Review Article

Technologies in Transdermal Drug Delivery System: A Review

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ABSTRACT

Transdermal drug delivery system is the system in which the delivery of the drug occurs through skin. It offers a convenient way to deliver drugs without the drawbacks as in case of standard hypodermic injections relating to issues such as patient acceptability and injection safety. The success of transdermal drug delivery has been severely limited due to the inability of most of the drugs to enter the skin at therapeutically useful rates. The stratum corneum acts as a barrier that limits the penetration of substances through the skin. In recent years various passive and active strategies have emerged to optimise delivery. However passive approach do not significantly improve the permeation of drugs with molecular weight > 500 Da. In contrast active methods, normally involving physical or mechanical methods of enhancing delivery has been shown to be generally superior. The delivery of drugs of differing lipophilicity and molecular weight including proteins, peptides and oligonucletides has been showed to be improved by active methods. This review covers the recent findings in various advanced techniques of enhancement of drug delivery which includes jet injectors, iontophoresis, ultrasound, thermal ablation, biodegradable microneedles.

Keywords: Transdermal drug delivery system, iontophoresis, microneedles.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are defined as self-contained discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The main advantage of this approach is that the drug is entered into the body undistorted without being passed through the body's various defense systems. In contrast to oral administration the most convenient way of drug administration, the transdermal route does not suffer from drug degradation in the gastrointestinal tract and reduced potency through first-pass metabolism (i.e. in the liver). In addition, oral-specific side effects like liver damages are avoided. Transdermal patches were introduced in the late 1970's, starting with a 3 day patch to treat motion sickness. Since then, the market for drug administration through patches has been steadily increasing. However transdermal delivery is severely limited by the inability of the majority of drugs to cross skin at therapeutic rates due to the barrier imposed by the skin's outer stratum corneum layer.

To increase skin permeability, a number of different approaches has been studied, ranging from chemical/ lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves generated by ultrasound or photoacoustic effects. Although the mechanisms are all different, these methods share a common goal to disrupt stratum corneum structure in order to create "Holes" big enough for molecules to pass through. The size of disruptions generated by each of these methods is believed to be of nanometer dimensions, which is large enough to permit transport of small drugs and, in some cases, macromolecules, but probably small enough to prevent causing damage of clinical significance. An alternative approach involves creating larger transport pathways of micron dimensions using array of microscopic needles. These pathways are orders of magnitude bigger than molecular dimensions and, therefore, should readily permit transport of macromolecules as well as possibly supramolecular complexes and microparticles. Despite their very large size relative to drug dimensions,

on a clinical length scale they remain small. [6, 15]

Advantages of transdermal drug delivery systems

1. Easy elimination of drug delivery during toxicity.
2. Avoidance of first pass metabolism of drugs
3. Reductions of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half-life and low therapeutic index
4. Reduction of dosing frequency hence increased patient compliance.
5. Self administration is possible with these systems.
6. Simplified medication regimen leads to increased patient compliance.
7. Avoidance of gastrointestinal incompatibility.
8. When oral route is unsuitable as with vomiting and diarrhoea then transdermal route is an alternative to deliver the drug candidate.

Limitations of transdermal drug delivery systems

1. Only potent drugs are suitable candidates for transdermal delivery.
2. This system is uneconomical.
3. Skin irritation may occur in some patients at the site of application.
4. The system is not suitable for drugs that require high blood levels.
5. The barrier function of the skin changes from site to site in the same person, person to person and also with age.

Anatomy of skin

The skin is the largest organ of the human body and has several functions. It is a physical barrier towards the environment, it regulates body temperature and fluid loss, it conveys sensory information to the nervous system, and it processes immunologic information to the immune system. The skin has a surface area of about 1.5 to 2 m^2 in adults and it contains glands, hair and nails.

The skin can be divided into three layers : the superficial *epidermis*, *dermis* and *hypodermis* (fig 1). The epidermis is approximately 50-150 µm thick and consists of constantly renewing, outward moving cells called keratinocytes. The outermost layer of the epidermis is the stratum corneum, a 10-20µm thick layer of 15-30 stacked, dead cornified cells. The dermis represents the bulk of the skin and the predominant components are collagen fibers and a smaller amount of elastin. This fibrous network gives tensile strength and elasticity to the skin and also provides support for nerve and vascular networks. In the upper, papillary, region of the dermis the collagen fibers are small and loosely distributed. The deep reticular region contains densely packed, bundled collagen fibers mainly running parallel to the skin surface and along certain directions, called Langer's lines. The dermis rests on the hypodermis which is composed of loose fatty connective tissue. Its thickness varies considerably over the surface of the body as well as between individuals.[9, 14]

Drug delivery routes across human skin

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 (fig 2). The relative importance of shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years and is further complicated by the lack of suitable experimental model to permit separation of the three pathways. Scheuplein and colleagues[19], proposed that a follicular shunt route was responsible for the pre-steady permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum. However it is generally accepted that as the appendages comprise a fractional area for permeation of approximately 0.1 % their contribution to steady state flux of most drugs is minimal. This assumption has resulted in the majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum rather than *via* the appendages. Exceptions are iontophoretic drug delivery which uses an electric charge to drive molecules into the skin primarily *via* the shunt routes as they provide less electrical charge, and vesicular delivery.[5, 9]

1. Transappendageal route

This is also called as the shunt pathway. In this route the drug molecule may transverse through the hair follicles, the

sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands. The transappendageal pathway is considered to be of minor importance because of its relative smaller area (less than 0.1 % of total surface).

2. Transcorneal penetration

Intracellular penetration

Drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. Although this is the path of shortest distance, the drugs encounter significance resistance to permeation. This is because the drugs must cross the lipophilic membrane of each cell, then the hydrophilic cellular contents containing keratin, and then the phospholipid bilayer of the cell one more time. This series of steps is repeated numerous times to traverse the full thickness of the stratum corneum.

Intercellular penetration

Non polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non-aqueous lipid matrix imbibed between the protein filaments. Although the thickness of the stratum corneum is about 20µm, the actual diffusional path of most molecules crossing the skin is on the order of 400µm. The 20-fold increase in the actual path of permeating molecules greatly reduces the rate of drug penetration.

Table 1: Regional variations in water permeability of stratum corneum

S.No.	Skin region	Thickness (µm)	Permeation rate (mg/cm^2/hr)	Diffusivity (cm^2/sec*10^{10})
1	Abdomen	15.0	0.34	6.0
2	Volar forearm	16.0	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13.0	0.85	12.9
5	Scrotum	5.0	1.70	7.4
6	Back of hand	49.0	0.56	32.3
7	Palm	400.0	1.14	535.0
8	Plantar	600.0	3.90	930.0

Factors influencing transdermal drug delivery

The effective transdermal drug delivery can be formulated by considering three factors as drug, skin and the vehicles. So the factors affecting can be divided into classes as biological and physicochemical factors.[1, 7]

A. Biological factors

1. Skin condition

Acids and alkalis, many organic solvents damage the skin cells and promote skin penetration. Diseased state of patient alters the skin conditions.

2. Skin age

The young skin is more permeable than older. The permeability of the skin decreases as the age of the person increases.

3. Blood supply

Changes in peripheral circulation can affect transdermal absorption.

4. Regional skin site

Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors significantly affect permeation.

5. Skin metabolism

Skin metabolises steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines the efficacy of drug permeated through the skin.

6. Species differences

The skin thickness, density of appendages and keratinisation of skin vary from species to species so affects permeation.

B. Physicochemical factors

1. Skin hydration

The permeability of the skin increases significantly when in contact with water. Hydration is the most important factor increasing the permeation of skin therefore the use of humectants is done in transdermal drug delivery.

2. Temperature and pH

The permeation of drug increase ten folds with temperature variation. The diffusion coefficients decrease as the temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa

or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus temperature and pH are important factors affecting drug penetration.

3. Diffusion coefficient
Penetration of drug depends upon diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on its properties, diffusion medium and interaction between them.

4. Drug concentration
The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

5. Partition coefficient
The optimal K, partition coefficient is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also drugs with low K will not be permeated.

6. Molecular size and shape
Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination effect of molecular size is not known.

Transdermal patches
Transdermal patches were introduced in the late 1970's, starting with a three day patch to treat motion sickness. Since then the market for drug administration through patches has been steadily increasing.
Transdermal patches are divided into two categories based on their physical structure :Reservoir-based and Matrix-based. Reservoir-based patches hold the drug in a solution (usually a liquid or a gel) in a separate compartment. The drug is released through a rate- controlling permeable membrane placed as an interface between the reservoir and the skin (fig 3). Matrix-based patches have a more simple design in which the drug is incorporated with the adhesive layer. There is no membrane that controls the release rate of the drug. Instead, the permeability of the skin governs the rate control. Matrix-based patches are easier to fabricate and thus the production cost is lower than for reservoir-based patches (fig 4). On the other hand, reservoir-based patches offer better control of the drug release but may raise safety concerns since a possible rupture of the membrane could result in a sudden release of the drug. [10, 14]

Drug selection criteria for patch
The following are the properties required by the drug to be selected for delivery by transdermal route. It includes physico-chemical and biological properties of the drug. Also, the pharmacokinetic and pharmacodynamic parameters of the drug must be considered.[1, 8, 9]

Physico-chemical properties
1. The drug should have affinity for both lipophilic and hydrophilic phases.
2. The drug should have a low melting point.
3. The drug should have a molecular weight less than 1000 Daltons.
4. Since the skin has a pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin. However for a number of drugs, there may also be a significant transdermal absorption at pH values at which the unionized form is predominant.

Biological properties
1. The drug should be non-irritating and non-allergic to the site of application.
2. The drug should have a short life.
3. Drug should be potent with a daily dose of the order of a few mg/day.
4. Drugs which degrade in the gastrointestinal tract or inactivated by hepatic first pass effect are suitable candidates for transdermal delivery.

General clinical considerations in the use of transdermal patches
The Patient should be advised regarding the proper and safe usage of transdermal patches. The patient must be made aware of the importance of using the recommended site and rotating locations. Rotating location is important to allow the skin to regain its normal permeability and to prevent skin irritation. [11] The following guidelines must be considered while applying a patch
1. A patch must be applied to a clean, dry skin free of hair and oily, inflamed, irritated or broken. Wet skin can accelerate the drug permeation rate. Oily skin can

impair the adhesion of patch. If hair is present at the application site then it should be carefully cut and not wet shaven nor should a depilatory agent be used, since later can remove the stratum corneum layer and affect the permeation rate and extent of the drug.

2. Use of skin lotion must be avoided at the site of application since it affects the hydration of skin and alter the partition coefficient of drug.
3. Patient should take care that the patch is not being physically altered, since it can destroy the integrity of the system.
4. The patch should be placed at a site that will not subject it to being rubbed-off by clothing or movement. While bathing or showering the transdermal patch should be left on.
5. The product's usage instructions must be carefully read and followed for the period to be worn as well as its removal and replacement with a fresh transdermal patch.
6. The patient or the person applying the patch should clean the hands before and after applying the patch. They should not rub eye or touch the mouth during handling of the patch.
7. If the patient exhibits sensitivity or intolerance to the transdermal system or if undue skin irritation results, the patient should seek revaluation or consult a physician.
8. Upon removal of the transdermal patch, it should be folded in its half with the adhesive layer together. The used patch must be discarded in a manner safe to childrens and pets.
9. It is important to use a different application site everytime the patch is changed to avoid skin irritation. Suggested rotation is :

Day 1 : Upper right arm
Day 2 : Upper right chest
Day 3 : Upper left chest
Day 4 : Upper left arm,
Then repeat from Day 1.

Table 2: List of transdermal drugs approved by the US FDA

Approval year	Drug	Indication	Product name	Marketing company
1979	Scopolamine	Motion sickness	Transderm-scop®	Novartis consumer health
1981	Nitroglycerin	Angina pectoris	Transderm-nitro®	Novartis
1984	clonidine	Hypertension	Catapress TTS®	Boehringer Ingelheim
1986	Estradiol	Menopausal symptoms	Estraderm®	Novartis
1990	Fentanyl	Chronic pain	Duragesic®	Janssen pharmaceutica
1991	Nicotine	Smoking cessation	Nicoderm®, Habitrol®, proStep®	GSK, Novartis, Elan
1993	Testosterone	Testosterone deficiency	Testoderm®	Alza
1995	Lidocaine/ epinephrine (iontophoresis)	Local dermal analgesic	Iontocaine®	Iomed
1998	Estradiol / norethidrone	Menopausal symptoms	Combipatch®	Novartis
1999	Lidocaine	Post-herpetic neuralgia pain	Lidoderm®	Endo
2001	Estradiol / norelgestromin	Contraception	Ortho Evra®	Ortho-McNeil
2003	Estradiol / levonorgestrol	Menopausal symptoms	Climara Pro®	Bayer healthcare
2003	Oxybutynin	Overactive bladder	Oxytrol®	Watson pharma
2004	Lidocaine (ultrasound)	Local dermal anesthesia	SonoPrep®	Echo therapeutics
2005	Lidocaine / tetracaine	Local dermal analgesia	Synera®	Endo pharmaceuticals
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana®	Shire
2006	Selegiline	Major depressive disorder	Emsam®	Bristol-myers squibb
2007	Rotigotine	Parkinson's disease	Neupro®	Schwarz pharma
2007	Rivastigmine	Dementia	Exelon®	Novartis
2013	sumatriptan	migraine	Zecuity®	NuPathe Inc.

Recent advanced techniques for enhancing drug delivery via transdermal route

In the past few years numerous methods and techniques have been developed to overcome the skin barrier. These methods can be broadly categorised into passive methods and active methods of drug delivery via transdermal delivery.

Passive methods for enhancing transdermal drug delivery

Passive approach involves the optimization of formulation or drug carrying vehicle to increase the skin permeability. The conventional means of applying drug to skin include the use of vehicles such as ointments, gels, creams and "passive" patch technology. In recent years, approaches such as the use of penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles has been developed. However, the amount of drug that can be delivered through these methods is still limited since the barrier properties of the skin are not fundamentally changed.

Active methods for enhancing transdermal drug delivery

Active approach involves the use of external energy to act as a driving force and/ or act to reduce the barrier nature of the stratum corneum in order to enhance the permeation of drug molecules across the skin. Recent progress in these technologies has occurred as a result of advances in precision engineering (bioengineering), computing, chemical engineering and material sciences which all have contributed to the creation of miniature, powerful devices that can generate the required clinical response. The use of active enhancement methods has gained importance due to the advent of biotechnology in the latter half of 20^{th} century, which has led to the generation of therapeutically-active, large molecular weight (> 500 Da) polar and hydrophilic molecules, mostly peptides and proteins. However gastrointestinal enzymes often cause degradation of such molecules and hence there is a need to demonstrate efficient delivery of these molecules by alternate route of administration. Passive methods of delivery are incapable of enhancing permeation of such large solutes, which has led to studies involving the use of alternative active strategies.

Electroporation

Electroporation involves the use of high voltages (≥ 100) and short treatment durations (milliseconds). It reversibly disrupts the cell membranes. Although the electric field applied for milliseconds during electroporation provides an electrophoretic driving force, diffusion through long-lived electropores can persist for up to hours, such that transdermal transport can be increased by orders of magnitude for small model drugs, peptides, vaccines and DNA.

Since the stratum corneum electrical resistance is orders of magnitude greater than deeper tissues, the electric field applied during electroporation is initially concentrated in the stratum corneum. However during electroporation of stratum corneum lipid bilayers, stratum corneum resistance rapidly and dramatically drops, and the electric field correspondingly distributes to a greater extent into the deeper tissues, which contain sensory and motor neurons. The associated pain and muscle stimulation can be avoided by using closely spaced microelectrodes that constrain the electric field within the stratum corneum.

Genotronics Inc. have developed a prototype electroporation transdermal device, which has been tested with various compounds in order to achieve gene delivery, improving drug delivery and aiding the application of cosmetics. Transdermal device based on electroporation has been proposed by various groups however, more clinical information on the safety and efficacy of the technique is required to assess the future commercial aspects.[6, 14]

Iontophoresis

Iontophoresis refers to the delivery of drugs across the skin by means of an electric field. By having two electrodes placed on the skin, drugs at the electrodes will start to migrate through the skin once a voltage is supplied to the electrodes. Once in the skin, the drug will be absorbed by the capillaries and systemically distributed. The current density is usually below 0.5 mA / cm^2 in order not to cause patient any discomfort. Three main physical mechanisms are involved in iontophoresis : charged species are driven from the electrodes as a result of the electric field, (electrophoresis), the flow of current increases the permeability of the skin; and, the established potential difference between the electrodes give rise to an electro-osmotic flow. Since electro-

osmosis occurs, uncharged species can be delivered as well.

Parameters that affect design of an iontophoretic skin delivery system include; electrode type, current intensity, pH of the system and competitive ion effect. The strongest asset of iontophoresis is that the rate of delivery scales with the electrical current, which can be readily controlled by a microprocessor or, in some cases, the patient. In this way, drug delivery can be turned on and off and even modulated over time to enable complex delivery profiles. However, the maximum current and the maximum delivery rate is limited by skin irritation and pain caused by the general inability of iontophoresis to localize its effect to the stratum corneum. Due to these strengths and weaknesses, current applications emphasize the ability of iontophoresis to provide control over drug dosing, because it scales with the amount of charge delivered to the skin.

In January 2013, FDA announced the approval of Zecuity™ by Nu Pathe Inc. Which is a sumatriptan iontophoretic transdermal system indicated for the treatment of migraine with or without aura. FDA also approved the Ionsys™ manufactured by ALZA corporation which is a fentanyl iontophoretic transdermal system indicated for the management of acute post-operative pain in adult patients requiring opioid analgesia during hospitalization.[6, 10]

Ultrasound (sonophoresis and phonophoresis)

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis.

Non-cavitational ultrasound

Ultrasound is an oscillating pressure wave at a frequency too high for humans to hear. Although some have hypothesized that pressure gradients and oscillation associated with ultrasound act as a driving force to move drugs into the skin, it appears that the dominant effect is to disrupt stratum corneum lipid structure and thereby increase permeability. The effects of non-cavitational ultrasound on skin permeability have generally been limited to enhancing small, lipophilic compounds.

Cavitational ultrasound

In addition to heating, ultrasound is also known to generate cavitation, which is the formation, oscillation and, in some cases, collapse of bubbles in an ultrasonic pressure field. Cavitation is only generated under specific conditions (e.g. low frequency ultrasound) that differ from those of ultrasonic heating or imaging devices. The opportunity for transdermal drug delivery is that cavitation bubbles concentrate the energy of ultrasound and thereby enable targeted effects at the site of bubble activity. Since bubbles are more difficult to grow and oscillate within densely packed tissue, cavitation preferentially occurs within the coupling medium (e.g. a hydrogel) between the ultrasound transducer and skin. The expected mechanism of cavitational ultrasound is that bubbles oscillate and collapse at the skin surface, which generate localized shock waves and liquid microjets directed at the stratum corneum. This disrupts stratum corneum lipid structure and thereby increases skin permeability for upto many hours without damaging deeper tissues.

In the year 2004, FDA approved the first sonophoretic transdermal system SonoPrep® by Sontra medical corp. 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 the skin to be treated. Cavitational ultrasound has been studied extensively in animals for delivery of insulin, heparin, tetanus toxoid vaccine and other compounds. Ultrasound can be applied using hand held devices, as well as low-profile, cymbal transducers that could be integrated into a patch.[13, 14]

Laser radiation and photomechanical waves

Lasers have been used in the clinical therapies for decades, therefore their effects on the biological membranes are well established and documented. Lasers are frequently used for the treatment of dermatological conditions such as acne and to confer “facial rejuvenation” where the laser radiation destroys the target cells over a short frame of time (~300 ns). Such direct and controlled exposure of the skin to laser radiation results in ablation of the stratum corneum without significant damage to the underlying epidermis. Removal of the stratum corneum via this method has been shown to enhance the delivery of lipophilic as well as hydrophilic drugs. The

extent of barrier disruption is known to be controlled by the parameters such as wavelength, pulse length, pulse energy, pulse number and pulse repetition rate.

A hand-held portable laser device has been developed by the Norwood Abbey Ltd. In a study involving human volunteers, the device was found to reduce the onset of action of lidocaine to 3-5 mins., whilst 60 mins. was required to attain a similar effect in control group. The Norwood Abbey system has been approved by the US and Australian regulatory bodies for the administration of a topically applied anaesthetic.

Photomechanical waves are the pressure pulses produced by ablation of a material target such as polystyrene by Q-switched or mode-locked lasers. Photomechanical 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 of 40,000 Da. Suggestions have been made that many clinically important proteins such as insulin (6000 Da) and hematoprotein (48,000 Da) are within or close to the delivery capability range of photomechanical waves. However this new technique does not yet seem to have produced any human clinical data.[12]

Radio-frequency

Radio-frequency involves the exposure of skin to high frequency alternating current (~ 100 KHz) resulting in the formation of heat-induced microchannels in the membrane similar to when laser radiation is employed. The rate of drug delivery is controlled by the number and depth of the microchannels formed by the device, which is dependant on the properties of the microelectrodes used in the device. The viaderm device (Transpharma Ltd) is a hand held electronic device consisting of a microprojection array (100 microelectrodes/ cm^2) and a drug patch. The microneedle array is attached to electronic device and placed in contact with the skin to facilitate the formation of the microchannels. Treatment duration takes less than a second, with a feedback mechanism incorporated within the electronic control providing a signal when the microchannels have been created, so as to ensure reproducibility of action. The drug patch is then placed on the treated area.

Experiments in rats have shown the device to enhance the delivery of granisetron HCL, with blood plasma levels recorded after 12 h rising to 30 times higher levels than that recorded for untreated skin after 24 h. A similar enhancement in diclofenac skin permeation was also observed in the same study. The device is reported not to cause any damage to the skin with the radio-frequency induced microchannels remaining open for less than 24 h. The skin delivery of drugs such as testosterone and human growth hormone by this device is also currently in progress. [6, 13]

Magnetophoresis

This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability. In vitro studies by Murthy showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field. Other In vitro studies using a magnet attached to transdermal patches containing terbutaline sulphate, demonstrated an enhancement in permeant flux which was comparable to that attained when 4 % isopropyl myristate was used as a chemical enhancer. In the same paper, the effect of magnetophoresis on the permeation of terbutaline sulphate was investigated In vivo using guinea pigs. The preconvulsive time of guinea pigs for those subjected to magnetophoretic treatment was found to last for 36 h which was similar to that observed after application of a patch containing 4 % isopropyl muristate. This was in contrast to the response elicited by the control (patch without enhancer), when the increase in preconvulsive time was observed for only 12 h. In human subjects, the levels of terbutaline sulphate in the blood was higher but not significantly different to that observed with the patch containing 4 % isopropyl myristate.

The fact that this technique can only be used with diamagnetic materials will serve as a limiting factor in its applicability and hence result in lack of interest.[13]

Thermophoresis

The temperature of the skin surface is 32°C in the humans which is regulated by homeostatic controls. Previous studies have demonstrated the 2-3 fold increase in the

flux for every 7-8°C rise in the temperature of skin surface. This has led to the interest of various development scientists and researchers in using thermoregulation as a means of improving the delivery profile of topical medicaments. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and an increase in drug diffusivity in the skin due to increased lipid fluidity. Vasodilation of the subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds.

The In vivo delivery of nitroglycerin, testosterone, lidocaine, tetracaine and fentanyl from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery.

The controlled heat-aided drug delivery patch (CHADD) by Zars Inc., consists of a patch containing a series of holes at the top surface which regulate the flow of oxygen in to the patch. Heat is generated chemically in a powder filled pouch by an oxidative process regulated by the rate of flow of oxygen through the holes in the patch. The CHADD technology was used in the delivery of a local anesthetic system (lidocaine and tetracaine) from a patch (S-Caine®) and found to enhance the depth and duration of the anesthetic action in human volunteers when the results obtained in active and placebo groups were compared. Zars Inc. Together with Johnson and Johnson, recently submitted an investigational new drug (IND) application to the FDA for Titragesia™ (a combination of CHADD disks and Duragesic® patches, the latter contains fentanyl for treatment of acute pain). The studies described above employed an upper limit skin surface temperature of 40-42°C, which can be tolerated for a long period (> 1 h)

In heat patch systems where patient exposure to heat is ≤ 24 h, such an upper limit may be necessary for regulatory compliance. In addition, the issue of drug stability may also need to be addressed when elevated temperatures are used. [3, 6, 14].

Microneedles

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on this method. The device (fig 5) as described in the patent consists of a drug reservoir and a number of projections extending from the reservoir. These microneedles of length 50-110 µm will penetrate the stratum corneum and epidermis to deliver the drug from the reservoir. As a result of the current advancement in microfabrication technology in the past years, cost effective methods of developing devices in this area are now becoming increasingly common.

Microneedles are promising microfabricated devices for minimally invasive drug delivery applications. Drug delivery with microneedles aims to deliver a drug through the skin rather than biological circulatory systems such as blood vessels or lymphatic vessels. Accordingly, the microneedles should not cause pain when they penetrate the skin, and should have sufficient length such that they can deliver drugs to the target site. In addition, the microneedles should have excellent physical hardness such that they can penetrate the stratum corneum having a thickness of 10-20 µm.

Microneedles are classified on the basis of fabrication process as : In-plane and 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 accurately controlled. A disadvantage is that it is difficult to fabricate two-dimensional arrays. Out-of-plane microneedles protrude from the substrate and are easy to fabricate in arrays. Instead the length and high aspect-ratios become significant challenges in the fabrication of these kind of needles. Another way of distinction is whether the needles are solid or hollow. Hollow needles with a needle bore or lumen allow an active liquid transport through the microneedle.

Various possible strategies can be employed to deliver drugs across skin via microneedles. 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. To maximize the delivery rate, a rational strategy is to distribute the delivery over several microneedles. That is, by using an array of microneedles over a larger skin surface area, it exposes a larger area of the drug which promotes further diffusion to the capillaries.

Theraject Inc. Has developed two patches with microneedles, Drugmat® and Vaxmat®, intended for topical, transdermal delivery. The company manufactures the microneedles from a sugar polysaccharide, combining it with drug and molding these components into sharp needles. The resulting product is inert and safe, and the needles dissolve with use, thereby avoiding issues of disposal and contamination.[10, 15, 16.]

Solid microneedle arrays

Solid microneedles can be used to create microscale holes in the skin through which molecules can more easily transport. The first microneedle arrays reported in the literature were etched into the silicon wafer and developed for intracellular delivery in vitro by Hashmi et al. These needles were inserted into cells and nematodes to increase molecular uptake and gene transfection. Shortly after this work was published, microneedles were developed for transdermal delivery applications, which have been shown to insert into skin and thereby deliver a variety of different compounds in vitro and in vivo.

Hollow microneedle arrays

In contrast to solid microneedles discussed above, microneedles containing hollow bore offer the possibility of transporting drugs through the interior of well-defined needles by diffusion or, for more rapid rates of delivery, by pressure driven flow. A variety of hollow microneedles have been fabricated, but only limited work has been published on their possible use to deliver compounds into skin.

Skin puncture and perforation

These devices are similar to microneedle devices produced by microfabrication technology. They include the use of needle-like structures or blades, which disrupt the skin barrier by creating holes and cuts as a result of a defined movement when in contact with the skin. Godshall and Anderson, described a method and apparatus for disruption of epidermis in a reproducible manner. The apparatus consists of a plurality of microprotrusions of a length insufficient for penetration beyond epidermis. The microprotrusions cut into the outer layers of the skin by movement of the device in a direction parallel to the skin surface. After disruption of the skin, passive (solution, patch, gel, ointment) or active (iontophoresis, electroporation) delivery methods can then be utilised. [6, 13]

Needleless injection

Needleless injection is reported to involve a pain free method to administer drugs across skin. This method therefore avoids the issues of safety, pain and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. Over the years there have been a numerous examples of both liquid (Ped-O-Jet®, Iject®, Biojector 2000®, Medi-jector®, Intraject®) and powder (PMED™ device formerly known as Powderject® injector) systems. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin.[1, 4, 12]

The problems facing needleless injection systems include the high developmental cost of both the device and the dosage form and the inability to control drug delivery to compensate for inter-subject differences in skin permeability.

Suction ablation

It involves the application of a vacuum or negative pressure to remove the epidermis, whilst leaving the basal membrane intact. The Cellpatch® (Epiport pain relief, Sweden) is a commercially available product based on this mechanism. It comprises of a suction pump, epidermatome (to form a blister) and device (which contains morphine solution) to be attached to the skin.

The disadvantages associated with this method include the prolonged length of time required to achieve a blister (2.5 h), although this can be reduced to 15-70 min by warming the skin to 38° C.[13]

Application of pressure

The application of modest pressures (upto 25 kPa) has been shown to provide a potentially non-invasive and simple method of enhancing skin permeability of molecules such as caffeine. These workers attributed the increase in transcutaneous flux to either an improved transappendageal route or an increased partition of the compound into the stratum corneum when pressure was applied.[13, 6]

Skin stretching

These devices hold the skin under tension in either a unidirectional or multidirectional manner. The authors claim that a tension of about 0.01 to 10 mP results in the reversible formation of micropathways. The efficiency of the stretching process was demonstrated by the monitoring the delivery of a decapeptide (1 kDa) across the skin of hairless guinea pigs using a microprotusion array. The results of the study showed that bidirectional stretch allowed the skin to remain open and facilitate drug permeation to a greater extent (27.9 ± 3.3 µg/ cm^2 h) than in the control group (9.8 ± 0.8 µg/ cm^2 h), where the skin was not placed under tension after microneedle treatment.[6]

Skin abrasion

This technique involves the direct removal or disruption of the upper layers of skin to enhance the permeability of the topically applied compounds. The delivery potential of the skin abrasion techniques are not restricted by the physic-chemical properties of the drug and previous work has illustrated that such methods enhance and control the delivery of a hydrophilic permeant, vitamin C, vaccines and biopharmaceuticals.[13]

Future outlook

Transdermal delivery offers compelling opportunities to the researchers and development scientists. Rising interest of the researchers to improve vaccine administration via this route since vaccine delivery via the skin targets the potential epidermal langerhans and dermal dendritic cells generate a strong immune response at much lower doses than deeper injection. Elimination of the need for hypodermic needles further motivates transdermal vaccine development.

In the future, It is likely that transdermal patches will continue to be used for delivery of small molecule drugs. The techniques such as iontophoresis, ultrasound, microneedles 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.

CONCLUSION

The transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. The use of transdermal drug delivery has experienced a remarkable increase in recent years due to the advancements in techniques for transdermal drug delivery system. With the rising interest of the researchers more number of drugs are becoming available for delivery via this route. The properties of the drug, the characteristics of the skin and the status of patient's skin are all important factors for safe and effective delivery of the drug.

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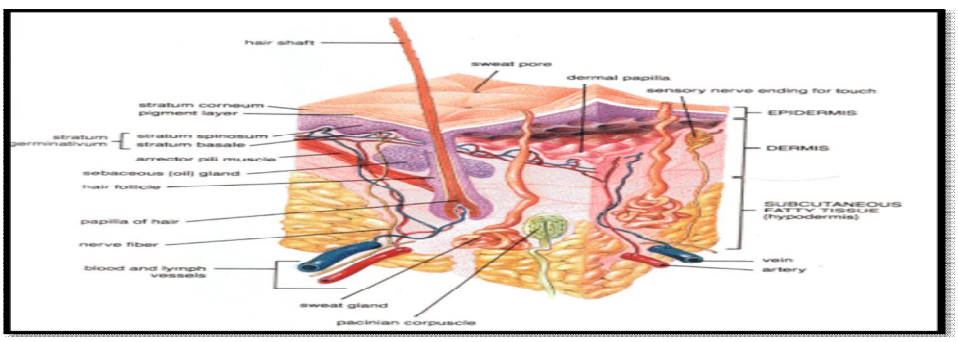

Fig. 1: Structure of skin

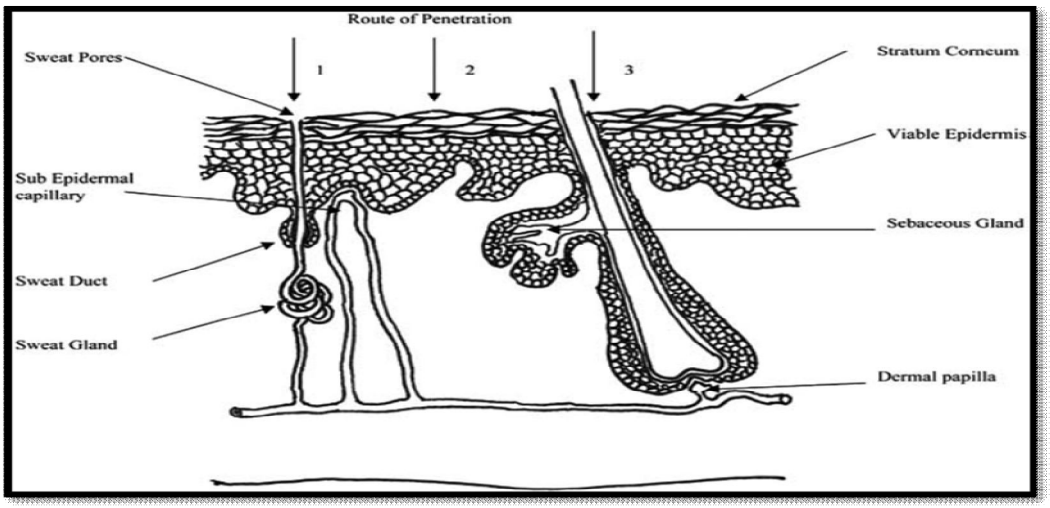

Fig. 2 : Routes of drug delivery across skin : 1,3- transappendageal route, 2- transcorneal route

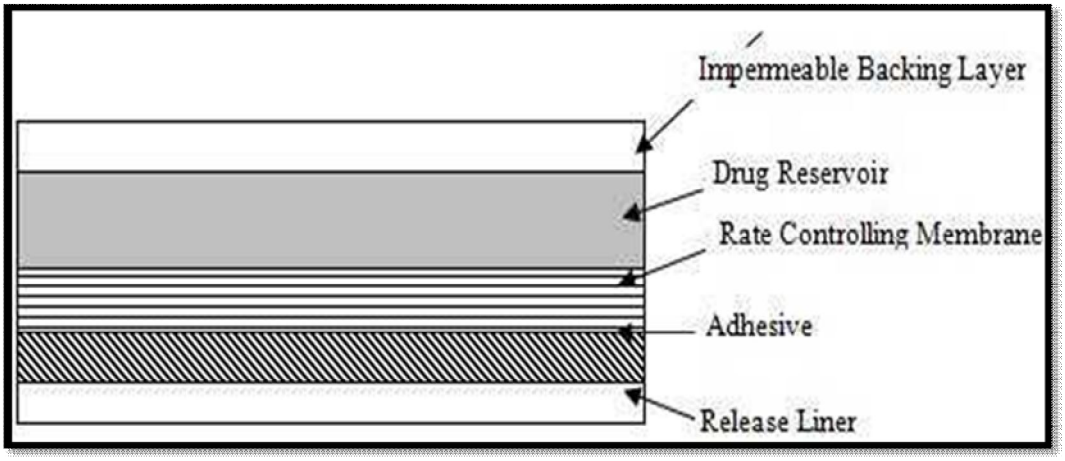

Fig. 3: Reservoir-based transdermal patch

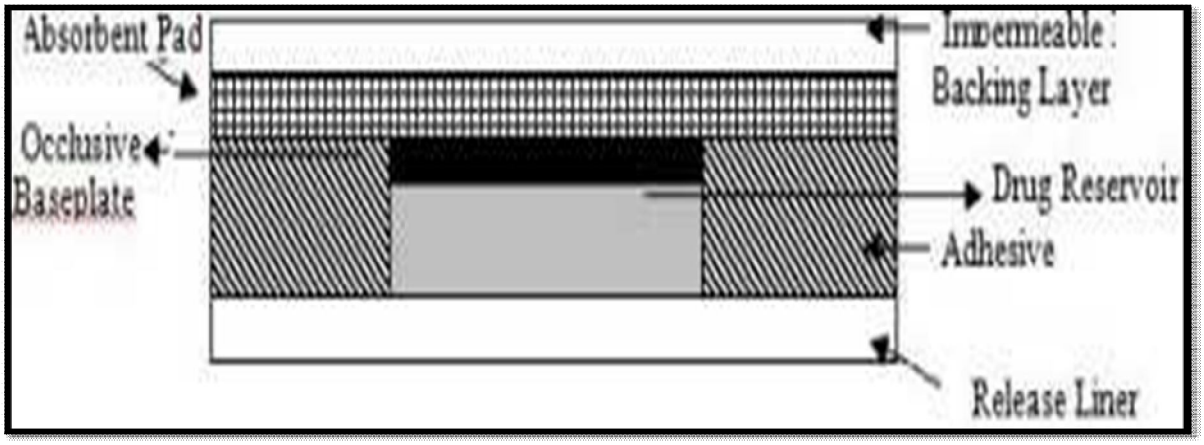

Fig. 4: Matrix-based transdermal patch

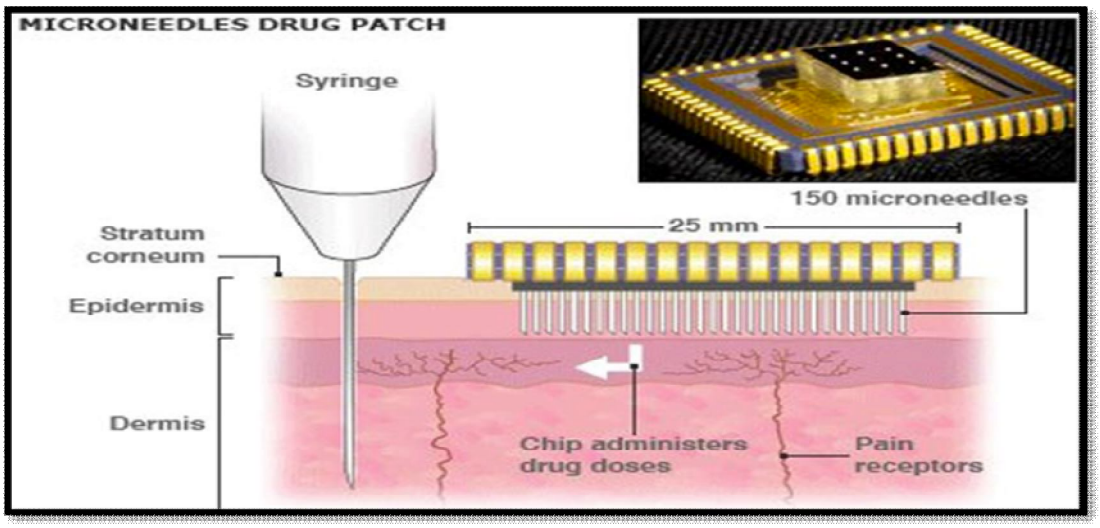

Fig. 5: Microneedle-based transdermal system

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