

Recent trends in challenges and opportunities of Transdermal drug delivery system

P.M.Patil¹, Dr.P.D.Chaudhari¹, Jalpa K.Patel¹, K.A.Kedar¹, P.P.Katolkar²
Modern College of Pharmacy, ¹Sector 21, Yamunanagar, Nigdi, Pune 44(M.S) India
Sharad Pawar College of Pharmacy, Wanadongari Nagpur² (M.S) India

Abstract

Drug delivery system relates to the production of a drug, its delivery medium, and the way of administration. Drug delivery systems are even used for administering nitroglycerin.

Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Various types of transdermal patches are used. There are various methods to enhance the transdermal drug delivery system. But using microfabricated microneedles drugs are delivered very effectively to skin patch.

There has been great progress in the Transdermal drug delivery system for the delivery of different forms and our aim is to collect the information about what progressed have done in Transdermal drug delivery system and developments in Transdermal drug delivery systems in theoretical form. Also, to collect the information about the advantages and application of the Transdermal drug delivery systems.

*Corresponding author, Mailing address:

P. M. Patil

E-mail: pallavipatil_2007@yahoo.com

psadanshio@yahoo.co.in

Key words:

Electroporation, Iontophoresis, sonophoresis and phonophoresis, Magnetophoresis, Needleless injection

How to Cite this Paper:

P. M. Patil, Dr. P. D. Chaudhari, Jalpa K Patel, K. A. Kedar, P. P. Katolkar "Recent trends in challenges and opportunities of Transdermal drug delivery system", Int. J. Drug Dev. & Res., Jan-March 2012, 4(1): 39-50

Copyright © 2010 IJDDR, P. M. Patil et al. This is an open access paper distributed under the copyright agreement with Serials Publication, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Article History:-----

Date of Submission: 21-09-2011

Date of Acceptance: 18-01-2012

Conflict of Interest: NIL

Source of Support: NONE

INTRODUCTION [1,4,5,6]

Drug Delivery System relates to the production of a drug, its delivery medium, and the way of administration. Drug delivery systems are even used for administering nitroglycerin. In addition, it is also used in nicotine patches thereby helping people to cease and withdraw tobacco consumption.

Transdermal drug delivery(TDDS) is the non-invasive delivery of medications from the surface of

skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy. Designing and development of transdermal patches can be described as state of the art. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems.

The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it over comes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems. So, this Transdermal Drug Delivery System has been a great field of interest in the recent time. Many drugs which can be injected directly into the blood stream via skin have been formulated. The main advantages of this system are

that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin.

Transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance.

Since the first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more than 35 transdermal patch products, spanning 13 molecules. Transdermal drug delivery system was first introduced more than 20 years ago.

A Transdermal Patch has several components like liners, adherents, drug reservoirs, drug release membrane etc. which play a vital role in the release of the drug via skin. Various types of patches along with various methods of applications have been discovered to delivery

the drug from the transdermal patch. Because of its great advantages, it has become one of the highly research field among the various drug delivery system.

BENEFITS OF SKIN AS DRUG DELIVERY SYSTEM ⁷

1. The avoidance of first pass metabolism
2. Sustained and controlled delivery over a prolong period of time
3. Reduction in side effects associated with systemic toxicity
4. Direct access to target or diseased site.
5. Ease of dose termination in any adverse reactions either systemic or local
6. Convenient and painless administration

LIMITATIONS OF SKIN AS DRUG DELIVERY SYSTEM ⁸

1. A molecular weight less than 500 Da is essential to ensure ease of diffusion across the SC, since solute diffusivity is inversely related to its size.
2. Pre systemic metabolism the presence of enzymes in the skin such as peptidases might metabolise drug in inactive form and reduce efficacy of drug.
3. Skin irritation and sensitization; referred to as Achilles heel of dermal and transdermal delivery.

In the last twenty five years numerous methods of overcoming the skin barrier have been described but they can broadly be divided in to two main categories defined as either passive or active methods.

1] PROGRESS IN TRANSDERMAL DRUG DELIVERY SYSTEM: SKIN PATCH^[9, 10]

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream^[Fig:2].



Fig: 2 Skin patch

The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979, which administered scopolamine for motion sickness.

2] COMPONENTS OF TRANSDERMAL PATCH:

- (1) Liner - Protects the patch during storage. The liner is removed prior to use.
- (2) Drug - Drug solution in direct contact with release liner.

(3) Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.

- (4) Membrane - Controls the release of the drug from the reservoir and multi-layer patches.
- (5) Backing - Protects the patch from the outer environment. [FIG: 3

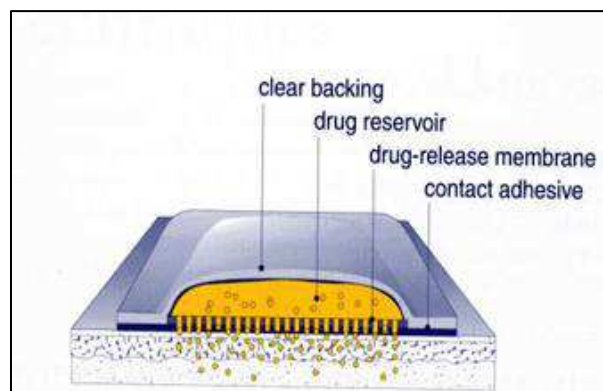


Fig: 3 Components of patch

3] CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED :

- (1) When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
- (2) Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
- (3) It can be used in combination with other enhancement strategies to produce synergistic effects.

4] CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED :

The use of transdermal patch is not suitable when:

- (1) Cure for acute pain is required.
- (2) Where rapid dose titration is required.
- (3) Where requirement of dose is equal to or less than 30 mg/24 hrs.

5] MECHANISM OF ACTION OF TRANSDERMAL PATCH:

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods [Fig: 4]

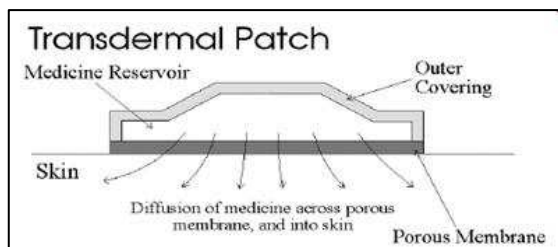


Fig: 4 Mechanism of patch

6] PASSIVE METHODS FOR ENHANCING TRANSDERMAL DRUG DELIVERY:

Ointments, creams, gels and “passive” patch technology. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. Such approaches include the use of penetration enhancers, supersaturated systems, prodrugs or metabolic approach liposomes and other vesicles. However, the amount of drug that can be delivered using these methods is still limited since the barrier properties of the skin are not fundamentally changed. As such there are still no medicines on the market in the US that contain a labelled penetration enhancer.

7] ACTIVE METHODS FOR ENHANCING TRANSDERMAL DRUG DELIVERY:

These methods involve the use of external energy to act as a driving force and/or act to reduce the barrier nature of the SC in order to enhance permeation of drug molecules in to 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 have all helped to achieve the creation of miniature, powerful devices that can

generate the required clinical response. The use of active enhancement methods has gained in importance due to the advent of biotechnology in the later half of the 20th 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 alternative administration routes.

- **Electroporation**

The use of electroporation, as a method of enhancing diffusion across biological barriers, dates back as far as 100 years. Electroporation involves the application of high voltage pulses to induce skin perturbation. High voltages (≥ 100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect delivery include pulse properties such as waveform, rate and number. The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation. 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 a molecular weight greater than 7kDa, the current limit for iontophoresis.

Genetronics Inc have developed a prototype electroporation transdermal device, which has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics. Other transdermal devices based on electroporation have been proposed by various groups.

- **Iontophoresis**

This method involves enhancing the permeation of a topically applied therapeutic agent by the application

of a low level electric current either directly to the skin or indirectly via the dosage form. Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms; electrorepulsion (for charged solutes), electro osmosis (for uncharged solutes) and electroperturbation (for both charged and uncharged). Parameters that affect design of an iontophoretic skin delivery system include; electrode type, current intensity, pH of the system, competitive ion effect and permeant type. The launch of commercialised systems of this technology has either occurred or is currently under investigation by various companies. Extensive literature exists on the many types of drugs investigated using iontophoretic delivery and the reader is referred to the following extensive reviews. The Phoresor™ device was the first iontophoretic system to be approved by the FDA. In order to enhance patient compliance the use of patient-friendly, portable and efficient iontophoretic systems have been under intense development over the years. Such improved systems include the Vyteris and E-TRANS iontophoretic devices. Previous work has also reported that the combined use of iontophoresis and electroporation is much more effective than either technique used alone in the delivery of molecules across the skin.

The limitations of iontophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA cm⁻²) and the irreversible damage such currents could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of >7000 Da.

- ***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. The

proposed mechanism behind the increase in skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound resulting in disruption of the SC. Ultrasound parameters such as treatment duration, intensity and frequency are all known to affect percutaneous absorption, with the latter being the most important. Although frequencies between 20 kHz-16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (< 100 kHz) are believed to have a more significant effect on transdermal drug delivery with the delivery of macromolecules of molecular weight up to 48 kDa.

The SonoPrep ® device uses low frequency ultrasound (55 kHz) for an average duration of 15 s to enhance skin permeability. This battery operated hand held device consists of a control unit, ultrasonic horn with control panel a disposable coupling medium cartridge, and a return electrode. The ability of the SonoPrep device to reduce the time of onset of action associated with the dermal delivery of local anaesthetic. The use of other small, lightweight novel ultrasound transducers to enhance the in vitro skin transport of insulin has also been reported by a range of workers.

- ***Laser radiation and photomechanical waves***

Lasers have been used in the clinical therapies for decades, therefore their effects on biological membranes are well 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 SC without significant damage to the underlying epidermis. Removal of the SC via this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. The extent of barrier disruption by laser

radiation is known to be controlled by parameters such as wavelength, pulse length, pulse energy, pulse number and pulse repetition rate.

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

Pressure waves (PW), which can be generated by intense laser radiation, without incurring direct ablative effects on the skin have also been recently found to increase the permeability of the skin. It is thought that PW form a continuous or hydrophilic pathway across the skin due to expansion of the lacunae domains in the SC. Important parameters affecting delivery such as peak pressure, rise time and duration has been demonstrated. The use of PW may also serve as a means of avoiding problems associated with direct laser radiation.

- **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 dependent 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/cm²) and a drug patch. The microneedle array is attached to the 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 feed back

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 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.

- **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 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 (TS), 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 TS was investigated in vivo using guinea pigs.

- **Temperature (“thermophoresis”)**

The skin surface temperature is usually maintained at 32°C in humans by a range of homeostatic controls. Recently, there has been a surge in the interest of using thermoregulation as means of improving the delivery profile of topical medicaments. Previous in vitro studies have

demonstrated a 2-3 fold increase in flux for every 7-8°C rise in skin surface temperature. 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) consists of a patch containing a series of holes at the top surface which regulate the flow of oxygen in to the patch. The patch generates heat chemically in a powder filled pouch by an oxidative process regulated by the rate of flow of oxygen through the holes in to the patch. The CHADD technology was used in the delivery of a local anaesthetic system (lidocaine and tetracaine) from a patch and found to enhance the depth and duration of the anaesthetic action in human.

Thermoperturbation refers to the use of extreme temperatures to reduce the skin barrier. Such perturbation has been reported in response to using high temperatures over a short duration (30 ms), with little or no discomfort, using a novel patch system. The heat pulse is regulated by means of a resistive heater, which ensures that the ablation is limited within the superficial of dead layers of the skin. Average temperatures of 130 °C are required for ablation to occur within 33 ms after which SC evaporation results. The exposure of skin to low (freezing) temperatures has been reported to decrease its barrier function but has however not been exploited as means of enhancing skin absorption.

- ***Microneedle based devices***

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 as described in the patent consists of a drug reservoir and a plurality of projections extending from the reservoir. These microneedles of length 50-110 µm will penetrate the SC and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel or solid particulates and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. As a result of the current advancement in microfabrication technology in the past ten years, cost effective means of developing devices in this area are now becoming increasingly common.

A recent commercialisation of microneedle technology is the Macroflux® microprojection array. The macroflux® patch can either be used in combination with a drug reservoir or by dry coating the drug on the microprojection array ; the latter being better for intracutaneous immunization. The lengths of the microneedles have been estimated to be around 50-200 µm and therefore are not believed to reach the nerve endings in the dermo-epidermal junction. The microprojections/ microneedles (either solid or hollow) create channels in the skin, hence allowing the unhindered movement of any topically applied drug. Clinical evaluations report minimal associated discomfort and skin irritation and erythema ratings associated with such systems are reportedly low. This technology serves as an important and exciting advance in transdermal technology due to the ability of the technique to deliver medicaments with extremes of physicochemical properties (including vaccines, small molecular weight drugs and large hydrophilic biopharmaceuticals).

- ***Skin puncture and perforation***

These devices are similar to the 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 the epidermis in a reproducible manner. The apparatus consists of a plurality of microprotrusions of a length insufficient for penetration beyond the 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 etc) or active (iontophoresis, electroporation etc) delivery methods can then be utilized.

- **Needleless injection**

Needleless injection is reported to involve a pain free method of administering drugs to the 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 numerous examples of both liquid and powder systems. The latter device has been reported to deliver successfully testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin.

Problems facing needleless injection systems include the high developmental cost of both the device and dosage form and the inability, unlike some of the other techniques described previously, to programme or control drug delivery in order to compensate for inter-subject differences in skin permeability. In addition, the long-term effect of bombarding the skin with drug particles at high speed is not known thus, such systems may not be suitable for the regular administration of drugs. It may however be very

useful in the administration of medicaments which do not require frequent dosing e.g. vaccines.

- **Suction ablation**

Formation of a suction blister, involves the application of a vacuum or negative pressure to remove the epidermis. The cellpatch is a commercially available product based on this mechanism. It comprises a suction cup, epidermatome (to form a blister) and device (which contains morphine solution) to be attached to the skin this method which avoids dermal invasivity there by avoiding pain and bleeding is also referred to as skin erosion. Such devices have also been shown to induce hyperaemia in the underlying dermis in vivo studies, which was detected via laser Doppler flowmetry and confirmed via microscopy, and is thought to further contribute to the enhancement of dextran and morphine seen with this method.

The disadvantages associated with the suction 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.

- **Application of Pressure**

The application of modest pressures (i.e. 25 kPa) has been shown to provide a potentially noninvasive 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 SC when pressure was applied. This method may also work due to the increased solubility of caffeine in the stratum corneum caused by the increase in pressure.

- **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 mPa results in the reversible formation of micropathways. The efficiency of the stretching process was

demonstrated by monitoring the delivery of a decapeptide (1 kDa) across the skin of hairless guinea pigs using a microprotrusion array. The results of the study showed that the bi-directional stretching of skin after microprotrusion piercing, allowed the pathways to stay open (i.e. delayed closure) hence facilitating drug permeation to a greater extent than in the control group, where the skin was not placed under tension after microneedle treatment.

Other methods involving the use of skin stretching with subsequent use of delivery devices based on electrotransport, pressure, osmotic and passive mechanisms have also been suggested but the value of skin stretching alone without the benefit of a secondary active delivery device remains to be seen.

- **Skin abrasion**

These techniques, many of which are based on techniques employed by dermatologists in the treatment of acne and skin blemishes (e.g. microdermabrasion), involve the direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied compounds. The delivery potential of skin abrasion techniques are not restricted by the physicochemical 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 biopharmaceutics. The device is rubbed against the area of interest, to abrade the site, in order to enhance delivery or extraction. The device functions by removing a portion of the SC without substantially piercing the remaining layer.

TYPES OF TRANSDERMAL PATCH [11, 12]

- **Single-layer Drug-in-Adhesive**

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The

adhesive layer is surrounded by a temporary liner and a backing.

- **Multi-layer Drug-in-Adhesive**

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

- **Reservoir**

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

- **Matrix**

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

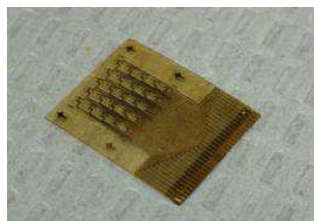
- **VAPOUR PATCH:**

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are Transdermal on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

Recent developments expanded their use to the delivery of hormonal contraceptives, antidepressants and even pain killers and stimulants for Attention Deficit Hyperactivity Disorder/ADHD.

➤ **IN-FREE DIABETIC MONITORING USING TRANSDERMAL PATCHES:**

Fig: 5 Prototype patch



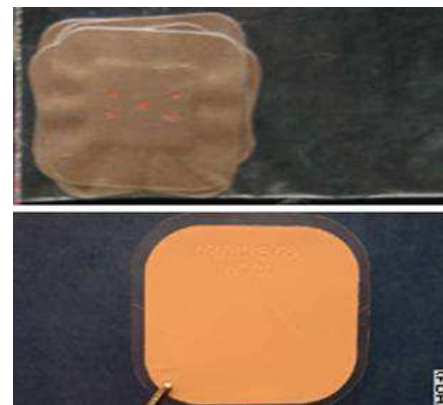
The first prototype patch measures about 1cm² and is made using polymers and thin metallic films. The 5×5 sampling array can be clearly seen, as well as their metallic interconnections. When the seal is compromised, the interstitial fluid, and the biomolecules contained therein, becomes accessible on the skin surface. Utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, a high-temperature heat pulse can be applied locally, breaching the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30ms duration. The temperature diminishes rapidly from the skin surface and neither the living tissue nor the nerve endings are affected. This painless and bloodless process results in disruption of a 40–50µm diameter region of the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.

➤ **TRANSDERMAL PATCH (ORTHO EVRA™) :**

The patch is 4.5 square centimeters in size and has three layers: the inner release liner which should be removed before application, a layer containing hormones, and an outer polyester protective layer. The patch contains 6 milligram of progestin, Norelgestromin 0.75 milligram of Ethinyle Estradiol. The patch is applied on the skin through which the hormones are absorbed in order to provide continuous flow of hormones during menstrual cycle.

The patch is marketed by Ortho McNeil Pharmaceutical with the brand name Ortho Evra. [FIG:6]

Fig: 6 Ortho evra patch



The patch is applied on the skin through which the hormones are absorbed in order to provide continuous flow of hormones during menstrual cycle. The patch is marketed by Ortho McNeil Pharmaceutical with the brand name Ortho Evra. [FIG:6]

➤ **ROTIGOTINE TRANSDERMAL PATCH:**

The rotigotine transdermal patch is used for symptom control in Parkinson's disease. The patches are effective in reducing the symptoms of early Parkinson's disease, and in reducing "off" time in advanced Parkinson's disease. It is available in market under the brand name of NeuproR.

➤ **A NOVEL APPROACH IN TRANSDERMAL DRUG DELIVERY:**

MICROFABRICATED MICRONEEDLES [13, 14, 15]

The development of more sophisticated drugs has demanded the need for more sophisticated methods to deliver those drugs. Conventional drug delivery techniques using pills and injections are often not suitable for Transdermal protein based, DNA-based, and other therapeutic compounds produced by modern biotechnology. An attractive alternative

method of delivery involves drug administration across the skin. This approach avoids degradation in the gastrointestinal tract and first-pass effects of the liver associated with oral delivery as well as the pain and inconvenience of intravenous injection.

Despite its many potential advantages, transdermal drug delivery is severely limited by the poor permeability of human skin; most drugs do not cross skin at therapeutically relevant rates. A number of methods have been developed to increase rates of transdermal transport with varied levels of success. Chemical enhancers can increase permeability of skin to small molecules but also trigger skin irritation or other safety concerns which limit their use. Iontophoresis employs an electric field to drive ionized molecules across skin by electrophoresis and nonionized molecules by electroosmosis. Despite concerns about skin irritation, iontophoresis may be useful to deliver some peptides and small proteins. Recently, physical methods to transiently increase skin permeability using electroporation and ultrasound have shown promise for delivery of both small drugs and macromolecules.

In this study, we present a novel approach to transdermal drug delivery which dramatically enhances transport of molecules across skin. We have used standard microfabrication techniques to etch arrays of micron-size needles into silicon. When these microneedle arrays are inserted into the skin, they create conduits for transport across the stratum corneum, the outer layer of skin which forms the primary barrier to transport. Once a compound crosses the stratum corneum it can diffuse rapidly through deeper tissue and be taken up by the underlying capillaries for systemic administration.

The design of microneedles which painlessly permeabilize skin is based on an understanding of skin anatomy. Human skin is made of three layers: stratum corneum, viable epidermis, and dermis. The outer 10-15 μm of skin, called stratum corneum, is a dead tissue that forms the primary barrier to drug

transport. Below lies the viable epidermis (50-100 μm), a tissue containing living cells and nerves, but no blood vessels. Deeper still, the dermis forms the bulk of skin volume and contains living cells, nerves, and blood vessels. Therefore, microneedles which penetrate the skin just a little more than 10-15 μm should provide transport pathways across the stratum corneum, but do so painlessly since the microneedles do not reach nerves found in deeper tissue.

Microneedles were made using microfabrication technology, which is the same technology used to make integrated circuits. An advantage of this approach is that microfabrication readily makes structures of micron dimensions in a way that is easily scaled up for cheap and reproducible mass production. To adapt this technology for transdermal drug delivery, we created three-dimensional arrays of sharp-tipped microneedles of approximately 150 μm in length.

A deep reactive ion etching process was used to microfabricate the needles for this study. In this process, a chromium masking material is deposited onto silicon wafers and patterned into dots which have a diameter approximately equal to the base of the desired microneedles. The wafers are then loaded into a reactive ion etcher and subjected to a carefully controlled plasma based on fluorine/oxygen chemistries to etch very deep, high aspect ratio valleys into the silicon. Those regions protected by the metal mask remain and form the microneedles.

Acknowledgment

The author would like to thank to the Principal, Modern college of pharmacy and Dr. N.J.Duragkar, Sharad Pawar College of Pharmacy, Nagpur, India, (or financial support, keen interest, and valuable guidance to carry out the work for providing necessary facilities to complete this research work successfully in the department of pharmaceuticals.

Reference:

- 1) Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems, pharmaceutical Technology 2002. www.pharmtech.com.
- 2) Gregoriades G, Florence AT, Patel HM. Liposomes in drug delivery. Amsterdam: Harwood Academic Publishers; 1993.
- 3) Courrier H. M. Laboratoire de Chimie Thérapeutique et Nutritionnelle, Biodisponibilité Tissulaire et Cellulaire, Faculté de Pharmacie, Université Louis Pasteur, France.
- 4) Williams, Adrian; Transdermal and Topical Drug Delivery Published by Pharmaceutical Press, 2003.
- 5) Arcangelo, Virginia P., Peterson, Andrew M.; Pharmacotherapeutics for Advanced Practice, Published by Lippincott Williams & Wilkins, 2005.
- 6) Kumar, Ritesh and Philip, Anil; Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin; Tropical Journal of Pharmaceutical Research, March 2007.
- 7) Elias, P.M. "Epidermal lipids, barrier function and desquamation", J. Invest. Dermatol.
- 8) Cevc, G. "Transferosomes: innovative transdermal drug carriers", In: Rathbone, M.J., Hadgraft, J. and Roberts, M.S., eds, Modified release drug delivery technology 2003
- 9) Banga, A.K., Bose, S. and Ghosh, T.K. "Iontophoresis and electroporation: comparisons and contrasts", Int. J. Pharm.
- 10) Subramony JA. Sharma A. Phipps JB. "Microprocessor controlled transdermal drug delivery". Int. J. Pharm. 2006.
- 11) Transdermal patch From Wikipedia, the free encyclopedia available : http://en.wikipedia.org/wiki/Transdermal_patch
- 12) Paranjape, Makarand; Biomedical Optics & Medical Imaging, Pain-free diabetic monitoring using transdermal patches Available: <http://spie.org/x27077.xml>

