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Innovations in Transdermal Drug Delivery System- A Review

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ABSTRACT

The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advance has been the development of transdermal delivery systems. The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivery of the drug molecules to the systemic circulation via this route. Various types of transdermal approaches used to incorporate the active ingredients include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Innovations in technologies continue to occur at a positive rate, making the technology a fertile and vibrant. This article deals with the innovations in the field of TDDS to improve the release rate and other parameters and most suitable to the patient.

KEYWORDS

Transdermal Drug Delivery, Microblades, Electroporation, Iontophoresis, Sonophoresis, Microneedles, Magnetophoresis.

INTRODUCTION

Novel drug delivery is geared towards developing friendly dosage forms of various formulations. The aim of the Novel drug delivery system (NDDS) is to increase patient convenience and compliance. The NDDS may involve a new dosage form e.g., from thrice a day dosage to once a day dosage form or developing a patch forms in place of injections. Today, about 74% of drugs are taken orally and are found not to be as effective as desired. Thus, various forms of NDDS such as transdermal delivery systems, controlled release systems; transmucosal delivery systems etc. have emerged.[1]

The potential of using intact skin as the site of administration for dermatological preparations to elicit pharmacological action in the skin tissue has been recognized for several years.

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Until the turn of the century, the skin was thought to be impermeable. However, this view has changed and the progress achieved in this area clearly demonstrates that the skin is a complex organ and allows the passage of chemicals into and across the skin. Skin is the most extensive and readily accessible organ in the body (Fig 1). Its chief functions are concerned with protection, temperature regulation, control of water output, and sensation. In an average adult it covers an area of about 1.73 m^2 and receives one third of circulating blood through the body at any given time.[2] The permeation of chemicals, toxicants, and drugs is much slower across the skin when compared to other biological membranes in the body. The understanding of this complex phenomenon has lead to the development of transdermal drug delivery systems, in which the skin serves as the site for the administration of systemically active drugs. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration,

to produce their therapeutic action.[3] Stratum corneum, located on the outer surface of the skin, is a non-living layer of keratin-filled cells surrounded by a lipid-rich extracellular matrix that provides the primary barrier to drug delivery into skin. The epidermis below is a viable tissue devoid of blood vessels. Just below the dermal-epidermal junction, the dermis contains capillary loops that can take up transdermally administered drugs for systemic distribution. Various layers of skin are schematically represented in fig 1.

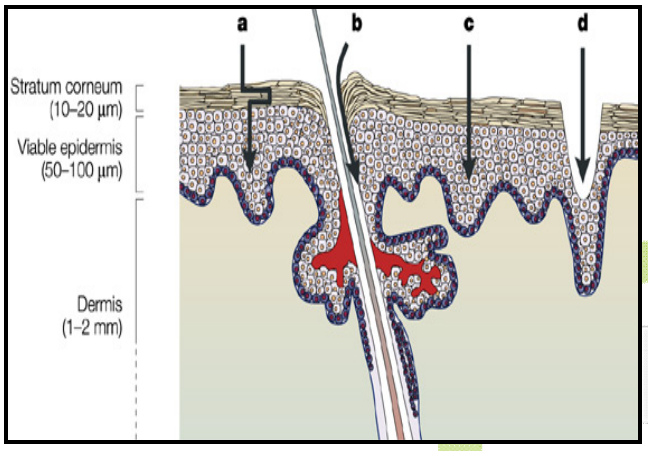

Figure: 1 Schematic representation of a cross section through human skin

Various transport mechanisms across skin include

a Transdermal diffusion, possibly in the presence of a chemical enhancer, takes place by a tortuous route across the stratum corneum, winding around cells and occurring along the interfaces of extracellular lipid bilayers.

b Low-voltage electrical enhancement by iontophoresis can make transport pathways through hair follicles and sweat ducts more accessible.

c High-voltage enhancement has been found to cause transcellular moment by disruption in lipid bilayers.

d The application of ultrasound seems to make pathways **a** and **c** more permeable by disorganizing lipid bilayer structure. Microneedles and thermal poration create micron-scale holes in skin to provide pathways for drug transport.[4]

Throughout the past 2 decades, the transdermal patches have become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. In addition, because transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance.[5]

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. The technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s. Transdermal drug deliveries in the text of research articles grow continuously in the 1980s, and have remained constant throughout the past decade. The market value for transdermal delivery was $12.7 billion in 2005, and is expected to increase to $21.5 billion in the year 2010 and $31.5 billion in the year 2015 – suggesting a significant growth potential over the next 10 years.[6] Innovations in transdermal drug delivery technologies continue to occur at a positive rate, making the technology a fertile and vibrant area of innovation, research and product development.[7]

This article deals with the innovations pertaining to formulation and techniques in the field of TDDS to improve the release rate and other parameters on need base system and most suitable to the patient.

INNOVATION IN TRANSDERMAL TECHNOLOGY

To achieve and to maintain a plasma drug concentration above the minimum therapeutic level, the barrier properties of the skin must be overcome before the effective transdermal

controlled delivery of drugs can be successfully accomplished. Modification of the conventional technology is increasingly being attempted for accomplishing the goal of reducing skin's barrier properties and enhancing transdermal permeation of drugs.

Advanced transdermal technologies include Microblades, Microneedles, Needleless syringe, Mechanical vibrations, Iontophoresis, Electroporation, abrasion, suction, stretching, ultrasound, magnetophoresis, radio frequency, lasers, photomechanical waves, and temperature manipulation.[8]

1. Microblades

Earlier studies were aimed at designing a device for percutaneous drug delivery by overcoming the skin's natural barrier using microprojections.[9] The need for such a device existed because it was hypothesized that once a drug penetrated through stratum corneum with the aid of the device, permeation through the remaining layers could proceed readily. The apparatus basically consists of a cutter having a plurality of microprotrusions having a height chosen with respect to the layer of skin that is to be disrupted and a 'stop' for preventing the apparatus from penetrating the skin beyond a predetermined distance.

As advancement to the basic technique, a microblade device along with negative pressure was patented for the percutaneous sampling of an agent. The device was designed to optionally include a drug-sensing element. The angle of leading edge was kept between 10º-40º or the convex/ concave shaped microblades were used. It was concluded that curving of microblade's tips outside the plane of microblade provided better anchoring.[10] Another device comprising of a piercing member having plurality of microblades was designed. These microblades have 25-400µm length and provision for applying partial vacuum in the range of 0.1-0.8 atm over a period of about 2-30 sec and used for piercing the stratum corneum for body fluid withdrawal.[11] A similar device consisting of a sheet member having plurality of microprotrusions and a rigid support contacting and extending across the sheet member for transmitting an applied force evenly across the length and width of the sheet. The microprotrusions were found to penetrate up to a depth of about 500 µm.[12] The use of electrotransport, osmosis or pressure along with protrusions for withdrawing body fluids via a hydrogel medium increased the permeation of decapeptide over the transport period as compared to an ordinary electrotransport device.

2. Microneedles based Devices

Transdermal patches with microscopic projections called microneedles (figure 2) were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in the development of cutaneous vaccines for tetanus and influenza.[13] The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long). These projections extended from the reservoir and penetrated the stratum corneum and epidermis to deliver the drug.[14] More recently, numerous cost-effective methods of producing microneedle devices have been developed as a result of the rapid advancement in microfabrication technology in the last 10 years.[15-17]

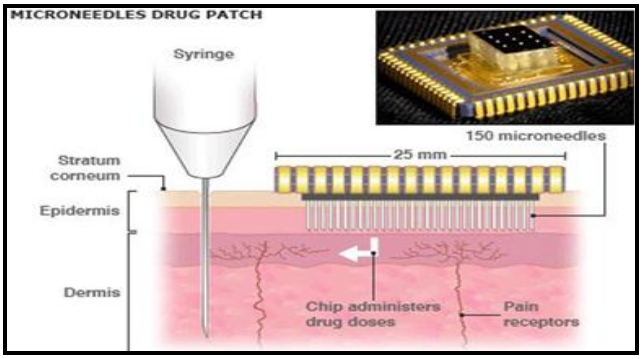

Figure: 2 Microneedle based Drug Delivery[18]

The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir[19] or by dry coating the drug on the microprojection array[20]; the latter being better for intracutaneous immunization.

3. Needless Syringe

This device features an elongate, tubular duct having a lumen for delivering the particles towards the target tissue. The device has a membrane which is ruptured by gas pressure to generate a supersonic gas flow in which therapeutic agent is injected (figure 3). Bellhouse[21] *et al*. injected insulin particles (10 µ diameter) at an initial velocity of 750m/sec into the skin and the penetration depth before the particles come to rest within the skin was about 200µm whereas, 20µ diameter particles injected at 1500 m/sec velocity, were found to penetrate to a depth of 480µm.

Figure: 3 Needless Syringe

4. Mechanical Vibrations

Mechanical vibrations may be used for increasing drug absorption through skin. The frequency and phase of electrical and mechanical vibrations were synchronized in order to increase the absorption effect. A syringe containing a permeation enhancer along with the drug is simultaneously actuated with electrical pulses to move the drug. The drug is passed through a tube and then into a groove surrounding a central electrode of the array of electrodes disposed on the plate. Abrasion of the skin to remove 100 µm layer followed by application of the technique resulted in prompt drug permeation. The frequency of electrical pulses applied were in the range of 2500-3000 Hz, with peak voltage of 160 V. Electrical resistance of 100-500 Kohm was provided to avoid high voltages when the array of electrodes were not applied to the skin. An electrical motor was employed to provide an eccentric motion, which generated vibrations on the vibrating plate. In addition, the use of vacuum pump generated a suction effect on skin and provided a massaging effect on the skin.[22]

This technique was modified to utilize two solution absorbing pads which were electrically insulated from each other and each of them were in electrical contact with one or more of electrodes on probe head. One of the pads was soaked in drug and other with a conductive physiological solution.[23]

5. Iontophoresis

Iontophoretic drug delivery systems are designed to overcome many of the limitations associated with other drug delivery methods. Iontophoresis passes a small direct current (approximately 0.5 mA/ cm) through a drug-containing electrode in contact with the skin as shown in figure 4. A grounding electrode elsewhere on the body completes the circuit.[24-26] Three main mechanisms enhance molecular transport: (a) charged species are driven primarily by electrical repulsion from the driving electrode; (b) the flow of electric current may increase the permeability of skin; and (c) electroosmosis may affect uncharged molecules and large polar peptides.

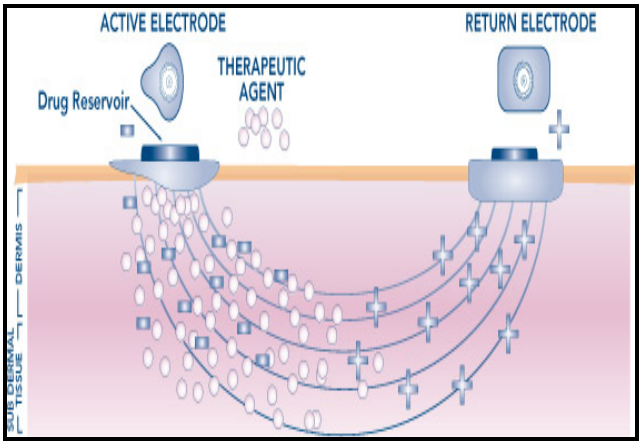

Figure: 4 Iontophoretic Delivery of Drug[27]

Efficiency of transport depends mainly on polarity, valency and mobility of the charged species, as well as electrical duty cycles and formulation components.

Among the many drug delivery methods available today, we believe the advantages of iontophoretic drug delivery are many and include the following:[28]

- Non-invasive, needle-free
- Site-specific drug delivery eliminates systemic side effects
- Rapid onset and cessation kinetics
- Controlled, programmable and titratable drug delivery capabilities
- Single delivery system provides smooth, variable or bolus plasma levels, singly or in combination
- Enhanced delivery of a broad range of compounds
- Minimal variability in the delivery profiles among patients and body sites
- Potential for enhanced patient compliance and control
- Compliance with Needle Stick Prevention Act of 2001.

However, in iontophoresis the apparent current density per unit area is low and most of the current penetrates via the low resistance route i.e. appendages, particularly hair follicles. Thus, the actual current density in the follicle may be high enough to damage growing hair.[29-31]

A lidocaine–epinephrine (adrenaline) device for local anesthesia is now available, and work proceeds on the development of iontophoretic patch systems.[32] An interesting development is reverse iontophoresis by which molecules in the systemic circulation (such as glucose) can be extracted at the skin surface using the electroosmotic effect.[33-34]

6. Electroporation

One of the newer approaches to deliver very large molecules across the skin is by the use of "high-voltage" treatment, known as electroporation, whereas in iontophoresis "low-voltage" is applied. Electroporation (electropermeabilization)[35] creates transient aqueous pores in the lipid bilayers (Fig. 5) by application of short (micro- to millisecond) electrical pulses of approximately 100–1000 V/cm. These pores provide pathways for drug penetration that travel straight through the horny layer.[36-38]

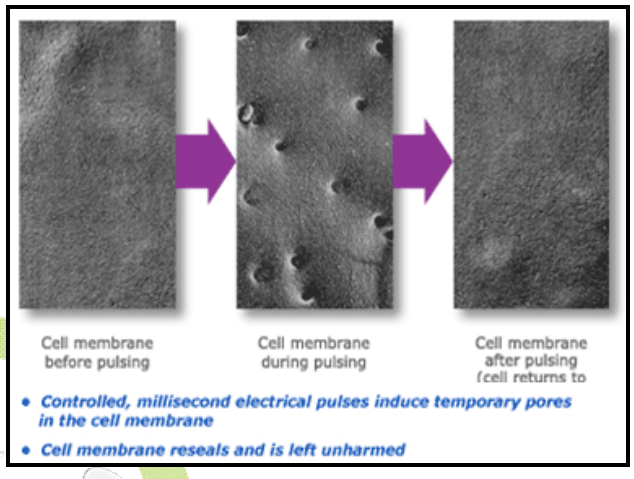

Figure: 5 Phenomenon of Electroporation[39]

There is an increase in flux to almost 10–10^4 folds for neutral and highly charged molecules of with 40 kDa. 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). Skin permeability of biopharmaceuticals with molecular weights greater than 7kDA has also increased by this technology.[40]

7. Ultrasound (Phonophoresis, Sonophoresis)

Sonophoresis or phonophoresis is the application of ultrasound to enhance the percutaneous drug delivery. It has been used by physiotherapists for over 30 years, especially the combination of ultrasound and steroids or analgesics, in order to treat a variety of muscular and arthritic conditions. Recently, sonophoresis has attracted lot of interest in transdermal delivery with a focus on peptide/protein delivery.[41] Phonophoresis (or sonophoresis) uses ultrasound energy in order to enhance the skin penetration of active

substances.[42] When skin is exposed to ultrasound, the waves propagate to a certain level and resulting in skin permeation via various mechanisms.

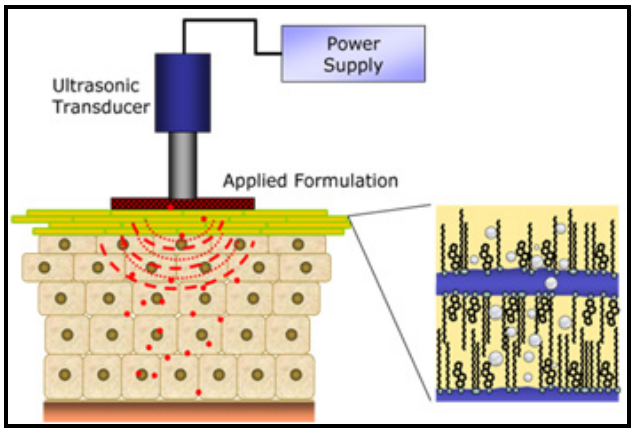

Figure: 6 Basic Principle of Ultrasound[43]

Figure 6 depicts the processes that can contribute to phonophoresis. One of these effects is the formation and subsequent collapse of gas bubbles in a liquid called cavitation. The force of cavitation causes the formation of holes in the corneocytes, enlarging of intercellular spaces, and perturbation of stratum corneum lipids. Another effect is heating which is mainly due to the energy loss in propagating the ultrasound wave due to scattering and absorption effects. The resulting temperature elevation of the skin is typically in the range of several degrees centigrade. This temperature rise will increase the fluidity of the stratum corneum lipids as well as directly increase the diffusivity of molecules through the skin barrier. In addition, ultrasound can push particles by increase in low intensity pressure in the skin.[43]

8. Magnetophoresis

Magnetophoresis, which is still in the research phase, enhances skin permeability by applying a magnetic field. The research data on animal models suggests that skin penetration can be enhanced by applying a magnetic field to therapeutic molecules that are diamagnetic or paramagnetic in nature.[44]

9. Laser Radiation

This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.[45-47] A handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia), which, in a study involving human volunteers, was found to reduce the onset of action of lidocaine to 3 to 5 minutes, while 60 minutes was required to attain a similar effect in the control group. Laser systems are also being developed to ablate the stratum corneum from the epidermal layer.[48] As with microneedles, the ablated regions offer lower resistance to drug diffusion than non-ablated skin.[49]

10. Photomechanical waves

A drug solution, placed on the skin and covered by a black polystyrene target, is irradiated with a laser pulse. The resultant photomechanical wave stresses the horny layer and enhances drug delivery.[50] The technique is likely to remain experimental.

11. Increase in Temperature

Local increase in temperature increases blood flow and in turn, rate of permeation/transport of active substance into the skin increases. This technique has the advantage of not employing a chemical, is non-invasive and hence, does not require activation of self-repair mechanism by the skin.

Stanley[51] *et al*. developed a transdermal device that employed an oxidation reaction for controlled heating of skin. Heat generating component comprised of a mixture of activated carbon, iron powder, saw dust, sodium chloride and water. Application of heat (42-44ºC) for 4 hr was found to be sufficient to decrease the time (14-18 hr to 3-4 hr) required for the patch to deliver fentanyl at a steady state serum concentration.

Another invention reported serum fentanyl concentration to increase very rapidly (within 5-10 min) and significantly (>75%) following the commencement of heating. The elevated concentration stayed elevated for an extended

period of time. Reduction of heating area to half still produced 30% higher serum fentanyl concentration.[52]

Koch[53] *et al*. used an effective component Opraflex to increase the local skin temperature and observed an increase in the transdermal absorption rate of morphine base from 5.7 to 26.4%.

CONCLUSION

Transdermal drug delivery is hardly an old technology, and the technology is no longer limited to adhesive patches. In recent years, the transdermal route of drug delivery has evolved considerably and it now competes with oral route. Most of the device-induced transdermal drug delivery techniques are still in the early stages of commercialization. All device induced transdermal delivery techniques have a common concern regarding the safety of use, and skin reactions arising due to perturbing the stratum corneum – even though it is only temporary. However, combining electrical or mechanical device induced skin penetration methods with improved formulations is likely to produce the ideal transdermal drug delivery devices.

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