermal drug delivery, overcoming the skin's barrier function. Pharm Sci Tech Today 2000;3(9):318–26.

36 Gupta J, Prausnitz MR. Recovery of Skin Barrier Properties after Sonication in Human Subjects. Ultrasound Med Biol 2009;35(8):1405–08.

37 Yuh EL, Shulman SG, Mehta SA, Xie J, Chen L, Frenkel V, et al. Delivery of systemic chemotherapeutic agent to tumors by using focused ultrasound: study in a murine model Radiology 2005;234(2):431–37.

38 Schratzberger P, Krainin JG, Schratzberger G, Silver M, Ma H, Kearney M, et al. Transcutaneous ultrasound augments naked DNA transfection of skeletal muscle. Mol Ther 2002;6(5):576-83.

39 Smith AH, Kuliszewski MA, Liao C, Rudenko D, Stewart DJ, Leong-Poi H. Sustained improvement in perfusion and flow reserve after temporally separated delivery of vascular endothelial growth factor and angiopoietin-1 plasmid deoxyribonucleic acid. J Am Coll Cardiol 2012;59(14):1320-8.

40 Chen JX, Ma Q, Wu H, Zhou A, Chen X, Peng YM, et al. Enhancing effect of ultrasound-mediated microbubble destruction ongene delivery into rat kidney via different administration routes. Asian Pac J Trop Med 2012;5(7):561-5.

41 Han X, Cheng W, Jing H, Zhang JW, Tang LL. Neuroepithelial Transforming Protein 1 Short Interfering RNA-MediatedGene Silencing With Microbubble and Ultrasound Exposure Inhibits the Proliferation of Hepatic Carcinoma Cells In Vitro. J Ultrasound Med 2012;31(6):853-61.

42 Chen ZY, Liang K, Qiu RX, Luo LP. Enhancing microRNA transfection to inhibit survivin gene expression and induce apoptosis: could it be mediated by a novel combination of sonoporation and polyethylenimine? Chin Med J (Engl) 2011;124(21):3592-4.

43 Katz MG, Fargnoli AS, Swain JD, Tomasulo CE, Ciccarelli M, Huang ZM, et al. AAV6-βARKct gene delivery mediated by molecular cardiac surgery with recirculating delivery (MCARD) in sheep results in robust geneexpression and increased adrenergic reserve. J Thorac Cardiovasc Surg 2012;143(3):720-726.e3.

44 Li Y, Wang J, Grebogi C, Foote M, Liu F. A syringe-focused ultrasound device for simultaneous injection of DNA and gene transfer. J Gene Med 2012;14(1):54-61.

45 Liao ZK, Tsai KC, Wang HT, Tseng SH, Deng WP, Chen WS, et al. Sonoporation-mediated anti-angiogenic gene transfer into muscle effectively regresses distant orthotopic tumors. Cancer Gene Ther 2012;19(3):171-80.

46 Ka SM, Yeh YC, Huang XR, Chao TK, Hung YJ, Yu CP, et al. Kidney-targeting Smad7 gene transfer inhibits renal TGF-β/MAD homologue (SMAD) and nuclear factor κB (NF-κB) signalling pathways, and improves diabetic nephropathy in mice. Diabetologia 2012;55(2):509-19.

47 Huang Q, Deng J, Wang F, Chen S, Liu Y, Wang Z, et al. Targeted gene delivery to the mouse brain by MRI-guided focusedultrasound-induced blood-brain barrier disruption. Exp Neurol 2012;233(1):350-6.

48 Kowalczuk L, Boudinet M, El Sanharawi M, Touchard E, Naud MC, Saïed A, et al. In vivo gene transfer into the ocular ciliary muscle mediated byultrasound and microbubbles. Ultrasound Med Biol 2011;37(11):1814-27.

49 Song S, Shen Z, Chen L, Brayman AA, Miao CH. Explorations of high-intensity therapeutic ultrasound and microbubble-mediated gene delivery in mouse liver. Gene Ther 2011;18(10):1006-14.

50 Zhong X, Chung AC, Chen HY, Meng XM, Lan HY. Smad3-mediated upregulation of miR-21 promotes renal fibrosis. J Am Soc Nephrol 2011;22(9):1668-81.

51 Paula DM, Valero-Lapchik VB, Paredes-Gamero EJ, Han SW. Therapeutic ultrasound promotes plasmid DNA uptake by clathrin-mediated endocytosis. J Gene Med 2011;13(7-8):392-401.

52 Kuliszewski MA, Kobulnik J, Lindner JR, Stewart DJ, Leong-Poi H. Vascular gene transfer of SDF-1 promotes endothelial progenitor cell engraftment and enhances angiogenesis in ischemic muscle. Mol Ther 2011;19(5):895-902.

53 Lin CR, Chen KH, Yang CH, Cheng JT, Sheen-Chen SM, Wu CH, et al. Sonoporation-mediated gene transfer into adult rat dorsal root ganglion cells. J Biomed Sci 2010;17:44.

54 Skorpíková J, Dolníková M, Hrazdira I, Janisch R. Changes in microtubules and microfilaments due to a combined effect of ultrasound and cytostatics in HeLa cells. Folia Biol (Praha) 2001;47(4):143-7.

55 Kaushik S, Hord AH, Denson DD, McAllister DV, Smitra S, Allen MG, et al. Lack of pain associated with microfabricated microneedles. Anesth. Analg 2001;92:502–4.

56 Sivamani RK, Stoeber B, Wu GC, Zhai H, Liepmann D, Maibach H. Clinical microneedle injection of methyl nicotinate: stratum corneum penetration. Skin Res Tech 2005;11(11):152–56.

57 Wang PM, Cornwell M, Hill J, Prausnitz MR. Precise Microinjection into Skin Using Hollow Microneedles. Journal of Investigative Dermatology 2006;126:1080-87.

58 Sulli N, Shashaj B. Long-term benefits of continuous subcutaneous insulin infusion in children with Type 1 diabetes: a 4-year follow-up. Diabetic Medicine 2006; 23(8):900–6.

59 Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov 2004;3:115–24.

60 Campbell PK, Jones KE, Huber RJ, Horch KW, Normann RA. A silicon-based, three-dimensional neural interface: manufacturing processes for an intracortical electrode array. IEEE Trans Biomed Eng 1991;38(8):758–68.

61 BeMent SL, Wise KD, Anderson DJ, Najafi K, Drake KL. Solidstate electrodes for multichannel multiplexed intracortical neuronal recording. IEEE Trans Biomed Eng 1986;33(2):230–41.

62 Bledsoe SC. A multichannel neural probe for selective chemical delivery at the cellular level. IEEE Trans Biomed Eng 1997;44(8):760–69.

63 Griss P, Enoksson P, Tolvanen-Laakso H, Merilainen P, Ollmar S, Stemme G. Micromachined electrodes for biopotential measurements. IEEE ASME J Microelectromech Syst 2001;10(1):10–16.

64 Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel method to increase transdermal drug delivery. J of Pharmaceutical Sci 1998;87:922–25.

65 Prausnitz MR. Microneedles for transdermal drug delivery. Advanced Drug Delivery Reviews 2004;56:581–87.

66 Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. J Contr Rel 2007;117(2):227–37.

67 Lee JW, Park JH, Prausnitz MR. Dissolving microneedles for transdermal drug delivery. Biomaterials 2008;29:2113–2124.

68 Wermeling DP, Banks SL, Hudson DA, Gill HS, Gupta J, Prausnitz MR, et al. Microneedles permit transdermal delivery of a skin-impermeant medication to humans. Proc Natl Acad Sci U S A 2008;105(6):2058-63.

69 McAllister DV, Wang PM, Davis SP, Park JH, Canatella PJ, Allen MG, et al. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: Fabrication methods and transport studies. Proc Natl Acad Sci USA 2003;100(24):13755–60.

70 Chabri F, Bouris K, Jones T, Barrow D, Hann A, Allender C, et al. Microfabricated silicon microneedles for nonviral cutaneous gene delivery. Br J Dermat 2004;150(5):869–77.

71 Migalska K, Morrow DI, Garland MJ, Thakur R, Woolfson AD, Donnelly RF. Laser-engineered dissolving microneedle arrays for transdermal macromolecular drug delivery. Pharm Res 2011;28(8):1919-30.

72 Roxhed N, Samel B, Nordquist L, Griss P, Stemme G. Painless drug delivery through microneedle-based transdermal patches featuring active infusion. IEEE Trans Biomed Eng 2008;55(3):1063-71.

73 van der Maaden K, Jiskoot W, Bouwstra J. Microneedle technologies for (trans)dermal drug and vaccine delivery. J Control Release 2012;161(2):645-55.

74 Lee JW, Choi SO, Felner EI, Prausnitz MR. Dissolving microneedle patch for transdermal delivery of human growth hormone. Small 2011;7(4):531-9.

75 Prausnitz MR, Mikszta JA, Cormier M, Andrianov AK. Microneedle-based vaccines. Curr Top Microbiol Immunol 2009;333:369–93.

76 Glenn GM, Kenney RT. Mass vaccination: solutions in the skin. Curr Top Microbiol Immunol 2006; 304:247–268.

77 Weniger BG, Papania MJ. Alternative vaccine delivery methods. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Amsterdam: Elsevier; 2008. p. 1357-92.

78 Miller MA, Pisani E. The cost on unsafe injections. Bull World Health Organ 1999;77:808–11.

79 Dubin CH. Proteins & Peptides: Dependent On Advances In Drug Delivery, Drug Delivery Technology 2009; 8(3).

(http://www.emisphere.com/pdfs/Drug_Dlvry_Tech-Protein-Peptide-3-09.pdf) (Accessed 1st july, 2012)

80 Bashir SJ, Chew AL, Anigbogu A, Dreher F, Maibach HI. Physical and physiological effects of stratum corneum tape stripping. Skin Res Technol 2001;7(1):40–48.

81 Dickel H, Bruckner TM, Erdmann SM, Fluhr JW, Frosch PJ, Grabbe J, et al. The ”strip” patch test: results of a multicentre study towards a standardization. Arch Dermatol Res 2004;296(5):212–19.

82 Dover JS, Hruza GJ, Arndt KA. Lasers in skin resurfacing, Semin Cutan Med Surg 2000;19(4):207–20.

83 Gadre AP, Nijdam AJ, Garra JA, Monica AH, Cheng MC, Luo C, et al. Fabrication of a fluid encapsulated dermal patch using multilayered SU-8. Sens Actuators A:Phys 2004;A114(2-3):478–85.

84 Park JH, Lee JW, Kim YC, Prausnitz MR. The effect of heat on skin permeability. International Journal of Pharmaceutics 2008;359:94–103.

85 Bachhav YC, Heinrich A, Kalia YN. Using laser microporation to improve transdermal delivery of diclofenac: Increasing bioavailability and the range of therapeutic applications. European Journal of Pharmaceutics and Biopharmaceutics 2011;78:408–14.

86 Lee S, Doukas AG. Laser-generated stress waves and their effects on the cell membrane. IEEE J Selected Topics Quantum Electron 1999;5:997–1003.

87 Lee WR, Shen SC, Fang CL, Liu CR, Fang JY. Skin pretreatment with an Er:YAG laser promotes the transdermal delivery of three narcotic analgesics. Lasers Med Sci 2007;22(4):271-8.

88 Gómez C, Costela Á, García-Moreno I, Llanes F, Teijón JM, Blanco MD. Skin laser treatments enhancing transdermal delivery of ALA. J Pharm Sci 2011;100(1):223-31.

89 Gómez C, Costela A, García-Moreno I, Llanes F, Teijón JM, Blanco D. Laser treatments on skin enhancing and controlling transdermal delivery of 5-fluorouracil. Lasers Surg Med 2008;40(1):6-12.

90 Yu J, Kalaria DR, Kalia YN. Erbium:YAG fractional laser ablation for the percutaneous delivery of intact functional therapeutic antibodies. J Control Release 2011;156(1):53-9.

91 Hsiao CY, Huang CH, Hu S, Ko YS, Sung HC, Huang SY. Skin pretreatment with lasers promotes the transdermal delivery of vitamin C derivatives. Lasers Med Sci 2011;26(3):369-76.

92 Fang JY, Lee WR, Shen SC, Wang HY, Fang CL, Hu CH. Transdermal delivery of macromolecules by erbium:YAG laser. J Control Release 2004;100(1):75-85.

93 Lee S, McAuliffe DJ, Mulholland SE, Doukas AG. Photomechanical transdermal delivery of insulin in vivo. Lasers Surg Med 2001;28(3):282-5.

94 Nelson JS, McCullough JL, Glenn TC, Wright WH, Liaw LH, Jacques SL. Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. J Invest Dermatol 1991;97(5):874-9.

95 Levin G, Gershonowitz A, Sacks H, Stern M, Sherman A, Rudaev S, et al. Transdermal delivery of human growth hormone through RF-microchannels. Pharm Res 2005;22(4):550-5.

96 Fein H, Maytin EV, Mutasim DF, Bailin PL. Topical protease therapy as a novel method of epidermal ablation: preliminary report. Dermatol Surg 2005;31(2):139-47; discussion 147-148.

Corresponding Author:

Ukawala Ravikumar D*[1],

Email: *r.d.ukawala@gmail.com*