REVIEW ARTICLE ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

REVIEW ON PENETRATION ENHANCEMENT TECHNIQUES IN TRANSDERMAL DELIVERY SYSTEM

Thosar.Milind M.[1]*, S. S. Pancholi[1]

1. Department of Pharmaceutics, Babaria Institute of Pharmacy, Varnama, Vadodara. Gujarat.

ABSTRACT

Transdermal absorption of the drugs are controlled primarily by physiochemical property of stratum corneum.Intercellular lipid domain and lipoprotein gel offers major resistance to penetration of drugs through stratum corneum to deep into epidermis. Penetration enhancement techniques are designed to modify the physiochemical properties of stratum corneum and in some to deliver drugs by piercing the skin to bypass skin barrier. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which transdermal delivery is a viable option. Various chemical techniques like ion pairs, medical tattoos,prodrug administration, Inclusion of penetration enhancers, Metered dose transdermal spray etc. along with some physical method of transdermal delivery including Iontophoresis,Electro-osmosis,Ultrasound,laser radiation etc. are reviewed in this article.

Key words: Transdermal delivery, stratum corneum, penetration enhancement

*Corresponding Author Email: amthosar@gmail.com

Received 17 December 2011, Accepted 25 January 2012

Please cite this article in press as: Thosar MM *et al.*, Review on Penetration Enhancement Techniques in Transdermal Delivery System. American Journal of PharmTech Research 2012.

INTRODUCTION

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Since absorption of drugs to systemic circulation doesn't undergo first pass effect and unwanted effects associated with oral route are also avoided, transdermal delivery of drugs is increasingly preferred. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness,clonidine and nitroglycerin for cardiovascular disease,fentanyl for chronic pain, nicotine to aid smoking cessation,oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism.Transdermal products for cardiovascular disease, Parkinson's disease, Alzheimer's disease, depression, anxiety, attention deficit hyperactivity disorder (ADHD), skin cancer, female sexual disfunction,post-menopausal bone loss, and urinary incontinence are at various stages of formulation and clinical development. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is associated primarily with the outermost stratum corneum layer of the epidermis. Many drugs penetrate human skin poorly, and many efforts have attempted to optimize the intake of such drugs. The key factor is the ability to push small and large molecules through the skin faster. Lag time in transdermal administration is still of the order of 2-4 h for most drugs, and this may be unacceptable if immediate relief is desired. In another example, the flux requirements for a given drug are so high that very large patches are needed and consequently the daily dose of drug that can be delivered from a transdermal patch is 5-10 mg, effectively limiting this route of administration to potent drugs in these cases, advancement will occur through the invention/discovery of new enhancing methods. This review is detailed with penetration enhancement of drugs by chemical and physical method.[1]

Anatomy and Organization of Human Skin

Microscopically, the skin is a multilayered organ composed of many histological layers. It is generally subdivided into three layers: the epidermis, the dermis, and the hypodermis. The uppermost nonviable layer of the epidermis, the stratum corneum, has been demonstrated to constitute the principal barrier to percutaneous penetration. The excellent barrier properties of the stratum corneum can be ascribed to its unique structure and composition. The viable epidermis is situated beneath the stratum corneum and responsible for the generation of the stratum corneum. The dermis is directly adjacent to the epidermis and composed of a matrix of connective tissue, which renders the skin its elasticity and resistance to deformation. The blood

Table 1: Penetration enhancement techniques and their mechanism.

Method	Mechanism
Chemical	
Penetration enhancers	Reversible alteration of intercellular lipid package and
Prodrug administration	Increased partition coefficient
Chemical potential adjustment	Increased thermodynamic activity
Complex coacervates	increased lipophilicity of the coacervate oil phase can increase the transdermal flux of charged species
ion pairs	Increased partition to aqueous channels of viable Epidermis
Hydration	Hydration causes swelling and opens the structure of the stratum corneum leading to an increase in penetration
Co-administration of synthesis inhibitors in stratum corneum	Reversibly inhibits the formation of lipid content .
Modification of drug to lipophilic analog	increased partition coefficient
Delipidization	depleting lipid content of stratum corneum
Metered-Dose Transdermal Spray (MDTS)	simple diffusion
Medicated Tattoos	simple diffusion
liposomes and vesicles	Squeezes through channels in the stratum corneum
Physical	
Iontophoresis	Electrical repulsion leads partitioning of drugs
Photomechanical Waves	Alteration of intercellular lipid package.
Electroporation	Creates aqueous pores in lipid bilayers
Electro-Osmosis	Diffusion driven by voltage difference to drug reservoir
Controlled Heat Aided Drug Delivery (CHADD) System	Increased microcirculation of blood increases Permeability
Skin Abrasion	Ablation of stratum corneum reduces skin barrier
Powderject Device	Fires particles through skin into lower layers
Needle-Free Injections	Pushes the liquid formulation through a narrow orifice into the skin.
Ultrasound (sonophoresis,ultraphonophoresis)	Disruption of the stratum corneum lipids, thus allowing phonophoresis and the drug to pass through the skin
Laser radiation	Ablation of the stratum corneum
Magnetophoresis	Magnetic field repulsion increases permeation of Diamagnetic drugs
Micro needles array	Delivering large molecules across the stratum corneum
Macro flux	Formation of transient pores in sac.

vessels that are present in the dermis provide the skin with nutrients and oxygen. The hypodermis or subcutaneous fat tissue is the lowermost layer of the skin. It supports the dermis and epidermis and provides thermal isolation and mechanical protection of the body. The outer layer of the skin forms an effective barrier to retain water within the body and keep exogenous compounds out of the body. As a result, the major problem in dermal and transdermal drug deliveries is the low penetration of drug compounds through the stratum corneum. Dermal drug delivery comprises the topical application of drugs for the local treatment of skin diseases. It

requires the permeation of a drug through the outer skin layers to reach its site of action within the skin, with little or no systemic uptake. The application of drugs to the skin for systemic therapy is referred to as transdermal drug delivery. Hence, it is required that a pharmacologically potent drug reaches the dermis where it can be taken up by the systemic blood circulation. In either case, the drug has to cross the outermost layer of the skin, the stratum corneum.[2]

CHEMICAL METHOD:

Among the myriad strategies employed to increase both the amount of a therapeutic agent traversing the skin and the range of drugs that can be effectively delivered through this route, lies in the application of chemical penetration enhancers. These agents interact with stratum corneum constituents to promote drug flux. Such materials have been used empirically in topical and transdermal preparations for as long as pastes, poultices, creams, and ointments have been applied to skin, though it is only over the last four decades that enhancers have been employed deliberately for this specific purpose. Here, we review some applications of the more widely investigated chemical penetration enhancers and consider some of the complex mechanisms by which they may exert their activities. Accelerants operate in complex, interacting ways to change the intercellular region of the horny layer by fluidization, alteration of polarity, phase separation, or lipid extraction. More drastically, they may form vacuoles within corneocytes, denature their keratin or split Squames and Penetration of drug through skin is shown Figure 2& 3 respectively.

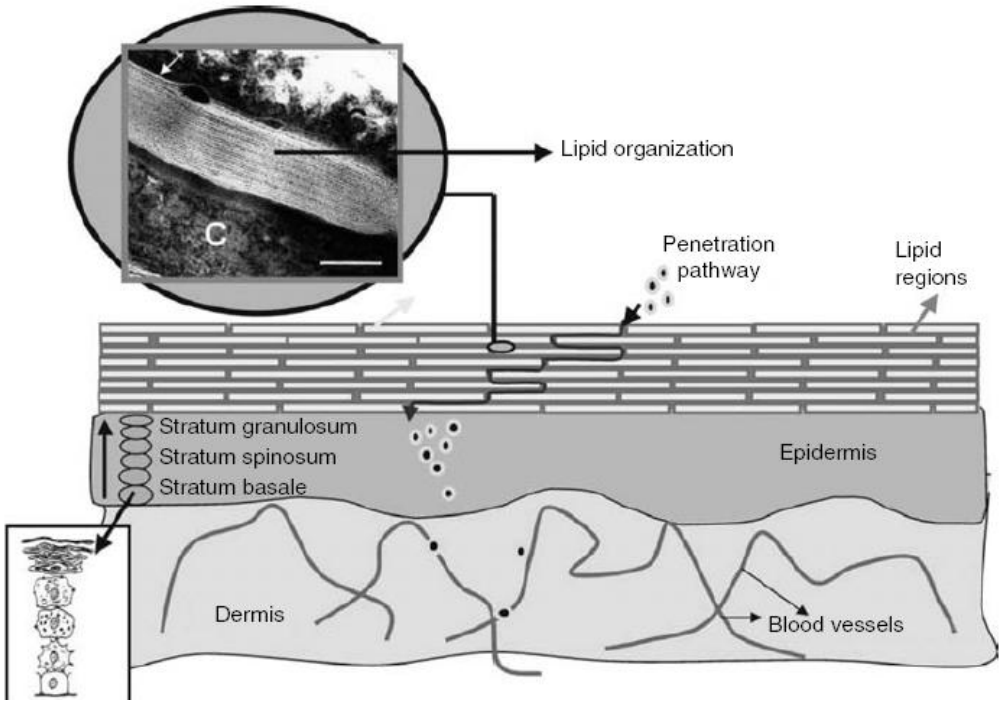

Figure 1. A schematic drawing of a skin crosses section.[2]

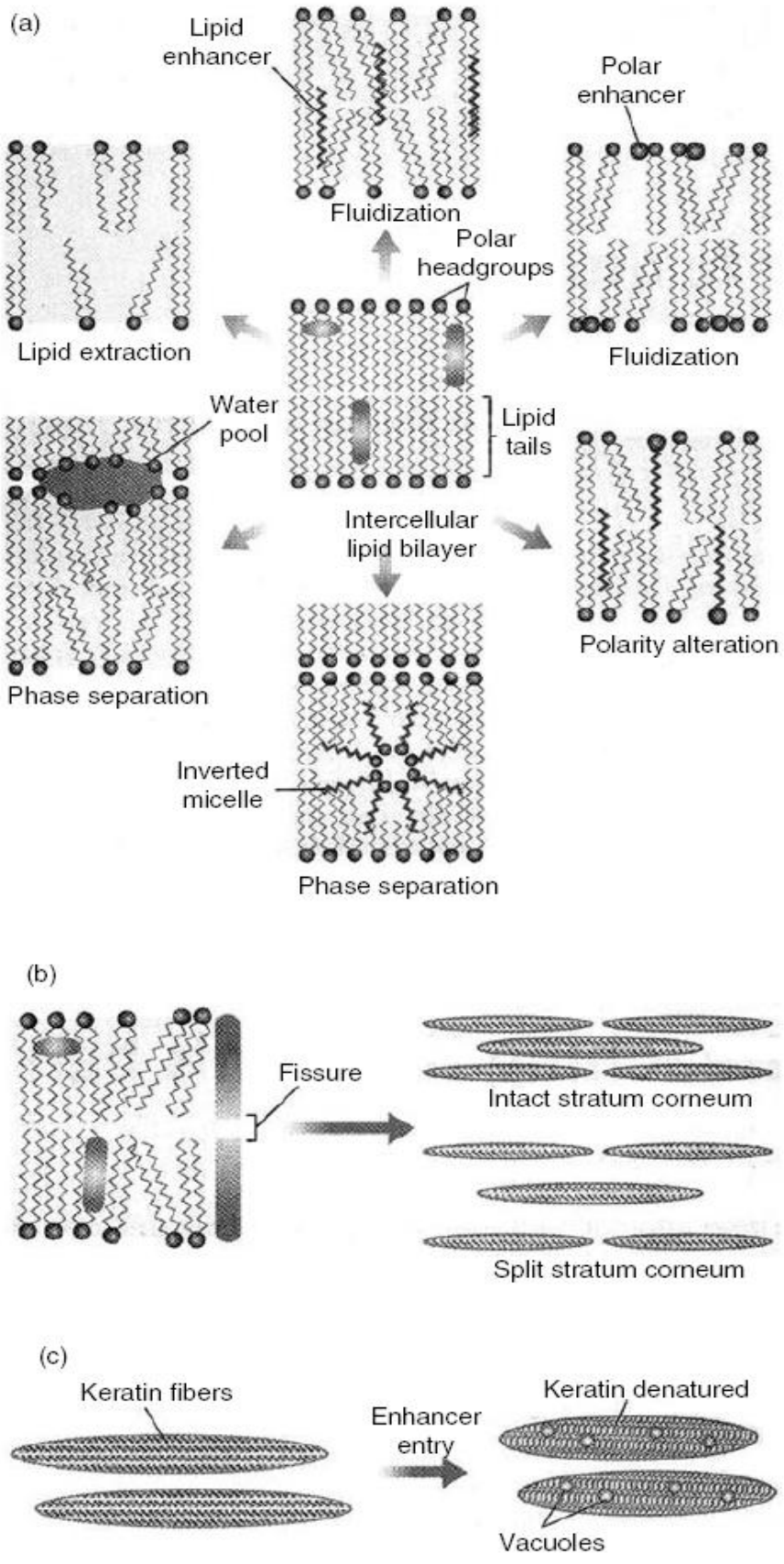

Figure 2 (a) Action at intercellular lipid (b) at protein structure (c) at corneocytes [2]

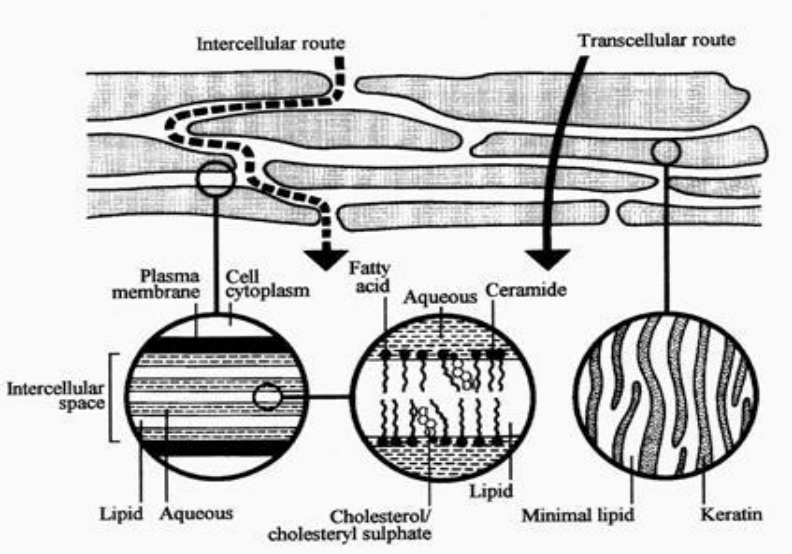

Figure 3: Intercellular and Tran cellular route of drug penetration[3]

Penetration Enhancers

These are Chemical Substances which temporarily diminish the impermeability of the skin. Such materials, known as accelerants or sorption promoters. These act by Disrupting organized intercellular lipid structure of the stratum corneum or interacting with the keratin in corneocytes to open dense keratin structure or altering the solubility of stratum corneum. These effects have been demonstrated using differential scanning calorimetry (DSC) to measure the phase transition temperature , electron spin resonance (ESR) studies, Fourier transform infrared (FTIR), Raman spectroscopy and x-ray diffractometry. These enhancer compounds consist of a polar head group with a long alkyl chain and are more effective for hydrophilic permeants, although increased delivery of lipophilic permeants has also been reported. Different types of penetration enhancers are water, sulphoxides, pyrrolidones, fatty acids and alcohols, azone and its derivatives, surfactants, urea and its derivatives, alcohols and glycols, essential oils, terpenes, synergistic mixtures, biodegradable enhancers, cyclodextrin etc.[1]

Prodrug Administration

Prodrug may be designed to obtain an optimal partition coefficient for entering the skin barrier. After absorption and diffusion to the viable tissues, enzymes convert the prodrug to the active species. Many steroids have designed in this way. The intrinsic poor Permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6-acyloxymethyl and 9-dialkylaminomethyl promoieties and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives . The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory

drugs, naltrexone, nalbuphine, buprenorphine, b-blockers and other drugs. Well established commercial preparations using this approach include steroid esters (e.g.betamethasone-17-valerate), which provide greater topical anti-inflammatory activity than the parent steroids.[1]

Chemical Potential Adjustment

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. This can be demonstrated based on rewritten in terms of thermodynamic activities.

$$dm/dt=\alpha D/\gamma h \qquad \text{Equation 1}$$

Where α is the thermodynamic activity of the permeants in its vehicle and γ is the effective activity coefficient in the membrane. This dependence on thermodynamic activity rather than concentration was elegantly demonstrated by Twist and Zatz. The diffusion through a silicone membrane of saturated solutions of parabenes in eleven different solvents was determined. Due to the different solubility of the parabenes in the various solvents, the concentration varied over two orders of magnitude. However, parabenes flux was the same from all solvents, as the thermodynamic activity remained constant because saturated conditions were maintained throughout the experiment. Supersaturated solutions can occur due to evaporation of solvent or by mixing of co solvents. These systems are inherently unstable and require the incorporation of antinucleating agents to improve stability.Magreb et al reported that the flux of oestradiol from an 18-times saturation system was increased 18-fold across human membrane but only 13-fold in silastic membrane. They suggested that the complex mixture of fatty acids, cholesterol, ceramides, etc. in the stratum corneum may provide an antinucleating effect thereby stabilizing the supersaturated system.[1]

Complex Coacervates

Complex coacervation is the separation of an aqueous mixture of oppositely charged ions into a dense coacervate oil phase, rich in ionic complex, and a dilute equilibrium phase. Coacervation was investigated by Paul W. Stott between cationic tricyclic antidepressants (amitriptyline, imipramine and doxepin) and counter-ions of anionic bile salts sodium cholate (NaC) and sodium deoxycholate (NaD), and the surfactant sodium lauryl sulfate (SLS). Systems were analyzed by microscopy, HPLC, Karl Fischer titration, thermo gravimetric analysis and particle size analysis. Two systems were selected to investigate the potential of this formulation for enhancing transdermal flux of charged species - amitriptyline (AMI) with NaD, which separates into two distinct phases, and AMI with SLS which remains as a sol. Octanol/vehicle partition

coefficients were determined and the AMI:NaD coacervate produced an 18-fold increase and AMI:SLS 22-fold compared with aqueous solution. The results indicate that the increased lipophilicity of the coacervate oil phase can increase the transdermal flux of charged species. [4]

Ion Pairs

In this technique a lipophilic ion pair is form by adding opposite charge to that of drug ion. Complex thus formed readily penetrates through lipid layer of skin to aqueous viable epidermis where it dissociates into charged Species. In general permeability increases of only two to three-fold have been obtained although Sarveiya *et al.* recently reported a 16-fold increase in the steady-state flux of ibuprofen ion pairs across a lipophilic membrane. The ion pair skin transport of cephalexin was investigated by Tomomi Hatanaka using various counter ions and solvents. The permeability of cephalexin was enhanced by 1-alkylsulfonates (ASs) at pH 3.0 and by tetra alkylammoniums (AAs) at pH 7.0; the enhancing ratio increased with the number of carbon atoms in their alkyl chains. The corresponding effects of these additives were observed on the partitioning of cephalexin. These results suggest that the enhanced transport of cephalexin results from the ion pair formation with additives. To obtain the maximum enhancement of skin transport of zwitterionic drugs via ion pair concept, one should select a counter ion having high lipophilicity and small volume, and a solvent with suitable pH and low dielectric constant.[5]

Hydration

Water is the most widely used and safest method to increase skin penetration of both hydrophilic and lipophilic permeants. The water content of the stratum corneum is around 15 to 20% of the dry weight. Additional water within the stratum corneum could alter permeant solubility and there by modify partitioning from the vehicle into the membrane. In addition, increased skin hydration may swell and open the structure of the stratum corneum leading to an increase in penetration, although this has yet to be demonstrated experimentally. For example, Scheuplein and Blank showed that the diffusion coefficients of alcohols in hydrated skin were ten times that observed in dry skin. Hydration can be increased by occlusion with plastic films; paraffins, oils, waxes as components of ointments and water-in-oil emulsions that prevent transepidermal water loss; and oil-in-water emulsions that donate water. Of these, occlusive films of plastic or oily vehicle have the most profound effect on hydration and penetration rate]. A commercial example of this is the use of an occlusive dressing to enhance skin penetration of lignocaine and prilocane from EMLA cream in order to provide sufficient local anesthesia within about 1 hour. Also drug delivery from many transdermal patches benefits from occlusion.[1]

Co-Administration of Synthesis Inhibitors

More interventionist approaches to drug delivery through human skin have also been proposed. Strategies that alter barrier homeostasis by interfering with any or all of the processes of synthesis, assembly, secretion, activation, processing, or assembling and disassembling of the extracellular lamellar membranes, could promote permeation.[2] synthesis inhibitor blocks temporarily the synthesis of ceramide, fatty material and cholesterol. This aspect is being increasingly investigated to increase the transdermal delivery of drugs that exhibit poor permeability across normal skin.fluvastatin increases the octanol/water partition coeffient of lidocaine hydrochloride by 50 times, the in vivo uptake increases only 2 fold.[8] Such an approach would pose significant regulatory problems, not least of which would be issues related to increased xenobiotic or microbial access. The concept of interfering with barrier homeostasis on a relatively long timescale poses many clinical considerations and objections.[2]

Modification of Drug to Lipophilic Analog

Many drugs are having more partition coefficient when they are administered in their free base form than their salt form. Due to their lipophilic nature they easily solubilise, diffuses deep into epidermis. Permeability of Poorly permeable drug molecule bupropion hydrochloride was increased by chemically modifying it to non polar lipophilic analog bupropion .[7]

Delipidization

Lipid content of stratum corneum may be decreased by solvent extraction. These solvent removes the lipid from the applied area temporarily and their by enhancing the partitioning of hydrophilic drugs. Lipid content is restored naturally. A study was carried to explore the effect of lipid extraction by the simple alkyl acetates of increasing carbon chain lengths (e.g. methyl, ethyl, propyl, butyl, pentyl, hexyl, and octyl acetates) and Iontophoresis on the in-vitro transport of leuprolide acetate through porcine epidermis. The extent of lipid extraction from the stratum corneum (SC) by alkyl acetates was studied by Fourier transform infrared (FT-IR) spectroscopy. Ethyl, propyl, pentyl, hexyl, and octyl acetates significantly increased ($P<0.05$) the permeability of leuprolide acetate through the epidermis in comparison to the control (epidermis without alkyl acetate treatment). Iontophoresis further increased ($P<0.05$) the permeability of leuprolide acetate for all the alkyl acetates studied, when compared to their corresponding passive permeability. Ethyl acetate produced the maximum passive (13.47 μg/cm^2/h) and Iontophoresis (89.79 μg/cm^2/h) flux among all the alkyl acetates studied. Chloroform: methanol (2:1) [C: M (2:1)] was used as a positive control for lipid extraction. Findings provided evidence that alkyl

acetates cause lipid extraction, which leads to an enhancement in the passive and Iontophoresis permeability of leuprolide acetate[8].

Metered-Dose Transdermal Spray (Mdts)

Metered-dose transdermal spray (MDTSTM), MDTS relies on the combination of a newly identified GRAS (generally recognized as safe) chemical penetration enhancer (Across TM) and the accurate and precise topical dosing of a volatile: nonvolatile vehicle. This MDTS can be classified, as an enhanced, passive TDDsystem. It is a topical solution made up of a volatile cum nonvolatile vehicle containing the drug dissolved as a single-phase solution. A finite metered - dose application of the formulation to intact skin results in subsequent evaporation of the volatile component of the vehicle, leaving the remaining nonvolatile penetration enhancer and drug to rapidly partition into the stratum corneum during the first minute after application, resulting in a stratum corneum reservoir of drug and enhancer. Following a once daily application of the MDTS, a sustained and enhanced penetration of the drug across the skin can be achieved from the stratum corneum reservoir. Different types of penetration enhancers, such as ethanol and azone, are commonly used. Clinical experience with estradiol-MDTS to post-menopausal women have shown increased higher plasma level ofestradiol than the baseline value measured by radioimmunoassay[9].

Medicated Tattoos

Med-Tats is a novel means of delivering compounds transdermally. Medicated Tattoo (Med-Tat) is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. Med–Tats are applied to clean, dry skin in the same manner as traditional temporary tattoos. There is no predetermined duration of therapy for Med–Tats; instead, 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. This visual comparison, which relies on the dyes incorporated into the patch, introduces a significant amount of interpatient variability. Drugs and other compounds used in Med-Tats prototypes include acetaminophen and vitamin C. The main advantage of medicated tattoos is the delivery of drugs to children who cannot tolerate more traditional dosage forms[9].

Liposomes and Vesicles

A variety of encapsulating systems have been evaluated including liposomes, deformable liposomes or transfersomes, ethosomes and niosomes.Liposomes are colloidal particles formed as concentric biomolecular layers that are capable of encapsulating drugs. Their potential for

delivering drugs to the skin was first reported by Mezei and Gulasekharam in 1980 who showed that the skin delivery of triamcinolone acetonide was four to five times greater from a liposomal lotion than an ointment containing the same drug concentration. Recent studies have tended to be focused on delivery of macromolecules such as interferon, gene delivery] and cutaneous vaccination, in some cases combining the liposomal delivery system with other physical enhancement techniques such as electroporation. Transfersomes are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant (such as sodium cholate) and 3-10% ethanol. The surfactant molecules act as "edge activators", conferring ultra deformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome. According to their inventors, where liposomes are too large to pass through pores of less than 50 nm in size, transfersomes up to 500 nm can squeeze through to penetrate the stratum corneum barrier spontaneously. They suggest that the driving force for penetration into the skin is the "transdermal gradient" caused by the difference in water content between the relatively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to 100%). Conventional liposomes remain near the skin surface, dehydrate and fuse, whilst deformable transfersomes penetrate via the pores in the stratum corneum and follow the hydration gradient. Extraordinary claims are made for the penetration enhancement ability of transfersomes, such as skin transport of 50-80% of the applied dose of transferosome-associated insulin. Other researchers who have evaluated transfersomes have also shown that ultra deformable liposomes are superior to rigid liposomes.For example, in a series of studies the skin penetration of estradiol was enhanced more by ultra deformable liposomal formulation (17-fold) than by traditional liposomes (9-fold). Ethosomes are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation. It is proposed that the alcohol fluidizes the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate. Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. This area continues to develop with further evaluation of current formulations and reports of other vesicle forming materials[1].

PHYSICAL METHOD

These methods involve utilization of newer machines which are designed to avoid Skin barrier for directly delivering the drug to viable epidermis by piercing skin or reversibly alteration of skin properties by electrical current. Most of these methods require medical supervision.

Iontophoresis

Iontophoresis may be defined as the facilitation of ionizable drug permeation across the skin by an applied electrical potential, the driving force of which may be simply visualized as electrostatic repulsion. A typical Iontophoresis device consists of a battery, microprocessor controller, drug reservoir and electrodes. The technique involves the application of a small electric current (usually 0.5 mA/cm2) to a drug reservoir on the skin, with the similarly charged electrodes (on the surface of the skin) placed together in the drug reservoir producing repulsion effect that effectively drives the solute molecules away from the electrode and into the skin. There are three explanations of how Iontophoresis increases transdermal drug delivery. The first, proposes that the drugs are forced across the skin by simple electronic repulsion of similar charges. Anionic drugs can cross the skin by using a negatively charged electrode. Similarly cationic drugs enter the skin more successfully when a positively charged electrode is used the second, explanation suggests that the electric current enhances permeation by inhibiting the skin's ability to perform its protective barrier function. The third, states that Iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum by electro-osmosis. Dissolved drugs can be carried across the skin along with the penetrating water during Iontophoresis. At physiological pH, human skin has slight negative charge; therefore, certain cationic drugs can more easily cross the skin during Iontophoresis due to reduced resistance. Several studies have addressed the application of Iontophoresis to the delivery of low molecular weight solutes (< 500 Da). For delivery of macromolecules, proteins and peptides such as calcitonin, corticotrophin-releasing hormone, dextrin sulphate, inulin, insulin, gonadotropin releasing hormone, growth hormone releasing factor, parathyroid hormone and vasopressin Iontophoresis may also be utilized. To date, clinical studies have been limited to smaller molecules such as lidocaine, ketorolac dexamethasone, etofenamate, naproxen, vincristine, cortisone and fentanyl[9].

Photomechanical Waves

Photomechanical waves (PW's) are the pressure pulses produced by ablation of a material target (polystyrene) by Q-switched or mode-locked lasers. Photochemical waves are able to render the

stratum corneum more permeable to macromolecules via a possible transient permeabilisation effect due to the formation of transient channels. The largest molecule that has been reported to be delivered through the rat skin to date has a molecular weight of40,000Da. 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[9].

Electroporation

This method involves the application of highvoltage pulses to the skin, which has been suggested to induce formation of transient pores. High voltages in the form of direct current [DC (100 volts)] caused by electrical pulses with short treatment durations (milliseconds) are most frequently employed. Other parameters that affect delivery include pulse properties such as wave form, rate and number. 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 possible processes such as diffusion and local elctrophoresis. The electrical resistance of the skin is reported to drop as much as three orders of magnitude within microseconds of administration of an electric pulse. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7KDa. Increase in transdermal penetration of up to 104 fold have been reported *in vitro* for various sizes of molecules such as metoprolol, lidocaine,tetracaine, vitamin C, timolol and fentanyl dyes, including calcein and methylene blue, and macromolecules up to 40 KDa including cyclosporine A, heparin, leutenising hormone releasing hormone, insulin, oligonucleotides and dextrans (MW 4.4 – 39 KDa) **[9].**

Electro-Osmosis

If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volume flow, called electro osmosis occurs without concentration gradients, suggesting that this flow is not diffusion. This bulk fluid flow by electro osmosis was found to be of the order of micro liters per hour per square centimeter of hairless mouse skin. The electro – osmotic flow occurs from anode to cathode, thus enhancing the flux of positively charged (cationic) drugs and making it possible to deliver neutral drugs[9].

Controlled Heat Aided Drug Delivery (Chadd) System

Heat increases skin temperature that leads to increase in microcirculation and blood vessel permeability, thus facilitating drug transfer to the systemic circulation. Drug solubility, both in the patch formulation and within the skin increase with a rise in temperature. Zars, lnc [Salt Lake City, UT, USA] has developed a technology that takes advantage of heat's ability to increase transdermal permeation. This technology is known as Controlled Heat-aided Drug Delivery (CHADD) system. CHADD system is a small heating unit that can be placed on top of a traditional patch. An oxidation reaction within the unit provides heat at a limited intensity and duration[9].

Skin Abrasion

The abrasion technique involves the direct removal or disruption of the upper layers of the Skin to facilitate the permeation of topically applied medicaments. Some of these devices Are based on techniques employed by dermatologists for superficial skin resurfacing (e.g., microdermabrasion) which are used in the treatment of acne, scars, hyper pigmentation and other skin blemishes. Microscissuining is a process which creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. *In vitro* data have shown that the application of the device can increase the penetration of angiogenesis into the skin 100- fold compared to untreated human skin[9].

Powderject device

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. 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. The use of compressed gas to force solid drug particle through a convergent divergent nozzle was reported by Bell house et al. using compressed helium. 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. Particle velocity is controlled within the device by three parameters namely nozzle geometry, membrane burst strength and gas pressure. 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.

Powderject device has been reported to successfully deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin[9].

Needle-Free Injections

The highest value, least developed and most technically challenging group of needle-free Technologies are 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:

(a)-Intraject®: 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.

(**b)-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.

(c)-Jet Syringe®: The jet syringe, which can deliver up to 0.5 ml; can be configured with an adjustable dose fillable ampoule or proprietary prefilled glass ampoule for fixed dose applications. It is suitable for short-term infrequent injection therapies.

(d)-Iject®: The design of Iject is based on Biojector 2000. It is a light weight, hand-held liquid NFI [Needle-free injectors]. It can deliver 0.1 to 1.0 ml subcutaneously and intramuscularly.

(e)-Mini-ject®: 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. It can target specific tissue layers including the dermal, subcutaneous and intramuscular layers.

(f)-Cross jet®: 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[9].

Ultrasound (Sonophoresis, Phonophoresis and Ultraphonophoresis)

It is a technique for increasing the skin permeation of drugs using ultrasound (20 KHZ to 16 MHZ) as a physical force. It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. In this technique, the drug is mixed with a coupling agent usually a gel but sometimes a cream or ointment is used which

transfers ultrasonic energy from the device to the skin through this coupling agent. Application of low – frequency ultrasound (20 -100 KHZ) enhances skin permeability more effectively than high – frequency ultrasound (1 -16 MHZ). The mechanism of transdermal skin permeation involves disruption of the stratum corneum lipids, thus allowing the drug to pass through the skin. A corresponding reduction in skin resistance was observed due to cavitation,microstreaming and heat generation. Reverse ultrasound technology may also be used for the extraction of interstitial fluid samples for analysis[9].

Laser Radiation

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. In 1991, Nelson et al. reported that mid-infrared laser (1 J/cm2) ablation of pig stratum corneum enhanced the permeation of both hydrocortisone and interferon[9].

Magnetophoresis

Magnetophoresis is a novel approach in enhancing drug delivery across biological barriers. Benzoic acid, a diamagnetic substance, was selected as a drug candidate. The influence of magnetic field strength on diffusion flux was determined and was found to increase with increasing applied strength. The efficacy of a magnetic field to act as a permeation enhancer for terburalin sulphate was demonstrated .the effect could be due to diamagnetic nature of drug, which tends to escape from the applied magnetic field[10]**.**

Micro Needles Array

Micro fabricated micro needles are devices which are hybrids of the hypodermic needle and transdermal patch through the use of microscopic needles that can deliver the drug effectively (like a hypodermic needle). Their small size offers the potential advantages of delivering large molecules across the stratumcorneum without extreme pain to the patients. The micro needle concept employs an array of micron-scale needles that can deliver drug into the epidermis and dermis, which ultimately leads to uptake by the capillaries for systemic delivery but not so far that micro needles hit the nerves. These silicon.microneedles have extremely sharp tips(radius of curvature, <1µm) that facilitate easy piercing of the skin & fabricated onto Powder Ject Needle free injections arrays of approximately 400 micro needles. A broad range of compounds such as calcein (623 Da), insulin (6000Da), BSA (66000Da) and polymeric nanoparticles are delivered at significant rates through skin permeabilized by micro fabricated microneedles[9].

Macro Flux®

Macro flux technology is a innovative novel transdermal drug delivery system that is 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 micro projection 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. Macro flux® has an area of up to 8cm2 and contains as many as 300 micro projection per cm2 with individual icroprojection length being < 200µm. The maximal adhesive patch is 10 cm2. A coating process is used to apply drug to the tip of each micro projection in the array. When the patch is applied to the skin, the drug-coated micro projections penetrate through the skin barrier layer into the epidermis. The micro capillaries for systemic distribution absorb the drug. The rate of absorption is promoted by the high local drug concentration around the micro projections Therapeutic peptides, proteins and vaccines such as decompressing, human growth hormone (HGH), TH 9507 (a human growth hormone releasing factor analog), ovalbumin(45000 Da protein) are in the developmental stage[9].

CONCLUSIONS

Many efforts are made to develop and investigate the new Penetration enhancement techniques for various classes of drugs. A new method shows interesting results but their formulation and avability to market need more study. A interesting area would be to combine chemical method with physical method to have synergistic action on penetration. Physical methods needs patient compliance hence their therapeutic role is still under development. In recent years the use of a number of biophysical techniques has aided to understand nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal unwanted effects.

REFERENCES

1. Heather AE. Benson Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery 2005; 2: 23-33.
2. Elka Touitou, Brian W. Barry. Enhancement in Drug Delivery. Boca Raton,CRC Press Taylor & Francis Group,2007:218,236.
3. www.ijpr-online.com./image002.jpg

4. Stott PW, Williams AC, Barry BW. Characterization of complex coacervate of some tricyclic antidepressants and evaluation of their potential for enhancing transdermal flux**.** J Controlled Release 1996, 41(3): 215-22.7
5. Hatanaka T. Kamon T.Morigaki S. Katayama K. Koizumi T. Ion pair skin transport of a zwitterionic drug, cephalexin. J Controlled Release 2000; 66(1):63-71
6. Tsai JCG, Thornfeld CR, Gao WN, Feingold KR, Elias PM. Metabolic approaches to enhance transdermal drug delivery. Effect of lipid synthesis inhibitors. J Pharm sci 1996, 85:643-8.
7. Rastogi SK, Singh J. Lipid extraction and transport of hydrophilic solutes through porcine epidermis International J Pharma 2001; 225(1–2): 75-82.
8. Gondaliya DP, Pundarikakshudu K. Enhanced Transdermal Permeation of Bupropion Hydrochloride by Chemical Modification Indian J Pharm Sci 2003; 65 (6):671-674.
9. Ritesh Kumar, Anil Philip. Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin Tropical. J Pharma Res 2007; 6 (1):633-644.
10. S.Narasimha Murthy, Shobha Ranir. Hiremath Physical and Chemical Permeation Enhancers in Transdermal Delivery of Terbutaline Sulphate. AAPS Pharm SciTech, 2001; 2(1) Technical notes 1.