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TRANSDERMAL DRUG DELIVERY –ITS APPROACHES, UTILITY AND CURRENT ADVANCEMENT

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Abstract:

Transdermal drug delivery system comprises one of the most important routes for new drug delivery system. Providing a means to sustain drug release it offers a large number of advantages over conventional drug delivery system. These are self-contained, discrete dosage forms which are known to deliver drug through intact skin at a controlled rate into systemic circulation. This delivery system has undergone a large number of modifications since its introduction in 1800's, starting from the first generation which included delivery of small, lipophilic, low dose drugs to later ones which target their effects to skin barrier layers of stratum corneum using micro needles, thermal ablation, electroporation, etc.This review also focus on the potential of ionic liquids for transdermal application. This review details about various approaches to transdermal delivery system and describes numerous pharmaceutical developments which have been employed to overcome limitation related to skin delivery system.

Key words: *Transdermal Drug Delivery System, Skin, Microneedle, Iontophoresis, Ionic Liquid.*

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INTRODUCTION:

The human skin is a readily accessible surface for drug delivery. Controlled drug release can be achieved by transdermal drug delivery (TDDS); also known as "Patches", are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin to systemic circulation at a predetermined rate over a prolonged period of time.[1]Transdermal delivery provides pain-free administration of the drug. The delivery can terminate if any toxicity or adverse effect is observed. The hepatic first pass metabolism and gastrointestinal incompatibility can be avoided by using the transdermal delivery. The short biological half life drug can be utilized. Reduce in drug level fluctuation and increased patient compliances.[2,3]

Transdermal drug delivery has gone under many processes since 1979 with tremendous changes in technologies.[4] The first transdermal patch was prepared in 1979 and now it's more than 35 marketed product available at the market. The technology was kept on upgrading from 1979 to 2017 in order to facilitate transdermal delivery transport. The journey of transdermal delivery start from the scopolamine and then kept on increasing. The functions and capabilities of transdermal drug delivery have been expanding in the last few decade due to the innovation in the technology.[3] The transdermal market still remains limited because it neither suited to all drugs, nor it justified to all therapy.[4] The transdermal drugs require very specific physiochemical properties and a very high potency to enable their efficacious delivery through the skin.

Skin is a major factor in determining the various drug delivery aspects like permeation and absorption of the drug. The skin consists of three basic layers: epidermis the upper most layer, dermis, and subcutaneous tissue. The most important is the outermost layer of the epidermis, the horny layer that is stratum corneum, which is the skin barrier.[5] The penetration through the stratum corneum is limited. It is a challenge to deliver the hydrophilic compound such as peptides and protein and the high molecular weight compound through the skin. Drugs which are effective to overpass the barrier may enter the blood by the diffusion process. The diffusion rate depends on the weight of the molecule and the concentration gradient. Due to this, there is a limited number of drug which easily penetrates the skin. Therefore, there is an advancement in the technique to deliver the high molecular weight and the highly hydrophilic drug. In transdermal drug delivery system, the drug can deliver via active or passive techniques, the stratum corneum get disrupted by the active technique/physical approaches while the passive technique /chemical approaches do not disrupt stratum corneum.[6][7][8]

There is a wide range of technologies for enhancing transdermal drug delivery, with a number of approvals by the FDA over the last 20 years. The renewal of interest in transdermal drug delivery has been achieved by the improvement in physical and chemical permeation enhancement technologies.[8] Many academic and industrial laboratories have discovered the various approaches for overcoming the skin barrier. The approaches that can be used are chemical approaches such as, using penetration enhancers or physical approaches such as iontophoresis, sonophoresis, jet injectors and microneedle array.[9]

APPROCHES TO TRANSDERMAL DELIVERY

The transdermal can be classified into a 3 different generation.In the first generation, the small, lipophilic and uncharged drug can be delivered by the passive diffusion. Most of the marketed formulation of transdermal based on this generation. Use of the enhancement methods such as chemical enhancer, iontophoresis and non cavitational ultrasound technology belongs to the second generation. The currently employed technique such as electroporation and microneedle cavitational ultrasound ,thermal ablation and microdermabrasion comes under the third generation.[4]

Chemical enhancer

These are the compounds or agent which increases the permeability of the skin with the help of the chemicals. Chemical is the most novel technique for the skin permeation enhancement. The chemical enhancer may act by improving the diffusion coefficient of the drug and by increasing the partitioning between drug and the stratum corneum of the skin.[6] A chemical penetration enhancer is the most widely used in the passive approaches of transdermal drug delivery. Chemical enhancer should be non-toxic, it should be compatible with the drug, pharmacologically inert and non-irritating in nature. The chemical enhancer can be classified into two types – according to the mechanism of action and according to their chemical structure. The chemical enhancer mainly classified according to the structure rather than their mechanism of action because of difficulty in determining the mechanism of action. According to the structure they were classified as – alcohol (ethanol and propylene glycol), amide, sulphoxide, esters, amide, fatty acid and surfactants.[10][11]

Alcohols

Alcohol is most widely used chemical enhancer for improving the drug delivery. The use of alcohols

in topical delivery was first published by the Flynn *et al*. in 1981. In his publication, he studied about the alcohol series to regulate the permeability of mouse skin.[12]Ethanol is commonly used as an enhancer and a vehicle solvent in topical delivery. It has excellent solvating influence, it is employed as co-solvent with water and it also rapidly permeates through the skin.[13] Alcohol enhances the skin permeability by a different mechanism like it increases the drug solubility, protein and lipid extraction from the skin and swelling of stratum corneum.[6]

Sulphoxide

Dimethylsulphoxide (DMSO), dimethylacetamide and dimethylformamide (DMF) are widely used enhancer in sulphoxide class. DMSO is the initial and first chemical which is studied as a penetration enhancer. It is colorless, hygroscopic and aprotic solvent in nature. It is also used as a universal solvent in various areas of pharmaceutical science. The enhancement effect of the DMSO is based on the concentration. For optimum enhancement effectiveness, cosolvent containing greater than 60% DMSO are required. As a penetration enhancer sulphoxide denature the protein of the skin.[13] DMSO increases the partitioning between the drug and skin and it also extracts lipid and making skin more absorptive.[6] If DMSO is used in higher concentration it can cause erythema, burning sensation in skin and contact urticaria.[14] Some examples of different types of chemical enhancer were given in figure 1.[11,13]

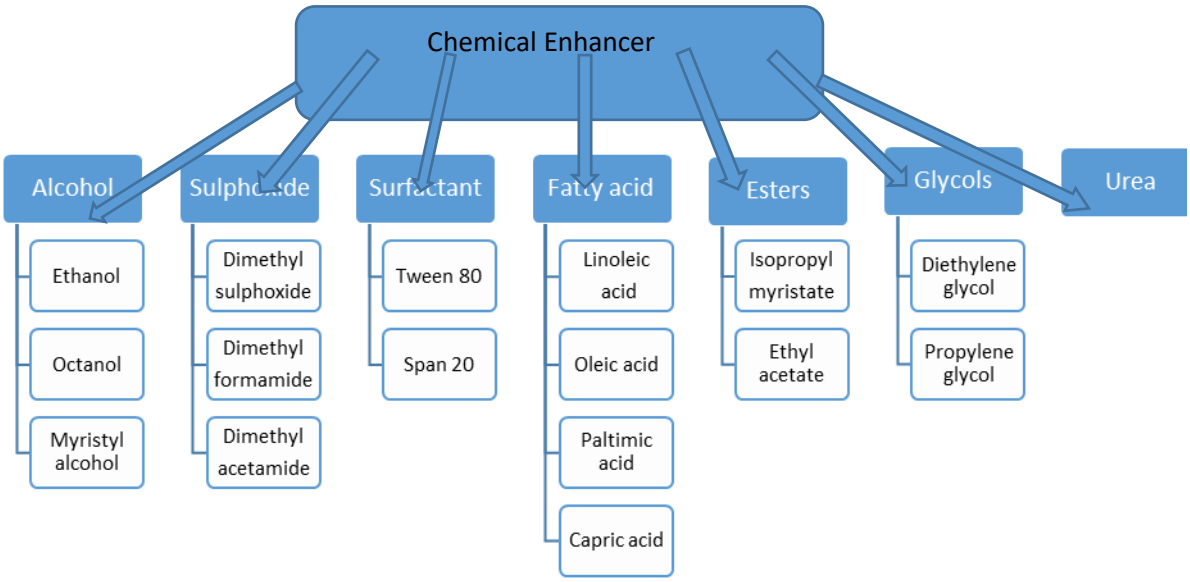

Fig. 1: Examples of different class of chemical enhancer

Surfactant

Surfactant is amphiphilic in nature having low to moderate molecular weight compound. Surfactant consists of a non-polar hydrophobic portion having a straight or branched chain containing 8-18 carbon atoms which attached to the hydrophilic portion which can be non-ionic, ionic or zwitterion.[15] Surfactant solubilizes the lipophilic constituent, so they probable to solubilize the lipid of stratum corneum. They disrupt the lipid of the skin barrier and denature the protein of skin surface. Example of surfactant as penetration enhancer include anionic surfactants [sodium lauryl sulphate (SLS), sodium laureate sulphate], nonionic surfactants [poloxamer (188,407,338,184)].[6]

Fatty acid

Long chain fatty acids are used to increased percutaneous drug absorption. Oleic acid is one of the most popular fatty acids as an enhancer.[16]Fatty acid enhances the penetration by a various mechanism such as improving drug partition between drug and the stratum corneum and it also disrupts the lipid layer of the skin.[17]

Glycols

Among the glycols, propylene glycol is most widely used penetration enhancer. It is used as a cosolvent in the topical drug delivery. The propylene glycol is the effective enhancer in compare to water and alcohol in caffeine permeation from the pig ear skin.[18] Within the stratum corneum, propylene glycol disrupts the intercellular lipid and increase the drug permeability.[17]

Urea

Urea is a moisturizing agent which is used to enhance the hydration of stratum corneum and formed the hydrophilic diffusion channel with in the skin. Due to the chemical stability and the skin irritating effect, the use of the urea is limited as a penetration enhancer.[14]Many transdermal products which were available at the market used

the chemical penetration enhancer for the enhancement technique. A marketed product such as Nitro-Dur in the year 1982 uses fatty acid esters as a chemical enhancer. Urea and propylene glycol used as a chemical enhancer in the marketed transdermal formulation of Lidoderm. The chemical enhancer is widely used enhancement technique over the last decade but its use is limited because it cannot deliver the macromolecules such as a peptide, small proteins and oligonucleotides.[7] The advancement is done in transdermal drug delivery to minimize the problem or limitation. Because of these limitation, new innovative technique came in contacts such as physical enhancement technique.

Iontophoresis

In the year 1947, Pivati describes the method of iontophoresis. The attractiveness of the 0method of administrating biological agent by iontophoresis arises at the beginning of 20'century. Being a non-invasive method, it proves to be a good substitute for the chemical enhancer. Chemical enhancer causes complications like toxicity, the adverse reaction in transdermal drug delivery but iontophoresis method eradicates such complications. The drug used in iontophoresis technique are lesser in amount as compared to other technique used in transdermal delivery.[19]

Iontophoresis is a technique of introducing ionic and non-ionic medication into the body, which applies electric current as a driving force for permeation. Ions are moved across the skin by using electric current between two electrodes. 0.5A/cm2 current density is physiologically safe for iontophoresis method. The principle mechanism of iontophoresis technique by which a drug can facilitate across the skin is -

- Electroreplusion, in which similar charges repel each other from the electrode of identical charge.
- Electro-osmosis, in which electric field prompt the flow of solvent.
- Electroporation, in which electric field upturns the absorbency of skin.[20][21]

Iontophoresis technique is a programmed drug delivery system because the drug can be supplied and terminate in respect to the current input. The basic design of iontophoresis system were in figure 2.[22]

There are many FDA approved iontophoretics patch which are available in the market presently and in the past. Iontocaine® is the first iontophoretic delivery of lidocaine and epinephrine, a local anesthesia was approved in the year 1995. Then in the year 2004, FDA approved Lidosite® as a local anesthetic. After lidosite, Ionsys® was commercially available at the market in the year 2006. It is an opioid analgesic delivery of fentanyl. Now recently available marketed iontophoretic patch is Zecuity®. It is approved by the USA FDA in the year 2013. It is the delivery of sumatriptan used in the migraine treatment. Presently Iontocaine, lidosite and Ionsys are not available at the market due to some technical issue and adverse effect. Iontocaine® was withdrawn from the market in the year 2005. Lidosite® and Ionsys® get suspended from the market in the year 2006 and 2008 respectively due to the quality related issue.[7]

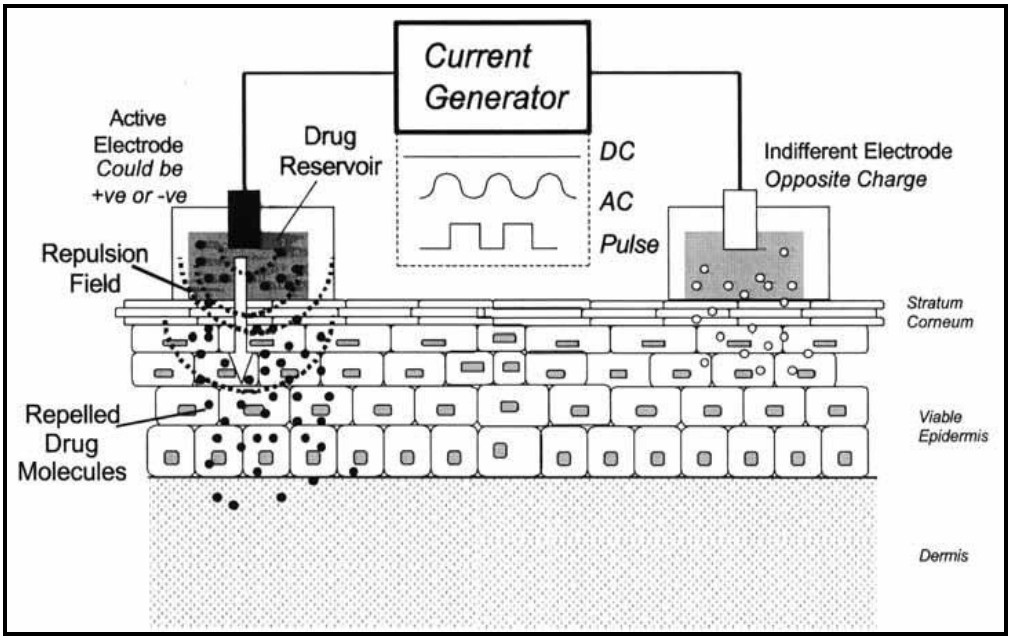

Fig. 2: The basic design of ionotphoretic delivery devices. Drug is placed on the skin under the active electrode, with the indifferent electrode positioned elsewhere on the body, and a current (<0.5mA) passed between the two electrodes effectively repelling drug away from the active electrode and into the skin.

Reverse iontophoresis is a technique which is used to extracting the endogenous substance from the body. Glucowatch® is the marketed product of the reverse iontophoresis technique and it is approved by the FDA in the year 2001.It is used for glucose level monitoring. The Glucowatch® is withdrawn from the market in the year 2007.[8][23]

There were some recent advancement in iontophoresis technique which includes combinational approaches such as chemical – iontophoresis, iontophoresis – ultrasound, iontophoresis – electroporation. These approaches are effective for the skin permeation enhancement compared to them alone. Some example of combinational method is –

- Electroporation and iontophoresis: increased the percutaneous absorption of insulin.
- Microneedles and iontophoresis: enhanced the flux in heparin.
- Iontophoresis and chemical enhancers: Increases flux with a decline in dermatotoxicity in metopimazine.[17]

The limitation associated with iontophoresis include cutaneous adverse actions such as burning or itching. Skin irritation is a most common side effect. Iontophoresis treatment is expensive and extreme current density result in pain.[7] Hence the concern showed toward the progress of new another technique.

Sonophoresis

Sonophoresis is a technique which uses the ultrasound to passage the drug across the human skin. In the year 1950, Fellinger and Schmidt firstly stated the concept of ultrasound in transdermal drug delivery. Ultrasound is used as a physical enhancer for the transdermal drug delivery. The frequency range between the 20 kHz to 16MHz used to enhance the permeability of the skin. The fundamental mechanism of sonophoresis is not yet characterized but some proposed mechanism includes thermal effect and cavitation.[10]

Thermal effect (temperature increase) – the local temperature of the skin is increased when the tissue absorbed ultrasound energy, the increased temperature resultant in the permeability enhancement. This mechanism depends upon the several factors such as ultrasound frequency, its intensity, duration of exposure and the area of the ultrasound beam.

Cavitation – It is the process of generation and distortion of gas bubbles. The cavitation is depended upon ultrasound frequency and the shape and size of the bubble.[24][25] The formation of bubbles by cavitation increases bilayer fluidisation and resultant permeability which was shown in figure 3.[22]

Sonoprep® is the first ultrasound device approved by FDA in the year 2004 for the transdermal application. This device delivers the lidocaine which acts as a local dermal anesthesia. But in the year 2007, this device is withdrawn from the market due to its reduced marketed acceptance. The limitation includes minor skin reaction and the skin burn.[8]

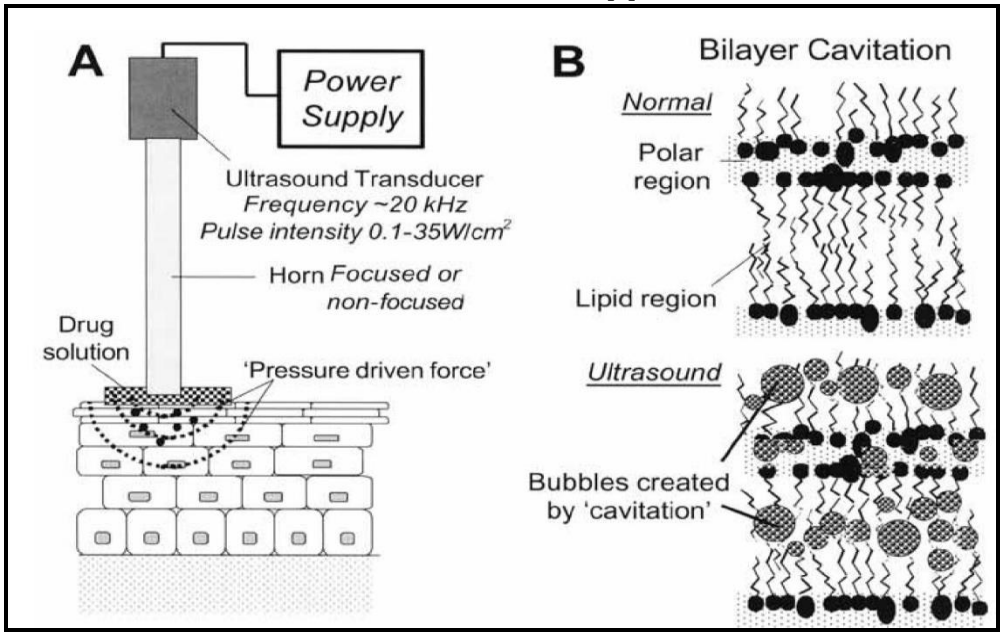

Fig. 3: The basic design of ultrasonic delivery devices. (A) Drug is placed on the skin beneath the ultrasonic probe. Ultrasound pulses are passed through the probe and drug molecules are hypothesised to move into the skin through a combination of physical wave pressure and permeabilisation of intercellular bilayers. (B) The formation of bubbles in the intercellular lipid space caused by cavitation increases bilayer fluidisation and resultant permeability.

Needle less jet injector or velocity based device

Velocity based device are the pain free needle less device for the administration of drug in the body. Jet injector concept in the drug delivery system was studied by the Arnold sutermesiter in year 1930.In this technique liquid and solid particles deliver to the skin with very high velocity. The velocity of the jet injector is range from 100-200m/s to rupture the skin.[10] The drug is deliver into the body by using appropriate power source (spring or compressed gas such as helium). This method avoid the fear of hypodermic needle.[26]

Liquid jet injector: There are two types of liquid jet injector, single-dose jet injector also known as disposable cartridge jet injectors and multi-use-nozzle jet injectors (MUNJIs).the single dose jet injector are the partly or fully disposable type while the MUNJIs does not have any disposable part. The liquid jet injector impel liquid from the nozzle orifice whose diameter ranging from 150-300 micrometre. By altering the jet velocity and orifice diameter the drug deliver into the different parts of skin. MUNJIs is mainly used in the vaccine application. Delivery of several proteins can be done by the single dose jet injector, mainly researched done for the delivery of insulin and growth hormone.[10][27]

Powder jet injector: These injector used the powder form to deliver the drug into the skin. The nano and micro particle are used as an active form in the powder jet injector it also increases the stability of the formulation. Particle properties and velocity range govern the particle delivery across the skin.[28] Compressed gas is used as a power source in the solid jet injector, a compartment containing drug in the form of powder which is attached to a nozzle for the direct flow of particle.[29]The particle puncture the stratum corneum into the micro-sized holes. It can be applicable for the delivery of the DNA and it also provide the defence against the tumour by deliver the DNA coated gold micro particles.[28]

Zingo® is the first marketed product of needle free injector which deliver the lidocaine in the powder form in year 2007.This product is withdrawn from the market in year 2008 but relaunched in the year 2014. Sumavel DosePro® is the needle free liquid injector of sumatriptan drug for the treatment of migraine launched in the market in year 2009. The irregular pain and bruising restricted the wide acceptance of jet injectors.[8]

Thermal ablation

Thermal ablation is a technique, which uses thermal energy for the improved drug transport across the skin. This technique involve heating of the outer part of skin, by which the stratum corneum get depleted at the place of heating merely, without damaging the inner tissue. The deeper feasible tissue remain normal and anatomically integral.[30] In selective thermal ablation technique, the micropores of diameter 30 µm and depth of 70 µm formed without the necrosis of skin. There are various parameter in which the thermal ablation design depend. These parameter are duration of heat, temperature and the localization of the thermal energy. The temperature should be 1000C for heat the skin.[28] The system of thermal ablation used in patch to improve transdermal drug delivery was explored by the Altea therapeutics company (founded in 1998). In year 2005, local delivery of lidocaine and tetracaine is the first commercial marketed product which enhance the skin absorptivity by using heat.[8]

Electroporation

In year 1982 the electroporation was first defined by Neumann *et al*. It is an electrically assisted technique which increase the permeability of the skin in transdermal delivery.[10] In the lipid bilayer, the electroporation can create the aqueous pore by applying the high intensities of electric pulses.[31] The transportation of the drug through the skin depend on the physiochemical properties of the drug and the electrical parameter such as voltage, duration and the interval concerning the pulses.[10] Recently, electroporation technique deliver a model peptide vaccine to generate a strong cytotoxic T lymphocyte respone which is shown in the skin of the mice. Electroporation techniques has been broadly studied in animals. However its use in humans is still limited due to complexity and device design.[4]

Microneedle array

The use of microneedle technology gain specific attention in transdermal delivery over the last few years. Microneedle are the micron sized needle which disrupt the skin barrier function by creating the pores. Microneedle array overcome the limitations of the hypodermic needle tradition and increase the patient compliances.[28] It is mainly used in the vaccine delivery.In the late 1990's, the first work is reported on the use of microneedle for transdermal delivery.[32] The length of the microneedle can be 25 to 2000 µm, the tip diameter range from 1 to 25 µm and base width from 50 to 250 µm.[28] When microneedle inserted into skin, it must avoid the nerve communication. The microneedle made from the insoluble silicon, metals, plastic and sugar. There are four different types of microneedle design-

- Solid microneedle.
- Solid microneedle coated with dry powder.
- Polymeric microneedle with encapsulated vaccine.

- Hollow microneedle.[10,28,33]

Solid microneedle perforate the skin and then enhance the permeability. Stainless steel, titanium and nickel iron are the metals which is used in solid microneedle. Microscopic holes can be create when the solid microneedle pressed or scraped into the skin and thus increased permeability.[10][33]

Solid microneedle coated with the dry drugs or vaccines, for the rapid dissolution in the skin. Within 1 minute after the patch insertion the coating can be dissolved, after which the microneedle can be removed from the skin.[33]

Polymeric microneedle with encapsulated vaccine is used for rapid and controlled release in the skin. Biodegradable and water soluble polymer such as polycarbonate, polylactic glycolic acid, carboxymethyl cellulose are the polymers which were used in the polymeric needle formulation.[32] Hollow microneedle is mainly used for the injection. Hollow microneedle rupture the skin and drug came out through the needle bore. The microneedle applicable to the low molecular weight compound, protein and even in the nanoparticles.[10][28] The insulin is deliver by the hollow microneedle and it also control blood glucose level.[32] The mechanism of various types of microneedle was shown in figure 4.[10]

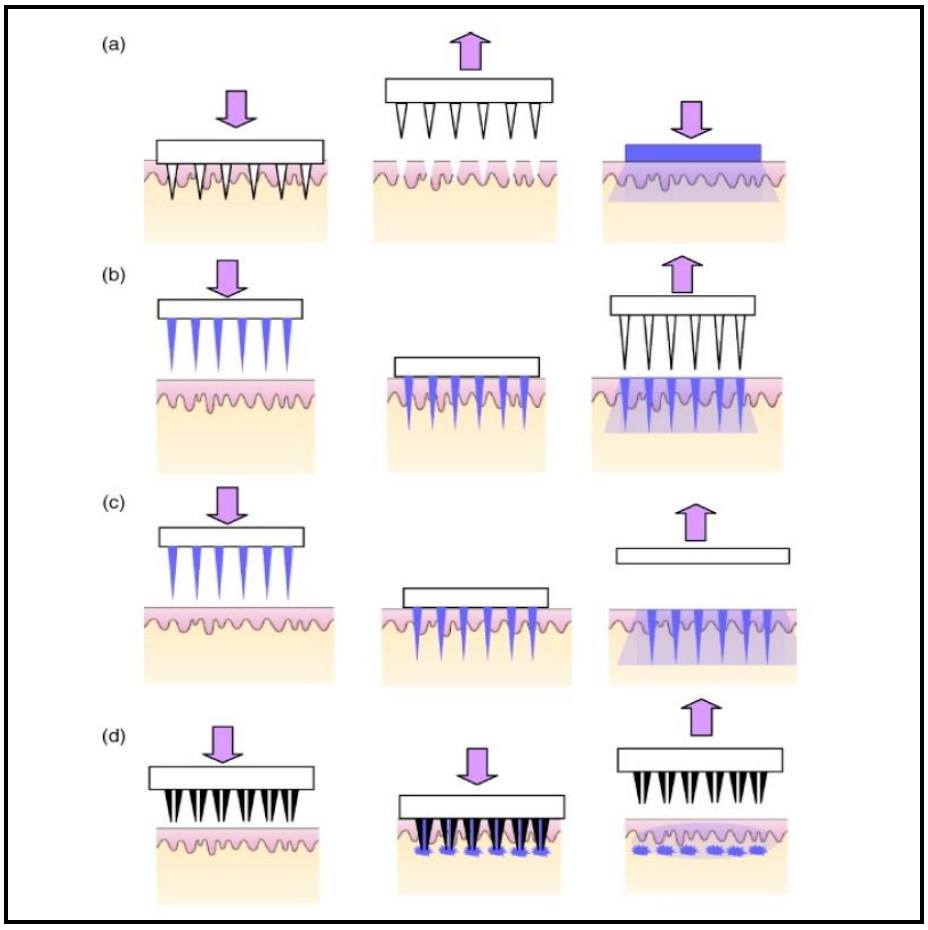

Fig. 4: - (a) Solid microneedles for permeabilizing skin via formation of micron-sized holes across stratum corneum. The needle patch is withdrawn followed by application of drug-containing patch (b) Solid microneedles coated with dry drugs or vaccine for rapid dissolution in the skin (c) Polymeric microneedles with encapsulated drug or vaccine for rapid or controlled release in the skin (d) Hollow microneedles for injection of drug solution

Advantages of microneedle array include pain less delivery and it does not cause bleeding. Intanzia® and Micronjet® were the first marketed based product of the microneedle. Intanzia® is used as the influenza vaccine and being marketed in two different quantities. For the adults whose age is between 18-59 used the Intanza® 9 µg and adults whose age is 60 years and above used the Intanza® 15 µg. Micronjet® is industrialized and licensed by Nano Pass. It is an intradermal delivery of drug which is single use disposable microneedle device. Many microneedle devices waiting for FDA approval and many of them in the clinical trials.[10][34]

Table I- Marketed preparation of TDDS approved by FDA.[8]

Drug	Year	Indication	Technique
Scopolamine	1982	Travel sickness	Passive diffusion
Nitroglycerin	1979	Angina	Passive diffusion
Clonidine	1984	Hypertension	Passive diffusion
Estradiol	1986	Female HRT	Passive diffusion
Fentanyl	1990	Chronic pain	Passive diffusion
Lidocaine & epinephrine	1995	Local anaesthesia	Iontophoresis
Testosterone	1995	Hypogonadism	Passive diffusion
Nicotine	1996	Smoking cessation	Passive diffusion
Estradiol & norethindrone acetate	1998	Female HRT	Passive diffusion
Ethinyl estradiol & norelgestromin	2001	Female contraception	Passive diffusion
Oxybutynin	2003	Enuresis	Passive diffusion
Lidocaine & epinephrine	2004	Local anaesthesia	Iontophoresis
Lidocaine	2004	Local anaesthesia	Sonophoresis
Lidocaine & tetracaine	2005	Local anaesthesia	Heated patch
Methylphenidate	2006	ADHD	Passive diffusion
Selegiline	2006	Depression	Passive diffusion
Fentanyl	2006	Pain relief	Iontophoresis
Rivastigmine	2007	Alzheimer's disease	Passive diffusion
Lidocaine	2007	Local anaesthesia	Needle free powder injector
Granisetron	2008	Chemo induced emesis	Passive diffusion
Sumatriptan	2009	Migraine	Needle free liquid injector
Buprenorphine	2010	pain relief	Passive diffusion
Rotigotine	2012	Parkinson's disease	Passive diffusion
Sumatriptan	2013	Migraine	Iontophoresis

The recent advancement and current trend in the transdermal drug delivery system is the use of ionic liquids (ILs). The ionic liquid is used as an enhancer in transdermal drug delivery across the skin. In transdermal drug Stemperature of 100°C or less. the ionic liquid comprises at least one anionic component and at least one cationic component. Ionic liquids have various features such as lower melting point, negligible vapour pressure, high thermal thermal stability, highly ionic conductivity and polarity. Ionic liquids are widely known as 'designer solvents' because with variation in ionic component,the ionic liquid properties can alter.According to the condition of particular method, the ionic liquid properties can be adjusted. Thus the ionic liquid can be used in the transdermal for the topical delivery of the macromolecular, hydrophilic and hydrophobic drugs. For transdermal delivery of drugs , ionic liquids proposed an ideal solvent system and due to there unique properties it solubilize diverse classes of drugs and increase formulation potency by act as a penetration enhancer.[35] Michael Zakrewskya et.al established the fact that ionic liquids are capable of penetrating bacterial biofilms, thus can serve as broad spectrum antimicrobial agent.[36]

Ionic liquids grasp promise as a novel and innovative platform for transdermal drug delivery.In recent year, the field of ionic liquids grown progressively and considered the most hopeful prospects of forthcoming transdermal drug delivery.

CONCLUSION:

Advancement in the transdermal drug delivery system are opening the door to the administration of macromolecules ,vaccines and hydrophilic molecules.This scenario remain same in the future . A vast number of works has been done related to transdermal drug delivey but due to certain limitations such as limited dosing ,skin irritation, delivery of macromolecules etc, the use of transdermal has been restricted. Presently, a number of techniques are used to overcome these problems which include chemical techniques (chemical enhancer), physical techniques(iontophoresis, sonophoresis, electroporation, micro needle, needle less jet injector and thermal ablation). Advancement in each technique with time further increase its credibility and use. In time, it is hoped that these invention and advancements will accelerates the success of transdermal market.

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