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TRANSDERMAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH TO DELIVER POTENT THERAPEUTIC AGENTS

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ABSTRACT

The skin provides an easily accessible and convenient place for medication management. To date, the flexible drug delivery industry, which aims to improve safe and effective skin delivery systems, has gone into the past and continues to accumulate more time and investment in the continuous development of new and innovative methods. This review describes the progress and current state of the flexible drug delivery sector and describes the many drug advances that have been used to overcome limitations related to skin delivery programs. The advantages and disadvantages of various methods are detailed, the products being marketed are highlighted and the focus is on the emerging field of micro needle technology.

KEYWORDS: transdermal, drug delivery, speed-based device, ultrasound, thermal ablation, mechanical and electrical methods, micro needle.

INTRODUCTION

The most common forms of drug delivery are oral and parental methods containing many small oral drugs.[1,2] The oral route has the benefit of pre-determined dosages, dosage and self-administration of the patient. For these reasons, the oral route remains the easiest way to deliver medication.[3,4] However, many therapeutic peptides or proteins are not delivered through the oral route, due to the rapid degeneration of the stomach and limited movement of size in the epithelium.[5] Thus the primary method of treating macromolecules with unrestricted injections,[1,5,6] such as the invasive nature of injections that express pain and low acceptance / adherence in patients, in addition to the requirement for professional human administration regulator.[5,6,7] Logically, conventional drug delivery methods have many natural limitations that can be overcome by advanced drug delivery methods such as transdermal drug delivery (TDD).

Transdermal Drug Delivery (TDD): TDD is a painless way of delivering drugs in a systematic way through the formation of the drug on the complete and healthy skin[2,5] The drug first enters the stratum corneum and then passes through the epidermis and deep dermis without accumulation of the drug in the skin layer. When the drug reaches the skin layer, it is absorbed into the system by dermal microcirculation.[8,9] TDD has many advantages over other conventional drug delivery methods[10,11,12] It can provide an insane alternative to parental routes, thus avoiding problems such as needle phobia[2] The large surface area and easy access allow for multiple skin placement options to absorb transdermal[5] In addition, the pharmacokinetic profile of the drug is very similar and has fewer peaks, thus reducing the risk of toxic side effects.[2] It can improve patient compliance due to reduced dosing frequency and is suitable for unconscious or vomiting patients, or those who rely on self- administration.[13] TDD prevents pre-systemic metabolism, thereby improving bioavailability.[2,4] Referring to the use of the skin as a novel immunization strategy, this organ is known to be packed with dendritic cells in both the epidermal and dermal layers that play a key role in the immune response making TDD an attractive immune system for therapeutic protein and peptides.[3,14] The need for affordable and effective vaccines, especially in developing countries,[3,14,15] has led to extensive research focusing on the development of simple, injectable programs such as TDD for vaccine purposes. This theme will be discussed further in Section 4.5.2 of this review.

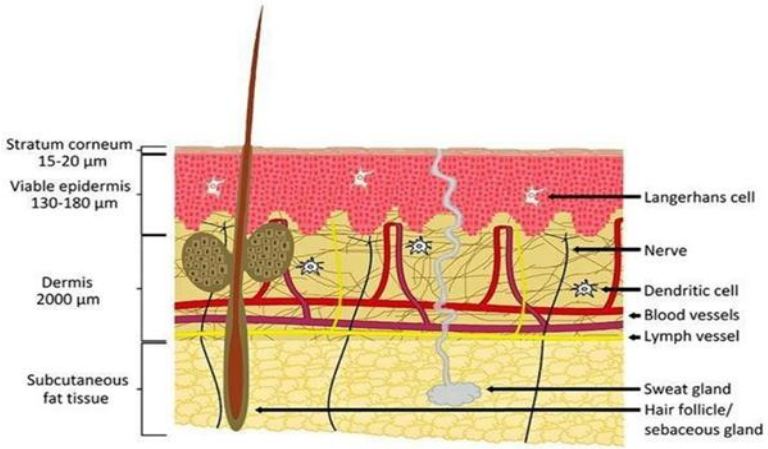

Figure-1: Anatomy of skin (Reprinted from [30] login. Copyright 2012 Elsevier).

A Brief Review of the Skin Structure: The skin is the most accessible and largest organ with an area of 1.7 m^2, which puts at least 16% of the average human body weight.[16,17,18] The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the flow of ultraviolet (UV) radiation, chemicals, allergies and water loss.[19] The skin can be divided into three main regions: (1) the outer layer, the epidermis, which contains the stratum corneum; (2) the middle layer, the dermis and (3) the inner layer, the hypodermis (Figure 1).[5,20,21]

Epidermis: The epidermis is the outer layer of the skin and varies in thickness by about 0.8 mm on the palms of the hands and soles of the feet.[19] It consists of regions with multiple layers of epithelial cells and the active epidermis is often referred to as the epidermal layers beneath the stratum corneum.[8,19] The cellular content of the epidermis consists mainly of keratinocytes (about 95% of cells), and other epidermal layer cells including melanocytes, Langerhans cells and merkel cells.[14] The stratum corneum is the highest layer of – epidermis.[19,23,24] It is in direct contact with the external environment and its barrier properties may be partially related to its very high density (1.4 g / cm^3 in dry area) and its low hydration of 15% –20%.[25] The stratum corneum cells are composed mainly of insoluble keratin (70%) and lipid (20%).[25] Water in the stratum corneum is associated with keratin in the corneocytes.[19,26]

Dermis: The dermis is approximately 2-3 mm thick and contains collagenous (70%) and elastin fibers that provide strength and elasticity to the skin.[17] The blood vessels found in the dermis supply nutrients to both the dermis and the epidermis. Nerves, macrophages and lymphatic vessels are also present in the dermis layer, as shown in Figure 1.[23]

Hypodermis: The hypodermis or subcutaneous layer is a deep layer of skin and contains a network of fat cells.[17] It is the contact layer between the skin and the underlying tissues of the body, such as the muscles and bones. Therefore, the main functions of the hypodermis are to protect against physical trauma, heat insertion and support and the activation of vascular and neural signals of the skin.[27] Hypodermis fat cells make up about 50% of body fat and other prominent hypodermis cells including fibroblasts and macrophages.[28]

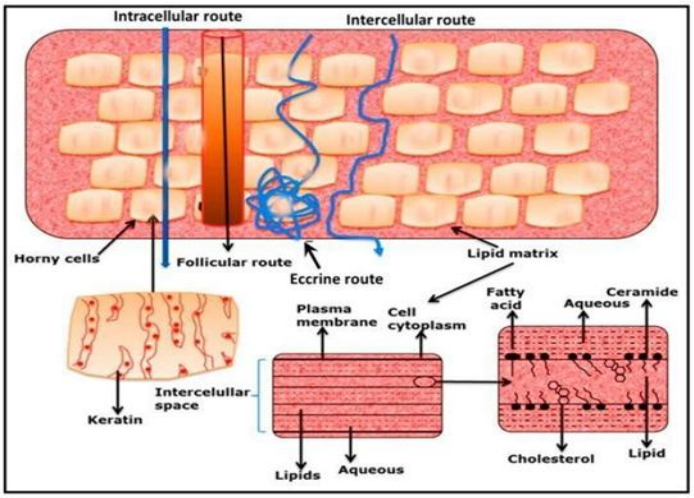

Figure-2: Methods of drug penetration into human skin. (Reprinted from[30] login. Copyright 2012 Elsevier).

Methods of Drug Intrusion: There are two ways the drug can penetrate the skin, namely trans-epidermal and trans-appendage pathways, which have been presented diagram in Figure 2. Trans-epidermal method involves the passage of molecules into the stratum corneum, i a variety of structures, with multiple layers and a multi-cellular barrier. Transepidermal infiltration can be termed intra- or inter-cellular.[29] I intracellular pathway through corneocytes, separated by death keratinocyte, allows the transport of hydrophilic or polar solutes. Transportation with intercellular spaces allows the diffusion of lipophilic or non-polar solutes through a continuous lipid matrix. The trans-appendageal route includes the passage of molecules through the sweat glands and throughout the hair follicles.[5,30]

Methods of drug penetration into human skin. (Reprinted from.[30] login. Copyright 2012 Elsevier).

Kinetics of TDD: Understanding the kinetics of skin permeation is essential for the development of effective TDD systems. To test for any TDD, percutaneous absorption of molecules is a very important step. Percutaneous absorption penetrates substances into various layers of the skin and penetration of the skin into systemic circulation.[8,31,32,33] Percutaneous absorption of molecules is a wise move that includes:

Infiltration: The penetration of an object into a specific layer of skin; Distinguish from stratum corneum to strong epidermis; Spread of active epidermis and upper skin.

Permeation: The penetration of molecules from one layer to another, which differs in both function and structure from the first layer.

Absorption: Absorption of a substance in a systemic circulation. In delivery systems involving transdermal patches, the drug is stored in a water reservoir (reservoir type) or a dissolved drug in a liquid or gel-based reservoir (matrix type). transdermal patch is a measure of the maximum flexibility of a drug compound on the skin (variable (J)) which is usually expressed in units of µg / cm^2 / h) (Figure 1) (Figure 3). Based on Fick's distribution law, the transport of medical molecules to the skin will be maintained until the concentration gradient remains.[33,34,35]

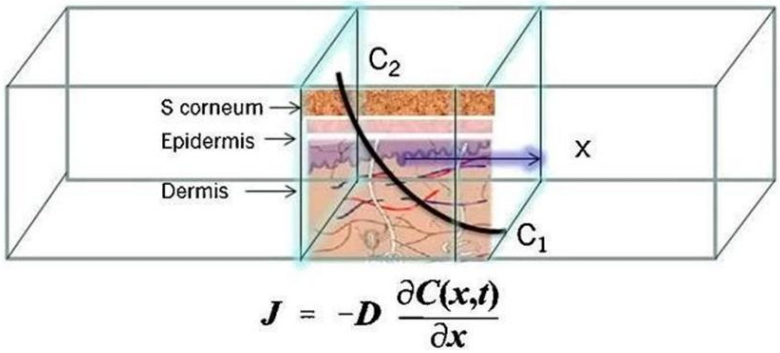

Figure-3: Definition of transformation in the skin from the transdermal patch.

Where J is the flow of cells, C2 is the concentration of the active molecule in the pool, C1 is the concentration of the active molecule in the body, D is the coefficient of distribution; L thickness of the opposite distribution phase, and t distribution time. Statistics show Fick's law of distribution. (Reprinted from.[33] login. Copyright 2013 Elsevier).
J = −D; dc dl (1)

Where D is the distribution coefficient and dc / dt is the concentration gradient. Normal TDD can only occur if the drug has certain physicochemical properties. Skin penetration rate (dQ / dt) is provided by.[35]
dQ / dt = P (Cd - Cr)(2)

where Cd and Cr are the focus of skin penetration into the donor area (i.e., the surface of the stratum corneum) and the reception area (i.e., the body), respectively. P is the coefficient of penetration of skin tissue into the infiltration area.
P = D ∗ K / L(3)

where D is the distribution coefficient obtained from the access coefficient, P, solute partitioncoefficient, K, and L is the total thickness of the skin tissue.

From equation (2) it is clear that a continuous level of drug penetration can only be achieved if Cd >> Cr that is, the concentration of the drug in the area of the stratum corneum. Cd is still sitting and much larger than the drug in the body of Cr. The equation becomes:
dQ / dt = P * Cd(4)

The combined value (Q) barrier with an effective entry point (A) at a given time (t) iscalculated using Equation (5)[35]:
Q = PACdt(5)

The permeability coefficient (P) can be obtained from the slope of the component permeation accumulated diffusant compared to the time obtained in the penetration test. A typical section of the entry study is shown in.

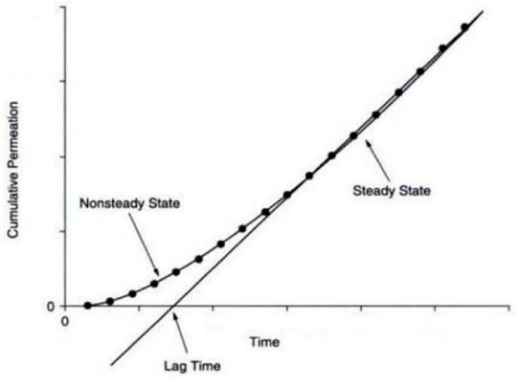

Figure-4: A typical article on permeation research L thickening of the swollen membrane.

As shown in Figure 4, the collection the permeation curve has two parts. The first part of the curve represents the spread of a constant state and part of the line corresponds to a stable state spread. The immovable part of the curve can be defined mathematically by Fick's second law, while part of the line can be expressed by Fick's first law.[35] The time required to reach a stable state is approx called lag time (tLag). The lag time can be determined by extrapolating part of the entry line competes with the time curve on the time axis. With a delay time, Number (6) is rewritten as (7).[35]

$Q = [DKACd (t - tL)] / L$ (6)

$Q = PACd (t - tL)$ (7)

The lag time can be calculated by Equation (8).[35]

$tL = L2 / 6D$ (8)

Transdermal systems should be designed to provide maximum thermodynamic driving power to temporarily spread the skin on a full charge of the drug to ensure the delivery of the drug to the entire skin. The ability of transdermal-approved drugs to penetrate the skin varies greatly from nicotine to highly concentrated compounds, such as buprenorphine and progestins, which have a much lower predictor fluxes.

The first transdermal episode approved for systemic delivery in 1979 was an episode of continuous, three-day delivery of scopolamine for the treatment of motion sickness.[1,34] Transdermal delivery is currently limited to approximately 17 drug molecules approved by the US Food and Drug Administration (FDA) (Table 1).[2,4] The approximate number of drug molecules identified in Table 1 shows the complexity of meeting the two major pharmacological activity and appropriate physicochemical structures to allow for skin penetration.[34,36] 500 Da), moderate lipophilicity (log P = 1-3), and moderate solubility in both oil and water because TDD systems require both breaking lipophilic stratum corneum and re-insertion in the central fluid systemic circulation.[8,34] In addition, high pharmacological strength of drug molecules is required for a person to develop TDD.[8,36,37] The limited penetration of molecules is due to the outer layer of the skin, the stratum corneum.[38,39] This layer of "dead" tissue has the ability to block the entry of foreign chemicals that bind to drug molecules and therefore acts as a very effective barrier.[39,40] To improve drug penetration into the skin, a number of chemical and physical therapies have been developed.[3,5,34]

Strategies for Improving Skin Permeabilization: The technology used to convert stratum corneum barrier structures can be classified into passive / chemical or functional / physical pathways (Figure 5). Non-invasive methods include influencing drug interactions with motor and optimal performance, in order to correct the structure of the stratum corneum.[29,41,42] Passive methods are easy to apply to transdermal patches such as chemical enhancers and emulsions.[43] However, a major setback of inactive methods may be a time of delay in drug withdrawal which has been found to have a clear negative effect on fast-acting drugs, such as insulin.

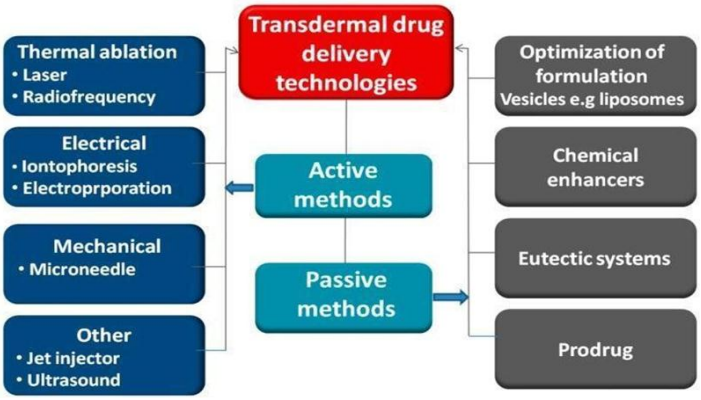

Figure-5: Ways to improve drug transport on the skin.

One of the most widely used methods of inactivation is the use of chemical penetration enhancers that facilitate drug penetration into the skin by increasing drug secretion in the stratum corneum block, without long-term damage to the skin.[11,44] Entry enhancers have several mechanisms of action such as: enlargement of stratum corneum lipid bilayers, interaction with intracellular proteins, disruption or removal of intercellular lipids, increased thermodynamic activity of the drug and increased stratum corneum hydration.[11,44,45] Several types of entry enhancements are known and can be classified into several groups based on their chemical composition, rather than their method of operation.[32,44] Most of these have mixed performance so it is difficult to distinguish them by this feature. Examples of commonly investigated additives are alcohol, sullfoxides, azone, pyrrolidones, essential oils, terpenes and terpenoids, fatty acids, water and urea.[44,45] However, the main limitation of entry enhancements is that their effectiveness is often closely related to the appearance of skin irritation.[32,45] Gels used in TDD and recent advances in technology have made new variations in semisolid vehicles such as proniosomes and microemulsion gels in the field of penetration enhancements.[43] Proniosomes are non-ionic based surfactant vesicles, known as ‘‘dryniosomes’’ because they may require water flow before drug release and penetration into the skin. Proniosomal gels have been used in TDD because they act as infiltration enhancers that enhance drug penetration from the skin barrier.[43,46] When hydration proniosomes are converted into niosomes they are able to disperse throughout the stratum corneum and then adhere to the cell surface resulting in a high thermodynamic drug gradient in place of the vesicle / stratum corneum, thus acting as a driving force. of lipophilic drugs on the skin (Figure 6).[43,46]

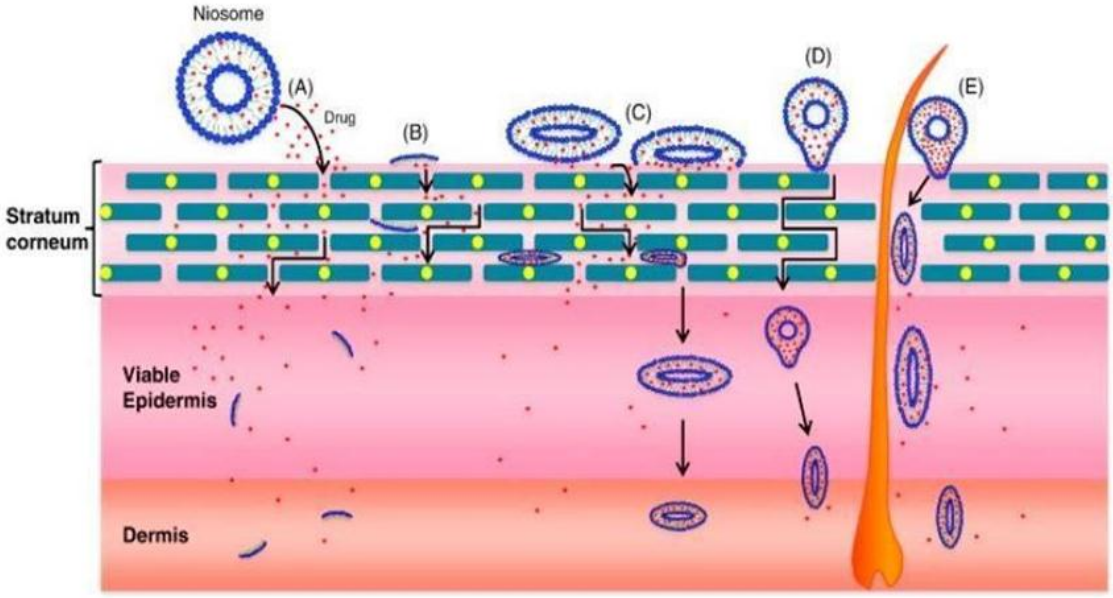

Figure-6: Possible mechanisms of action of vesicles emerging from skin and transdermal function.

Possible mechanisms of action of vesicles emerging from skin and transdermal function:

(1) drug molecules released by niosomes;
(2) niosome elements act as an entry enhancer;
(3) niosome adsorption and / or integration with stratum corneum;
(4) niosome penetration into stable skin;
(5) Niosome infiltration through hair follicles and / or pilosebaceous units. (Reprinted from.[46] login. Copyright 2014 Elsevier).

Some of the limitations associated with login enhancements are efficiency and security. They do not get the desired skin irritation and their ability to increase migration to the skin is low and varied.[46,47] In terms of safety considerations, entry enhancements have been shown in a limited number of cases that can cause skin irritation including local inflammation, erythema, inflammation and dermatitis.[47]

Effective methods of skin permeabilization include ultrasound, assisted electronics (electroporation and iontophoresis), speed-based devices (powder injections, jet injectors), thermal methods (laser and radio-frequency heating) and mechanical means such as microneedles (MN) and tape. Stripping.[2,48,49,50,51] These methods allow a wide range of drugs to be delivered to the skin. Effective methods include the use of external force to act as a driving force in the skin or by physically disrupting the stratum corneum.[48,49] These processes greatly increase the range of drugs that can be effectively delivered to the entire skin. This will also significantly increase the market value of transdermal delivery and will be even more important in the coming years as the number of new drugs of natural origin continues to grow. In addition, effective methods also provide repetitive control over drug delivery profiles, thereby reducing sleep intervals between application and the drug that reaches systemic circulation compared to inactive

methods.[11,48] Some of these effective methods will be explained in detail below.

Ultrasound Devices: Ultrasound is an oscillating sound pressure that has long been used in many areas of research including physics, chemistry, biology, engineering and various other frequencies.[2,50] Ultrasound, sonophoresis, or phonophoresis can be defined as the transport of drugs into the skin using ultrasound perturbation at frequencies of 20 kHz – 16 MHz strong enough to reduce skin resistance.[2,5] The use of ultrasound has led to the successful delivery of different phases and phases of drugs, regardless of their electrical properties, by increasing skin maturity. These drugs contain hydrophilic drugs and high molecular weight.[39] However, the mechanism is not yet fully understood or demonstrated.[50] Proposed methods in which ultrasound effects on tissues and cells include thermal and cavitation effects caused by collapse and acoustic diffusion can be described as oscillation of cavitation bubbles in the ultrasound field.[5] Ultrasound can increase the temperature of the insonated medium (skin) by absorbing sound waves with a frequency greater than the upper limit of human hearing. Clearly, the higher the average absorption coefficient, the greater the temperature increase and thus the greater the temperature effect.[50] All recent studies indicate that cavitation is believed to be the leading cause of TDD development through ultrasound treatment.[50]

The concept of ultrasound for use in TDD was first reported by Fellinger and Schmidt in 1950 for effective treatment of polyarthritis using hydrocortisone ointment combined with sonophoresis.[52,53,54] However, the first ultrasound device for transdermal application was approved in 2004 by the FDA for local dermal anesthesia by Sontra Medical, SonoPrep® (Figure 7). Since then, ultrasound has been widely used as a TDD system in the treatment of many other diseases including arthritis and bursitis.[2] Many challenges have to be overcome before such resources can be commercially acceptable. Some of these challenges include: the availability of easy-to-use equipment; determining the duration of treatment required; to gain a complete understanding of how technology works; expansion of the list of drugs that can be delivered and testing of machine safety profiles.[5,39,55,56] Examples of adverse effects of ultrasound methods were observed by Singer et al. (1998) where it has been shown that low- intensity ultrasound induced mild skin reactions in dogs while high-intensity ultrasound can induce second-degree heat.[56] Limits like these must be overcome before these new approaches can be fully accepted.

Figure-7: SonoPrep® ultrasound device.

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Electrical Strategies

Electroporation: The two main mechanisms of electrical TDD are iontophoresis and electroporation.[2,4] In electroporation, cells are temporarily exposed to high concentrations of electrical pulses that lead to the formation of aqueous pores in the lipid bilayers of the stratum corneum, thus allowing the drug to spread throughout the skin.[5,57,58,59] This process was first described by Neumann et al. in 1982.[59] The use of high voltage pulses (50-500 V) for short periods of only one second has been shown to increase transport in the skin with various molecular weight drugs ranging from small eg. fentanyl, timolol,[60,61] calcein,[62] to high-dose drugs such as LHRH, calcitonin, heparin or FITC-dextran has a molecular weight of up to 40 kDa.[58,63,64,65,66] However, the main barriers are the lack of volume delivery, the death of high-density cell death and potential damage to labile drugs, e.g., those of protein origin.[57,67]

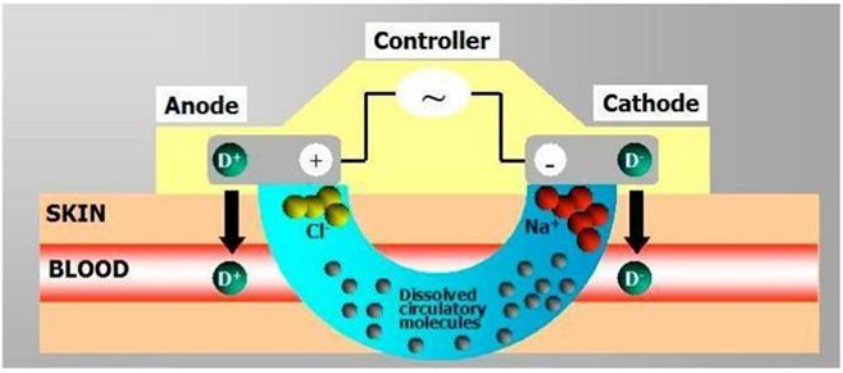

Figure 8: Schematic representation of an iontophoresis patch (Reprinted from [40] with permission. Copyright 2000 Elsevier).

Iontophoresis: Iontophoresis involves the use of acceptable electrical currents (0.1–1.0 mA / cm^2) to drive patents charged on the skin through electrostatic effects and to release ionic drugs through the skin into the body at its potential gradient.[5,20,58, 68, 69,70,71] Unlike other transdermal enhancement methods, it works primarily by incorporating secondary driving forces, a potential electric gradient as a concentration of concentration gradient throughout the skin as non-rechargeable species can also be brought about by electroosmosis (Figure 8).[5,70]

Phoresor®, Lidosite®, and E-trans® are examples of three commercially developed iontophoretic delivery systems (Figure 9). The first approved commercial iontophoretic patch system was LidoSite®, which was developed to deliver lidocaine for fast dermal anesthesia. The system was composed of a disposable pre-filled patch, re-usable battery-powered controller and a flexible interconnect module.[20] Iontophoresis has a minor effect on skin structure over short treatment periods due to the low-voltage nature of the applied electric current, when compared to electroporation.[5]

(a) (b)

Figure 9: Iontophoretic delivery systems are commercially developed: (a) Phoresor® and (b) Lidosite®.

Several factors affect iontophoretic TDD, which includes the pH of the donor solution, the electrode type, buffer concentration, current strength and the leased current type.[209,72,73,6] The cellular size of the solute / drug is an important factor in determining the probability of successful iontophoretic delivery. The flow of small and super hydrophilic ions is faster than that of large ions.[72,73,74] Numerous studies associated with flexibility as a function of molecular weight have been performed and it has been found that the transport of compounds decreases with increasing cellular weight (chloride> amino acid> nucleotide> tripeptide> insulin).[22,72,75,76, 77,78] There is a linear relationship between the current flow and the drug in the skin but it is currently limited to 1 mA to facilitate the patient's comfort and taking into account current increased safety concerns, the risk of indirect vasodilatation also increases.[72] In addition, the maximum time when the devices can be used is 3 minutes, to prevent local skin irritation or burns. The current acceptable iontophoretic threshold is 0.5 mA / cm^2.[79] At present it should be high enough to provide the required degree of flexibility but should not irritate the skin.[80] The use of continuous direct current (DC) can reduce the flow of the drug due to its polarization effect on the skin.[69] To overcome this problem, pulsed current.[81] was used. Overall, only a limited number of studies were performed comparing pulsed direct iontophoresis against continuous direct current iontophoresis. Recently, Kotzki et al. 2015 showed that pulsed iontophoresis treprostinil significantly improved cutaneous blood flow compared with progressive iontophoresis.[69] The most common electrodes used for iontophoresis are aluminum foil, platinum and silver / silver chloride electrodes.[73] However, preferred is Ag /

AgCl as it withstands changes in pH. In addition, the electrode materials used for iontophoretic delivery should be harmless to the body and flexible for use near the body surface.[73]

The molecular weight of iontophoretic delivery has not been extensively studied, although it is estimated that molecules with a molecular weight of less than 12,000 Da may be successfully delivered to the skin by iontophoresis.[79] In order to deliver more than 12,000 Da molecules, another way to overcome the stratum corneum barrier structures must be sought. However, it was found that a small protein, cytochrome c (12.4 kDa) was introduced without attack on the whole skin.[82,83] Subsequently, ribonuclease A, with an isoelectric score of 8.64 (13.6 kDa), was successfully exported to pig and human skin.[84] More recently, it has been shown that transdermal iontophoresis has also been able to produce biologically active human basic fibroblast factor (hbFGF; 17.4 kDa) with appropriate therapeutic values similar to those used in clinical trials and animal studies.[85,86]

Iontophoresis applications can be divided into therapeutic and diagnostic applications. Iontophoresis has been used for various types of diagnoses e.g. to diagnose cystic fibrosis.[87] and more recently to monitor blood glucose levels[88] The main advantage of iontophoresis in diagnostic use is that no mechanical penetration or skin disorders are involved in this method.[89,90]

Speed Support Devices: Speed-based machines, which can be powdered or liquid jets, use a high-speed aircraft with speeds ranging from 100 to 200 m / s to pierce the skin and deliver drugs using an energy source (compressed gas or spring).[91] The idea of injecting jets to be used in drug delivery was first explored in the early 1930's by Arnold Sutermesiter.[11] Since then, interest in this method of drug delivery has increased significantly and two types of jet injectors have been developed; single-dose jet injections (disposable cartridge jugs) and frequently used nozzle jet injections (MUNJIs).[91] Jet injections have been used for more than 50 years for the delivery of parents' vaccines, as well as small molecules, such as anesthetics and antibiotics.[11] A jet injector is a free injection device capable of delivering electronic controlled doses that lead to improved delivery consistency and reduced patient pain (Figure 10).[48,92]

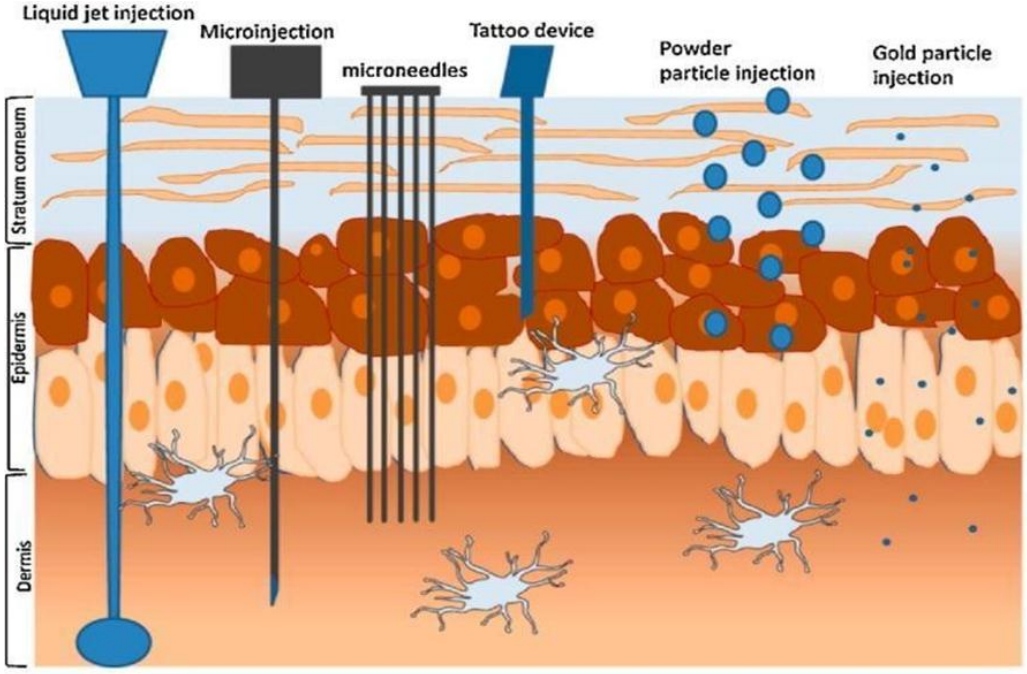

Figure-10: Methods of intradermal injection. (Reprinted from[93] login. Copyright 2005 Elsevier).

Liquid jet injections propel a fluid from a tube with a diameter of 50 to 360 μm, much smaller than the outer diameter of a normal hypodermic needle (810 μm 21G needle.[20,93,94] The jet can deliver drugs of different skin layers e.g., intradermal (i.d.), subcutaneous (s.c.) or intramuscular (i.m.), by changing jet velocity and orifice diameter.[20] The great advantage of using needle-free devices is related to concerns about safe needle disposal and the avoidance of accidental injection of the needle stick.[20] However, the risk of cross contamination is negligible, as spinal discharge of interstitial fluid from the skin may contaminate the mouth of the tube.[95] Therefore the use of nozzle jet injections is frequently discontinued and these devices are now only used for the delivery of high-dose drugs to the same person, e.g., T Jet®device that delivers somatropin (human growth hormone (hGH)) (Figure 11).

Figure-11: T-Jet® jet injection available for sale.

Powdered jet injections are more effective than liquid jet injections to deliver strong drugs or targets to the skin, so structural stability will increase and the need for cold storage will be avoided, making it easier to navigate and reduce associated costs. Powder jet injections may be made from nano- or small particles containing active or lyophilized drugs and antigens.[20,96] Excellent bioavailability of a number of drugs has been reported but short-term pain and injury caused by patients have limited the general acceptance of jet injections.[91] With regard to the levels of pain experienced by volunteers, some reports indicate that no pain difference was recorded compared to jet injections and standard injection injections.[97] but some have reported higher pain scores.[98] The basic design of solid jet injections consists of compressed gas as a source of energy, a drug-filled environment containing solid drug formation, and a tube that directs the flow of particles into the skin.[99] By initiating the opening process, the compressed gas expands and forces the drug powder through a microphone into the skin. When they touch the skin, the particles form small holes and attach to the stratum corneum or active epidermis. The most important parameters that control the delivery of particles to the stratum corneum are the characteristics of the particles (size, density) and impact speed.

Thermal Approaches (Lasers and Radio-Frequency Heating): Thermal extraction is a method used to deliver the drug systematically to the skin by burning the surface of the skin, reducing the stratum corneum selectively at that temperature only, without damaging the deep tissues.[49,100] Many methods can be used to trigger thermal emissions such as laser,[101] radiofrequency,[49,102] in addition to electric heating elements.[49] In order to produce the high temperatures needed to burn the stratum corneum without damaging the painted epidermis, the heat exposure should be short, so the temperature across the stratum corneum can be high enough to keep the skin surface very hot but the temperature of the active epidermis is not compatible with significant temperature rise.[100]

Laser Thermal Ablation: Laser methodologies have been used in clinics to treat dermatological conditions such as pigmented lesions.[101,103,104] The main method of laser thermal ablation removal is selective removal of stratum corneum without damaging deep tissue, thereby enhancing the delivery of lipophilic and hydrophilic drugs to the skin layers.[26,45,104,105] Lasers remove the stratum corneum by optical power induction, which causes water vapor and microchannel formation on the skin.[106] In addition, such methods have been used to extract interstitial fluids to measure blood sugar levels in diabetic patients.[49,101,103] However, the degree of disturbance achieved is determined by wavelength, pulse length, muscle thickness, pulse strength, tissue absorption coefficient, pulse number, laser exposure length and pulse frequency rate.[48,58,107] Baron et al., 2003 showed that previous laser treatment followed by lidocaine cream was found to reduce the onset of lidocaine action by 3-5 min in human volunteers.[106] However, structural changes in the skin should be evaluated, especially at the high levels of laser used that may be needed to improve the transport of large molecular therapeutic drugs.[108,109]

Radiofrequency (RF): Thermal Ablation Radiofrequency ablation of thermal ablation involves the placement of thin electrodes, such as a needle directly on the skin and the use of high frequency alternating current (~ 100 kHz) which produces very small pathways in the stratum corneum, where drugs can enter (Figure 12).[49,100] Exposure to skin cells at high frequencies (100–500 kHz) causes ionic vibrations within the tissue that attempt to set heat to a specific area of the skin and thus burn cells in that region, leading to drug transport to the skin.[110] This technology may allow the transdermal delivery of a variety of hydrophilic compounds and macromolecules using an inexpensive, completely discarded device.[49]

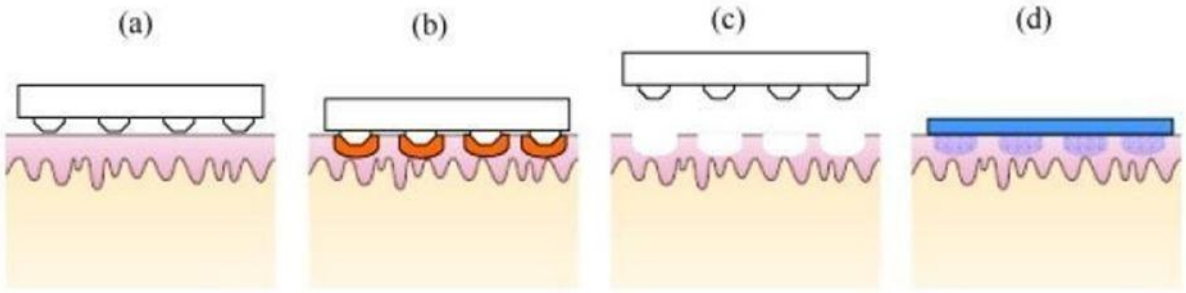

Figure-12: Design diagram of delivery of drugs using thermal ablation: (a) micro-electrodes are pressed into the skin, (b) the skin is heated exerted due to RF energy or opposing heat on the electrodes, (c) after extraction device, (d) micropores formed. (Reprinted from.[11] login. Copyright 2008 Elsevier).

Mechanical Methods for Intercropping Skin Contamination: The use of hypodermic needles, often associated with phobia, pain and the risk of needle injury has been used to overcome some of the limitations of delivery commonly found in macromolecular compounds.[111,112] Other new methods have been explored to overcome these problems and include the use of MN and tape removal. These ideas will be explained further below.

Tape Stripping: It is an easy way to remove the stratum corneum layer with repeated use of adhesive tapes.[113] The amount of stratum corneum removed with a single adhesive tape depends on many factors such as the size of the stratum corneum, the patient's age, composition and lipid volume that varies depending on the anatomical location and finally, skin parameters such as transepidermal fluid loss (TEWL) and pH. In addition, other factors also affect the amount of stratum corneum released by tape degradation, such as the ability to release the tape from the skin and the length of the pressure on the skin.[113,114] Removing the tape is a solid and easy way. However, many limitations must be considered before and during the application of this procedure, such as during pressure on the skin, in order to remove the stratum corneum evenly.

Microneedle (MN) Arrays: MN arrays, non-invasive drug delivery systems, have been developed to overcome some of the abnormalities commonly associated with hypodermic needle use and to address patient compliance. MN arrays have the potential to be used as an alternative to hypodermic and subcutaneous needle technology (Figure 13).[12,34,111,112] MN technology has undergone extensive research and development efforts by both academic and industrial researchers with some currently developing clinical tools and others awaiting FDA approval.[1,34] And the number of publications describing MN as novel devices that attack slowly for drug delivery purposes has grown significantly in recent years.[1,34,112,115] As MN combines the ease of transdermal patch with the success of delivery achieved using common hypodermic needles and syringes, they continue to seek interest and investment.[34,116]

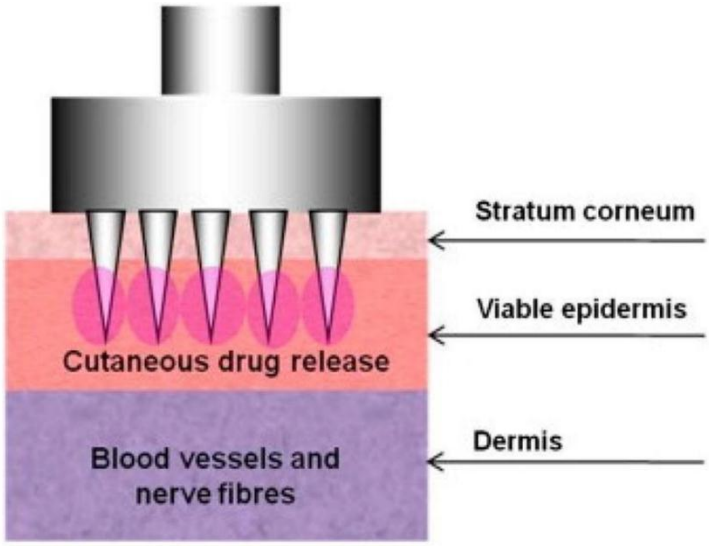

Figure-13: Systematic representation of the operating system of the microneedle array device. The device pierces the stratum corneum (SC) which provides direct drug access to the active epidermis, without access to the blood vessels and nerve fibers found in the dermis (Reprinted from [12] with permission. Copyright 2013 Elsevier).

MN Most microscopic projections are usually attached to one side of the base or supporting piece, usually ranging from 25 to 2000 µm height[5,12] 50 to 250 µm base diameter and 1 to 25 µm to tip diameter.[20,112,117,118] Needles should be of appropriate length, width and position to avoid contact with the nerves when inserted into the skin layers.[117,118,119] They are usually designed for arrays to improve surface contact and facilitate the penetration of therapeutic molecules into the skin.[112,120] MN is designed to create water passages that pass through the skin, thereby enhancing the flow of molecules from small hydrophilic molecules such as alendronate.[52] to macromolecules, including low-molecular heparin.[4,121] i insulin.[122] and vaccines.[123] painless.[112,124] Aside from the feature of painless delivery, there are many other benefits of MN technologies, such as: the fact that they do not cause bleeding.[125] eliminate transdermal dosing variations of small molecules.[45,126] only a small amount of germination through MN holes.[124,127] autonomous power[1,128]; the ability to overcome and reduce the incidence of accidental kidney injury and the risk of transmission.[12,112] in addition to the ease of disposal of MN waste.[11,112]

As previously acknowledged in this review, one of the main attractions of MN programs is to use them in vaccines and vaccination strategies. The skin contains a high concentration of flexible and innate immune cells including macrophages, Langerhans cells, and dermal dendritic cells. To date, only oral typhoid vaccine has been approved for self-administration in patients' homes.[129] Injecting the drug into the epidermis or dermis is much higher than injecting muscle in the lower extremities of the body and this MN method therefore provides excellent potential for enhancing the immune response you want.[21,130] As a result, the dose required to be vaccinated against the skin using MN will be significantly lower than that required for a standard injection and a syringe injection. Delivery of the vaccine through the skin provides easy and painless management. In addition, these MN vaccine devices can be made inexpensively.[5,34,112]

The first two commercially available MN products are Intanzia® and Micronjet® based on steel and silicon MN, respectively (Figure 14).[131] Intanza® is the first flu vaccine to target the dermis, a strong immune system. Developed and licensed by Sanofi Pasteur MSD Limited and marketed in dual capacity; Intanza® 9 µg for adults between the ages of 18 and 59 and Intanza® 15 µg for adults aged 60 and over. The Intanza® flu vaccine has a needle length of 1.5 mm.[132] MicronJet is a single-use, MN-based device for the delivery of vaccines and drugs. It was developed and licensed by NanoPass.

Several companies were working on MN-based drug development or vaccine products, including 3M, Clearside Biomedical, NanoPass Technologies, Corium International, TheraJect, Circassia, Radius Health, Lohmann Therapeutic Systems (LTS) and Zosano Pharma. Zosano developed a transdermal patch consisting of a layer of titanium MN composed of a parathyroid hormone (PTH) (20 to 40 µg) attached to an adhesive patch and applied with a re-application to the skin.[1,133] A second study involving the Zosano titanium MN patch system was conducted by Ameri et al. 2014 to assess the feasibility of using titanium MN to deliver a combined human growth hormone (rhGH).[126] In this study, it was found that the bioavailability of rhGHMNpatch and current subcutaneous injection products (Norditropin®) were similar indicating that this MN product could be used as a patient alternative to subordinate Norditropin®.[126,133] 3M Microneedle Technologies (MTS) developed an integrated MN to deliver water-soluble, polar and ionic molecules, such as lidocaine, to the skin. This program successfully delivers the drug to the skin in seconds and provides a rapid onset of local analgesia (~ 1 min) performing routine or emergency procedures.[51,134]

Figure-14: Current products based on MNs (a) Intanza® and (b) MicronJet®.

The shape and geometry of the MN are important during design and construction.[22,135,136,137] Needles should be able to penetrate the skin without breaking and the needles should be of the right length, width and shape to avoid contact with the nerves and perform effective mechanisms for the delivery of small particles,

macromolecules and nanoparticles, as well as fluids, depending on the purpose of each machine.[115,117,119,138] The stretchable structures of the human skin may prevent successful MN penetration by twisting the skin fibers around the needles during application, especially in the case of thin and short MN.[117] To date, many papers have described the formation of various MN from different materials using various microscopic processes or alternatives, such as lasers.[112,139,140] In general, there are four TDD strategies using MN (Figure 15).[22,123] These are solid, covered, melted and empty MN. The fifth novel of the genre MN, which is hydrogel MN has gained a lot of interest in the past and is presented in Figure 16.

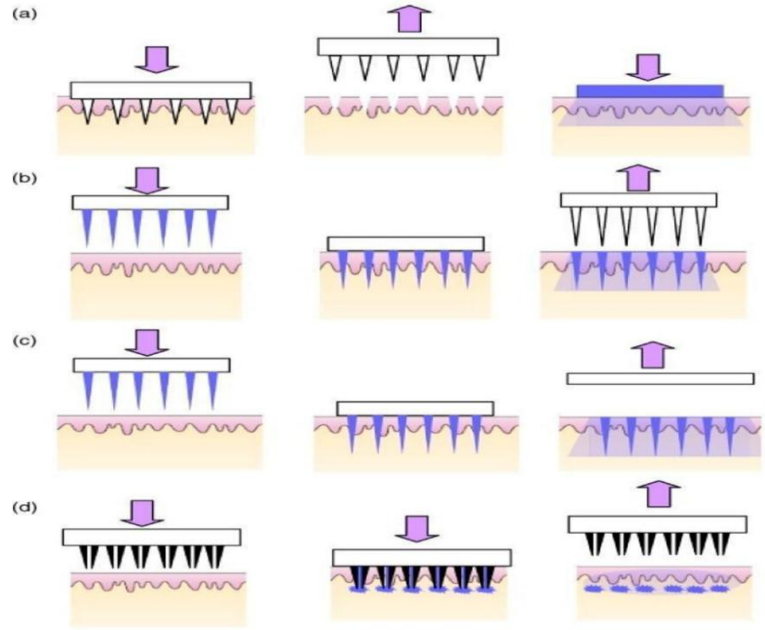

Figure-15: A schematic representation of four different MN application methods used to facilitate drug delivery transdermally.

(a) Solid MNs for increasing the permeability of a drug formulation by creating micro-holes across the skin; (b) Coated MNs for rapid dissolution of the coated drug into the skin; (c) Dissolvable MNs for rapid or controlled release of the drug incorporated within the microneedles; (d) Hollow MNs used to puncture the skin and enable release of a liquid drug following active infusion or diffusion of the formulation through the needle bores. (Reprinted from[11] with permission. Copyright 2008 Elsevier).

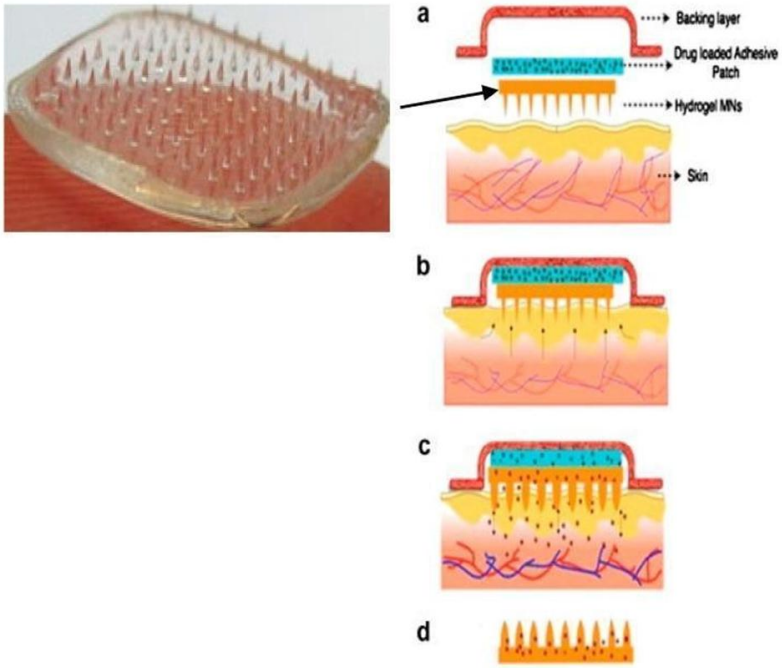

Figure-16: Novel hydrogel-forming MN facilitates the delivery of controlled drugs.

(a) Extended view of the supporting layer, the drug-laden attachment pool and the solid hydrogel MN liner that forms the integrated hydrogel MN pool; (b) Installation of a hydrogel MN component attached to the skin surface; (c) The distribution of water in the MN series resulting in a controlled swelling of the layers and the distribution of drug molecules from the adhesive surface using a hydrogel pipe; (d) Flexible hydrogel MN frames following removal from the skin. (Reprinted from.[12] login. Copyright 2013 Elsevier).

(1) Empty MN is used to deliver drug solutions in a "poke and flow" manner; which involves the insertion of MN into a muscle and the drug solution can be transported by MN bore in the same way as hypodermic needles[141,142] but empty MN usually requires more precise and advanced production technology.[111] Active distribution of drug solution is possible with MN, but active delivery allows faster delivery rates. Active delivery requires driving force, the syringe can be used to drive the solution through MN to the muscle but some studies have combined MN systems with a pump or compressed gas.[143,144]

(2) "Collect and compress" especially in strong MN by piercing the upper layers of the skin with strong MN and creating small ducts followed by the application of the drug formulation (e.g., patch, gel) to the piercing area.[5,112] Pre-treatment of the skin creates micro-conduits in the skin, thereby improving the flow of molecules to the skin.

(3) "Coat and rub" by piercing the skin with a strong drug-containing MN, which solves the problem of two-step insertion and provides a much faster drug delivery.[111,145] Delivery from bound MN was found to be particularly attractive for high-molecular weight molecules.[146] However, drug delivery is limited due to the small size of the MN shaft and tip.[146,147,148]

(4) "Poke and release" soluble / porous / hydrogel forming an MN where the drug will disperse around the circulation system (Figure 16). The substances produced in MN act as drug depots that hold the drug up until trigger release, i.e., decomposition in the form of soluble MN or inflammation in the form of hydrogel MN.[22,131,149] This strategy eliminates the need for sharp disposal, as well as the possibility of accidental reuse of MN. In addition, dissolving MN leaflets have been reported to successfully deliver both small molecules (MW 500 Da) and macro (MW 500 Da) pathways to "poke and release".[25,26]

A wide variety of MN species and designs have been shown to be effective in transdermal delivery of a wide range of molecules, both *in-vitro* and *in-vivo*.[10,12] The current capacity greatly increases the range and types of drugs that can be successfully applied to the entire skin. This will significantly improve the market value of transdermal delivery and will become even more important in the coming years as the number of new biological origin drugs continues to grow. Future studies will be needed to address the growing concerns of controlling the use of MN equipment, as well as to focus on the design and development of low-cost, efficient MN mass production processes. A number of other physiological mechanisms such as sonophoresis, electroporation, ultrasound and iontophoresis have been combined with MN to improve drug penetration. Kolli et al., 2012 determined that transdermal delivery of Prochlorperazine Edisylate was significantly improved when MN was used in conjunction with iontophoresis.[150] Moreover, the delivery of ropinirole hydrochloride by MN and iontophoresis was significantly higher compared to modified iontophoresis alone.[151]

CONCLUSIONS

In conclusion, the TDD sector continues to grow and develop with rapid growth in the basic knowledge that feeds industrial development. Over time, it is hoped that technological advances in TDD will lead to improved disease prevention, diagnosis and control, and improved health-related quality of care for patients worldwide. To date, this review has planned the development of several novel TDD approaches, highlighting the advantages and disadvantages of each approach. Due to the strong growth in investment and interest in MN technology and the many associated benefits of this approach, special attention is paid to this TDD program.

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