Advances in Biochemistry & Applications in Medicine

Chapter 7

Transdermal delivery of Drugs using bio-compatible hydrogels and microneedles

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1. Introduction

Transdermal delivery represents an attractive alternative to oral delivery of drugs and is poised to provide a substitute to hypodermic injection too. People have practiced transdermal delivery for thousands of years by placing topical drugs or formulations on the skin for remedial effects. This practice is still in use in current era and large number of topical formulations are available for local curative effects [1].

Transdermal drug delivery systems (TDDS) are also named also as "Transdermal patches" or "Skin patches". 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. By mid to late 1990s, the trend of Transdermal drug delivery system companies merging into larger organizations [2]. Transdermal drug technology specialists are performing extensive research for newer methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route.

Transdermal route of drug delivery provides various advantages such as improved patient acceptability, easy to use, by-passing the hepatic metabolism, non-invasive or minimally invasive.

Transdermal delivery has a variety of advantages compared with the oral route and hypodermal injections. For example:

- It is used when there is a significant first-pass effect of the liver that can prematurely metabolize drugs. Many orally delivered drugs irritate the gastrointestinal mucosa and a large number undergo extensive 'first-pass' inactivation by liver. Transdermal drug delivery can by-pass the liver inactivation of drugs.

- Improved patient compliance is big advantage in comparison to oral and hypodermic injections. It is of great advantage in patients who are nauseated or unconscious. Patients have difficulty in swallowing tablets and capsules and some patients are tempted to crush tablets to assist in swallowing which destroys any controlled release characteristics of the tablets.

- A controlled delivery of drugs through skin can provide less fluctuation in the circulating levels of drugs and reduce the drug spike concentrations observed after orally delivered drugs.

- The drug release is such that there is a predictable and extended duration of activity. Greater flexibility of dosage in that dosing can be easily terminated by removal of the skin patch which is not possible in case of oral or hypodermal injections.

- Transdermal delivery also has advantages over hypodermic injections, which are painful, and generate lesser or no dangerous medical waste and does not pose the risk of disease transmission by needle re-use, especially in developing countries [5].

- In addition, transdermal systems are non-invasive and can be self-administered hence does not require any expert training for application.

- They can provide release for long periods of time (up to one week).

- They also improve patient compliance and can be of utmost importance in diseases where continuous drug administration is required.

In 1981, first transdermal patch approved was of Socopolamine, a drug used to treat motion sickness leading to nausea, and vomiting. As per the literature there are now more than 35 transdermal products, containing at least 13 approved molecules [3]. The value of global market for transdermal delivery as reported by Jain PharmaBiotech, was $12.7 billion in the year 2005 and is predicted to increase to $21.5 billion in the year 2010 and $31.5 billion in the year 2015. New technology, in form of adjuvants that boost the transfer across the skin barrier, as well as 'active' delivery that uses some form of energy to convey the ingredient, are poised to accelerate this growth. Creams, ointments, and lotions, the original transdermal delivery vehicles, mostly treat localized skin diseases, although that is now changing [4]. Non-medicated patches include thermal and cold patches, weight loss patches, nutrient patches, skin care patches (therapeutic and cosmetic), aroma patches, and patches that measure sunlight exposure.

2. First Transdermal Patch

The first transdermal system drug delivery system for systemic delivery was a scopolamine patch. It was a three-day patch that delivers scopolamine to treat motion sickness was approved for use in the United States in 1979.

Michaels et al. [5] reported that scopolamine can cross through human skin as found in exvivo permeation studies had a substantial flux through excised human skin. This led to the quest for first ever transdermal patch. This study progressed to the further investigation of the mechanism of percutaneous delivery of scopolamine through stratum corneum into the systemic circulation [6]. All these studies led to development of transdermal therapeutic system (TTS) by the Alza Corporation. Patch was capable of controlled administration of scopolamine through the surface of the skin to the systemic circulation [7,8]. Further extensive studies included the analysis of skin site where patch can provide maximum permeation into the system. It was found that Zaffaroni design of the patch applied behind the ear is best for permeation. Zaffaroni design of the patch constitutes a drug reservoir containing drug and a microporous membrane that commands slow and controlled the delivery of scopolamine [9]. The device was tested with Alza employees sailing in a large sailboat through a rough stretch of water close to the Golden Gate Bridge known as the 'potato patch'. Employees wearing the placebo patch were sick, whereas most of those wearing the scopolamine patch did not feel any sickness (Hoffman, 2008). In 1979, a 2.5 cm2 -TTS (which is still one of the smallest patches on the market) designed to deliver 1.5 mg of scopolamine over 3 days (TransdermSco¯p®; Novartis Consumer Health, Parsippany, NJ, USA) was the first transdermal patch to reach the US market. Transdermal scopolamine was very effective against motion sickness but also associated with minimal side effects [11].

A nitroglycerin ointment was the only transdermal product on the market until the marketing of the transdermal scopolamine patch. Whereas the nitroglycerin ointment led to more sustained serum levels than sublingual and p.o. sustained release capsule dose forms [13].

In 1981, patches for nitroglycerin were approved, and currently there exists a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug being administered, the patches may deliver drug from one to seven days [12].

This list below includes transdermal patches and delivery systems approved by the US Food and Drug Administration (FDA [1]. Topical creams, ointments, gels and sprays are not included.

Table 1: List of FDA approved transdermal patches and delivery systems.

Approval year	Drug/Product name	Indication	Marketing company
1979	Scopolamine/TransdermScop	Motion sickness	Novartis Consumer Health (Parsippany, NJ, USA)
1981	Nitroglycerin/TransdermNitro	Angina pectoris	Novartis (East Hannover, NJ, USA)
1984	Clonidine/Catapres-TTS	Hypertension	Boehringer Ingelheim (Ridgefield, CT, USA)
1986	Estradiol/Estraderm	Menopausal symptoms	Novartis
1990	Fentanyl/Duragesic	Chronic pain	Janssen Pharmaceutica (Titusville, NJ, USA)
1991	Nicotine/Nicoderm, Habitrol, ProStep	Smoking cessation	GlaxoSmithKline (Philadelphia), Novartis Consumer Health, Elan (Gainesville, GA, USA)
1993	Testosterone/Testoderm	Testosterone deficiency	Alza (Mountain View, CA, USA)
1995	Lidocaine with epinephrine (iontophoresis)/Iontocaine	Local dermal analgesia	Iomed (Salt Lake City, UT, USA)
1998	Estradiol with norethidrone/Combipatch	Menopausal symptoms	Novartis
1999	Lidocaine/Lidoderm	Post-herpetic neuralgia pain	Endo Pharmaceuticals (Chadds Ford, PA, USA)
2001	Ethinyl estradiol with norelgestromin/ Ortho Evra	Contraception	Ortho-McNeil Pharmaceutical (Raritan, NJ, USA)
2003	Estradiol with levonorgestrel/Climara Pro	Menopausal symptoms	Bayer Healthcare Pharmaceuticals (Wayne, NJ, USA)
2003	Oxybutynin/Oxytrol	Overactive bladder	Watson Pharma (Corona, CA, USA)
2004	Lidocaine (ultrasound)/SonoPrep	Local dermal anesthesia	Echo Therapeutics (Franklin, MA, USA)

2005	Lidocaine with tetracaine/Synera	Local dermal analgesia	Endo Pharmaceuticals
2006	Fentanyl HCl (iontophoresis)/Ionsys	Acute postoperative pain	Alza
2006	Methylphenidate/Daytrana	Attention deficit hyperactivity disorder	Shire (Wayne, PA, USA)
2006	Selegiline/Emsam	Major depressive disorder	Bristol-Myers Squibb (Princeton, NJ, USA)
2007	Rotigotine/Neupro	Parkinson's disease	Schwarz Pharma (Mequon, WI, USA)
2007	Rivastigmine/Exelon	Dementia	Novartis

3. Transdermal Patch

A transdermal patch is defined as adhesive medicated patch that is applied on to skin and it delivers an exact dose of drug through the skin into the bloodstream with a predetermined rate of release to reach in the body. Today the most common transdermal systems present in the market mainly are based on semi permeable membranes which were called as patches. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream.

Recently, the use of transdermal patch technology is restricted to only a few drugs. To persuade a drug to penetrate the skin and reach the systemic circulation in sufficient quantities, in the right time frame to exert a desired pharmaco-therapeutic effect is no small task. In order to engineer the drug for passage through skin it is important to take into consideration the basic skin histology so as to comprehend possible percutaneous delivery routes and challenges associated with the quest.

4. Anatomy and Physiology of Skin [14,15]

Human skin comprises of three distinct but mutually dependent tissues (Figure 1): A) Epidermis: Constituted of two parts:

1. The stratified stratum corneum and underlying

2. vascular, cellular, viable epidermis

B) Underlying dermis of connective tissues and

C) Hypodermis.

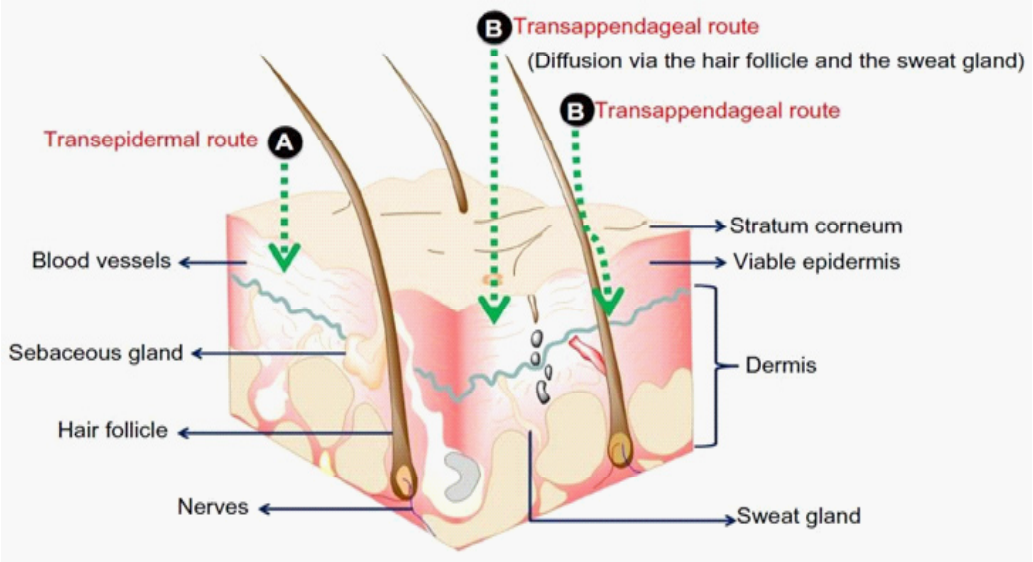

Figure 1: Structure of skin [16].

A. Epidermis: The uppermost multilayered layer of the skin which varies in thickness, because of changes in cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. It consists outer stratum corneum and viable epidermis underneath.

1) Stratum corneum (Horney layer): This is the outermost layer of skin and the major barrier to transdermal delivery of drugs. It is approximately 10 µm thick when dry, but swells to several times this thickness when fully hydrated. It has 10 to 30 layers of dead, keratinized cells called corneocytes.

2) Viable epidermis: This is situated beneath the outermost layer and varies in thickness ranging from 0.06 mm on the eyelids sole upto 0.8 mm on the palms. Going inwards, it consists of various layers as stratum granulosum, stratum lucidum, stratum spinosum and the stratum basal. In the basal layer, mitosis divisions of the cells constantly reproduce the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface.

B. Dermis: Dermis is made up of a mash network of connective tissue 3 to 5mm thick layer containing blood vessels, lymph vessels and nerves. Hence it provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeant very low which is responsible for concentration gradient across the epidermis essential for transdermal permeation through diffusion.

C. Hypodermis: The hypodermis constitutes subcutaneous fat tissue that works to support dermis and epidermis. It serves as a fat storage area. This layer functions to regulate tempera-

ture, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs.

5. Routes of Transdermal Drug Delivery

Percutaneous absorption involves passive diffusion of the substances through the skin occurring due to concentration gradient between epidermis and topical formulation. There can be two diffusional routes for a permeant to penetrate normal intact skin, the appendageal route and the epidermal route.

Appendageal route constitutes the transport via sweat glands and hair follicles with their associated sebaceous glands. These routes bypass the need of penetration through the stratum corneum hence also known as "shunt" routes. This route is considered tobe of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

Epidermal route: 1) Transcellular pathway uses epithelial cellular membrane for transport of molecules. This pathway involves passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

2) Paracellular: Paracellular pathway uses the space around or between the cells such as tight junctions for transport of molecules. Tight junctions or similar situations exist between the cells.

The principal pathway taken by a permeant depends upon the partition coefficient into the intracellular domains, whereas lipophilic permeants traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route.

6. Kinetics of Transdermal Drug Delivery

Zhan et al., (2015) have postulated that drug release from a drug-in-adhesive patch follows first-order kinetics hence rate of drug release depends directly upon the drug concentration in the patch. However, reservoir-type transdermal drug delivery could be observed the zero-order kinetics [17].

One of the major advantages of the zero -order kinetics is that a zero-order input is easily achieved and the rate is apparently independent of the reactant concentration. This kind of kinetics ensures that drug levels in the blood remain relatively constant and does not cause any hypo or hyper concentration of drug as occurs with multiple oral dosing and hypodermic injections. This ensures that This can be of significant therapeutic benefit for certain conditions where constant stimulation of receptors or continuous interaction with other molecular targets is required and for drugs having a narrow therapeutic index.

However, this is type of drug delivery is associated with a slow onset of effect with lag time associated with response. Passive transport across the epidermis and the dermis and entry into the systemic circulation is a multistep process that can give rise to significant lag-times before steady state is attained. Thus, not only there was a quest to enable the delivery of different drugs across the skin but also a push to have ‘‘faster’’ transdermal delivery.

The rate controlling membrane, as a most important component in the reservoir-type transdermal patch, is responsible for controlling drug delivery. The rate-controlling membranes reported in previous publications included ethyl cellulose [18], collagen and chitosan [19], ethylene-vinyl acetate (EVA) [20].

Knowledge of skin permeation kinetics is vital to the successful development of transdermal systems. This permeation can be possible if the drug possesses certain physico-chemical properties. The rate of permeation across the skin (d_Q/ d_t) is given by [21]:

$$d_Q/ d_t = P_s(C_d-C_r) \quad \text{------- Eq. 1}$$

Where, C_d = concentration of skin penetrant in the donar compartment (e.g., on the surface of stratum corneum)

C_r = concentration in the receptor compartment (e.g., body) respectively

P_s = the overall permeability constant of the skin tissue to the penetrant

$$P_s = K_s D_{ss}/h_s \quad \text{------- Eq. 2}$$

Where, K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system onto the stratum corneum,

D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and

h_s is the overall thickness of skin tissues. A_s K_s, D_{ss} and h_s are constant under given conditions, the permeability coefficient (P_s) for a skin penetrant can be considered to be constant.

Permeability coffiecient = $K_s D_{ss}/h_s$ = 1/ resistance

Resistance has many components: Vehicle, Stratum corneum (usually most significant), Epidermis, Dermis.

The resistance occurs one after another ‘in series’:

$$R_{total} = R_{vechicle} + R_{sc} + R_{epidermis} + R_{dermis}$$

Total Permeability= $1/ R_{vechicle} + 1/ R_{sc} + 1/ R_{epidermis} + 1/ R_{dermis}$

The membrane limited flux (J) under steady state condition is described by equation:

$$J=DK_0/_wC/h$$

Where, J = Amount of drug passing through membrane system per unit area per unit time.

D = Diffusion coefficient within the membrane h = Membrane thickness K = Membrane / vehicle partition coefficient C = Concentration gradient across the membrane.

Further mathematical processing [22], considering diffusion coefficient of the penetrant molecules in protein gel, H_{sc-} thickness of stratum corneum, K_{pl} – distribution coefficient of the penetrant molecules between the lipid matrix and protein gel, D_{ml} – diffusion coefficient of the penetrant molecules in lipid matrix, reveals that if the drug is applied on to the skin surface in a simple solution form, the concentration of the drug (C_b) absorbed into the body can be described by Eq. 8. If the pharmacokinetic pattern of the drug is known to follow a simple one compartment model

$$C_b=(Drug)_a/V_d X K_a/K_a.K_e (Exp^{-Ket}- Exp^{-Ket}$$

Where, $(Drug)_a$ – concentration of drug in the body, V_d – volume of drug distribution, K_a – rate constant for skin absorption, K_e - rate constant for drug elimination

If the drug is delivered to skin surface through a zero-order delivery system, then, at a steady state, a constant blood level will be achieved, which is a linear function of the rate of drug release (K_o) and is inversely proportional to the rate constant for drug elimination (K_e), and the volume of distribution (V_d).

$$C_b==K_o/K_eV_d(1-Exp^{-Ket})$$

On the other hand if the drug is administered via a Transdermal Drug Delivery System which releases the drug molecules at a first-order rate constant (K_1) the blood level of the drug will then be described by

$$C_b= K_1(Drug)_{dds}/(K_1-K_e)V_d(Exp_{-Ket}- Exp_{-K1t})$$

In this case, C_b will be dependent on the drug dose level the drug delivery system, $(Drug)_{dds}$.

The assessment of percutaneous absorption of molecules is a very important step in the evaluation of any dermal or transdermal drug delivery system. A key goal in the design and optimization of dermal or transdermal dosage forms lies in understanding the factors that determine a good in vivo performance.

7. Transdermal Drug delivery Systems [1]

7.1. First-generation of transdermal delivery systems (TDDS) utilize a topical formulation that can be a metered liquid spray, gel etc. to the skin without any transdermal patch application. Upon evaporation or absorption, these formulations can drive small lipophilic drugs into the stratum corneum. In such cases SC act as the drug reservoir for sustained release into the viable epidermis over hours [20]. For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery.

7.2. The second generation of transdermal delivery systems identifies that skin permeability enhancement is mandatory to expand the scope of transdermal drugs. The ideal penetration enhancer should (i) increase skin permeability by reversibly disrupting stratum corneum structure, (ii) provide an added driving force for transport into the skin and (iii) protecting underlying living tissues. This generation employs enhancement methods such as conventional chemical enhancers, iontophoresis and sonophoresis.

7.3. The third generation of transdermal delivery systems is poised to make significant impact on drug delivery with targets being stratum corneum. This targeting enables robust disruption of the stratum corneum barrier, and thereby more effective transdermal delivery, while still protecting deeper tissues. This generation TDDS novel chemical enhancers, electroporation, cavitational ultrasound and more recently microneedles, thermal ablation and microdermabrasion [23] have been shown to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials.

8. Techniques for Enhancement of Skin Permeabilization

It is certainly not difficult to remove the stratum corneum, as sandpaper will suffice, but the motive is to do this in a reversible and relatively painless manner that minimizes irritation, is practical for chronic conditions and with minimal risk of infection. Hence, the quest for physical methods to transiently perturb the skin barrier or to provide additional driving forces that facilitate molecular transport.

8.1. Iontophoresis

The term iontophoresis is literally means ion transfer (ionto = ion; phoresis = transfer). Iontophoresis uses an electric current to deliver a medicine or active compound or other chemical through the skin. In popular terms, it is sometimes called “an injection without the needle”.

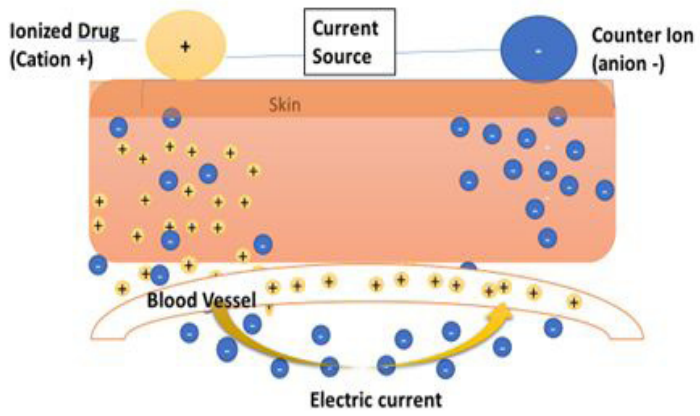

Figure 2: Diagramatic reperesentation of transdermal delivery using Iontophoresis.

This technique is not a new as it is being used since 1700's for various applications. Formally, ionotophoresis is defined as non-invasive method of thrusting high concentrations of a charged substance (a medication or bioactive agent), transdermally by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similar charged active agent and its vehicle.

Iontophoresis has advantages in pain management-as it can provide relief in response to acute pain episodes, such as post-operative pain and chronic pain, e.g. in cancer patients. The electric current controlled input kinetics allows the non-invasive administration of bolus doses as with conventional, in addition continuous current profile can be used for maintenance doses. Furthermore, iontophoresis can also be used for local pain relief or local anesthesia prior to minor surgical procedures also providing systemic pain relief [24].

8.2. Electroporation

Electroporation refers to the transient disruption of the skin using high voltage pulses [25]. This method creates temporarily aqueous pores in cell membranes, using electric pulses of high voltage and short duration. As reported by Denet *et al.,* the electrical resistance and the electrical breakdown potential of the stratum corneum (SC) is between 5 and 25kV/cm^2 and is approximately 75–100 V respectively. These along with other properties of the skin create the major barriers for permeation of drug molecules to reach systemic circulation.

Electroporation have been used successfully to facilitate the permeation of molecules through skin. It has also successfully been used to enhance skin permeability for molecules with different lipophilicities, sizes and high molecular weight biopharmaceuticals (proteins, peptides, and oligonucleotides). It has been postulated by Mori *et al.,* [26] that transdermal drug delivery enhancement using electroporation is the outcome of pore formation in the skin membrane. During electroporation, the SC is modified leading to increases in electrophoretic

mobility, molecular diffusivity, and electrical conductivity. It is well known fact that the high voltage for short duration electrical burst in transdermal electroporation can be more effective in enhancing transdermal flux of drugs in comparison with the continuous application of low voltage pulse as in the case of iontophoresis, as stated by Charoo *et al.,* [27]. Electroporation-assisted transdermal transport depends on the shape, amplitude, duration, number of electric pulses, as well as the distance between electrodes. Sugibayashi *et al.*, [28] investigated electroporation-mediated transdermal delivery of sodium benzoate. Pulse length and amplitude are also influential factors in electroporation when comparing different protocols [29]. It has been found that molecular and ionic transport across the skin exposed to a number of high voltage pulses is highly localized in sites termed local transport regions (LTRs) [29].

Transdermal electroporation is also called electropermeabilization [30]. Application of external field that exceeds the critical transmembrane potential leads to temporary electroporation of the skin [31].

Mechanism of structural changes in the skin during electroporation are still to be discovered. Backer *el al.*, [32] postulated that water pores form in the skin following application of high voltage pulses. It has been suggested that when voltage drop across the SC is more than 30 V, the skin experiences a sudden increase (up to four orders of magnitude) in permeability within 10 μs. According to this postulate, modification of SC lipid ultrastructure following application of high voltage pulses occurs due to the interaction between the water dipole and the electric field. The SC contains approximately 100 bilayer membranes in series and transient increase in permeability usually takes place when voltages of 30–100 V (100–1500 V applied voltages) are used. This is similar to the spectrum of voltages used for cell electroporation, i.e., 0.3– 1.0 V per bilayer [33]. Electroporation is a non-thermal process at the level of the cell.

8.3. Sonophoresis

Sonophoresis is a physical technique which employs the ultrasound waves onto the skin surface which to enhance skin permeability. Sonophoresis has been used successfully, to effectively deliver various types of drugs regardless of their electrical characteristics and coupled with other TDD methods to enhance drug delivery rates. These drugs have included hydrophilic and large molecular weight drugs [34]. Fellinger and Schmidt were first to bring the concept of ultrasound for TDD in 1950 for the successful treatment of polyarthritis using hydrocortisone ointment combined with sonophoresis [35,36,37]. However, the first ultrasound device for transdermal application was approved in 2004 by the FDA for the delivery of local dermal anesthesia by the Sontra Medical, SonoPrep®. Since that time, ultrasound has been widely used as a TDD system in the treatment of many other diseases including bone joint diseases and bursitis [38].

There are two main mechanisms currently known for skin permeation by sonophoresis:

thermal and cavitation effects. Between these two effects, cavitation is believed to be the predominant mechanism responsible for sonophoresis [39,40,41].

8.3.1. Thermal effect

When ultrasound passes through a medium, energy is partially absorbed in the form of heat energy [42]. In the human body, ultrasound energy absorbed by tissue causes a local temperature increase that is dependent upon ultrasound frequency, intensity, area of the ultrasound beam, duration of exposure, and the rate of heat removal by blood flow or conduction [43]. Merino *et al*. reported enhanced transdermal permeability caused by this temperature increase [44]. The skin temperature was increased by 20°C with low frequency ultrasound (20 kHz), and the delivery of mannitol was enhanced 35-fold. The resultant temperature increase of the skin may enhance permeability due to an increase in diffusivity of the skin.

8.3.2. Cavitation

Cavitation is defined as creation of cavities as well as expansion, contraction, and distortion of pre-existing gaseous bubbles in a liquid medium [45]. The likelihood of cavitation occurrence is closely related to ultrasound frequency as well as bubble characteristics such as size and shape. Since cavitation nuclei in biologic environments are random in size, type, and shape, the likelihood of cavitation is unpredictable.

8.4. Chemical Enhancement

The skin is meant to prevent excessive water loss from the internal organs and to limit the ability of xenobiotics and hazardous substances to enter the body. Recent studies have suggested that suitably designed combinations of chemical enhancers can balance trade-offs between enhancement and irritation based on the hypothesis that certain enhancer combinations are especially potent when present at specific, narrow compositions. This approach enables a strategy to target effects that enhance skin permeability in the stratum corneum, but avoids irritation in deeper tissues where the formulation composition becomes diluted or otherwise altered.

A study was carried out, examining close to 500 different pairs of chemical enhancers formulated to have more than 5000 compositions [46]. Finally a combination of sodium laureth sulfate (an anionic surfactant) and phenyl piperazine (a compound with aromatic nitrogen) at concentrations of 0.35 and 0.15 wt%, in a 1:1 mixture of ethanol and phosphate buffered saline dramatically increased enhancement with low skin irritation. *In vitro* screening results were validated with *in vivo* delivery of a peptide (leuprolide acetate) to hairless rats. These results suggest that combinations of chemical enhancers may succeed the delivery of macromolecules where individual enhancers have generally failed. Work on this approach continues in industry

[47].

Numerous compounds have been evaluated for penetration enhancing activity [48], including sulphoxides (such as dimethylsulphoxide, DMSO), Azones (e.g. laurocapram), pyrrolidones (for example 2-pyrrolidone, 2P), alcohols and alkanols (ethanol, or decanol), glycols (for example propylene glycol, PG, a common excipient in topically applied dosage forms), surfactants (also common in dosage forms) and terpenes.

8.5. Microneedles

Microneedles are fabricated to permeate the skin non-invasively to deliver drugs into through skin. Solid microneedles have been shown to painlessly pierce the skin to increase skin permeability for a variety of small molecules. Microneedles can be dip coated with a variety of compounds such as small molecules, DNA, proteins, and virus particles. In a recent study, naltrex one was administered to healthy volunteers whose skin was pre-treated with micro needles. After applying the naltrex one patch, therapeutic levels of naltrex one were achieved [2]. Transdermal patches with microscopic projections called microneedles 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 for painless adminstration. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza [15].

8.6. Needleless jet injectors

As name suggests a jet injector is a needle free device that can deliver drugs electronically in controlled doses of medication. Use of jet injectors lead to improved patient compliance due to reduced pain to the patient and improved consistency of delivery [49,50]. Jet injectors projects the liquid or solid particles at supersonic speeds through the outer layers of the skin using a reliable energy source for delivering the drug. The mechanism is basically, forcing compressed gas (helium) via a nozzle, such that the resultant drug particles entrained within the jet flow that travels at sufficient velocity for skin penetration [2].

8.7. Heat

It is already known fact that skin morphology changes in response to temperature changes, with more opened skin pores at high temperatures and dilated blood vessels. However, the effect of temperature on the delivery of penetrates greater than 500 Daltons has not been reported [2]. In order to generate the high temperatures needed to ablate the stratum corneum without damaging the underlined epidermis, the thermal exposure should be short, so the temperature gradient across the stratum corneum can be high enough to keep the skin surface

extremely hot but the temperature of the viable epidermis does not experience a significant temperature rise [51].

9. Ideal Characteristics of TDDS [52]

The skin has pH of 4.2 to 5.6, TDDS should have this pH range are used to avoid damage to the skin and maintain biocompatibility.. For the therapeutic action of the drug must have optimum partition coefficient, a low melting point (less than 2000°C), be non-irritating and non-allergic, a molecular weight less than approximately 1000 Daltons

9.1. Types of transdermal drug delivery systems [53]:

(I) Single–layer drug in–adhesive: The adhesive layer of this system also contains the drug. In this type patches the adhesive layer not only serves to adhere the various layer together, along with 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.

(II) Multi-layer drug in adhesive: The multi-layer drug in adhesive is similar to the single layer system in that both adhesive layers are also responsible for the releasing of the drug. But it is different however that it adds another layer of drug in–adhesive, usually separated by a membrane. This patch also has a temporary liner–layer and a permanent backing.

(III) Drug reservoir-in-adhesive: Reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the backing layer. In this type of system the rate of release is zero order.

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

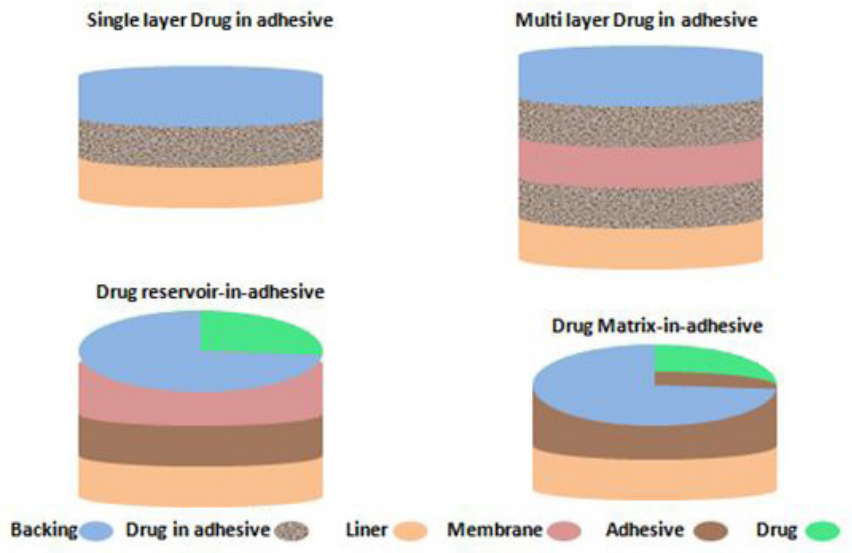

Figure 3: Different types of transdermal patches. [53]

In the fore-mentioned types of transdermal patches (Figure 3), hydrogels can act as drug reservoirs. This assembly of transdermal patch along with skin permeation method can make transdermal drug delivery devices more promising .

10. Hydrogels in Transdermal Drug Delivery

Hydrogels is a fancy word for three-dimensional, cross-linked mesh of water-soluble polymers. Hydrogels can be synthesized from any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Hydrogels can be formulated in different physical forms such as slabs, microparticles, nanoparticles, coatings, and films. Hydrogel has consistency between solid and liquid i.e. a gel form with properties of solids such as maintaining its network structure without losing its consistency and at the same time squishy nature which allows it to take the shape of the surface on which it is applied. These formulations have properties of massive water or fluid absorption. This property enables the encapsulation of high amount of drug in mash network of hydrogel. On water or fluid absorption in the spaces among pores, the hydrogels swell, this leads to drug elution. Topical or transdermal application of such biomaterials loaded with drug is how they can be used for transdermal drug delivery. Transdermal drug delivery occurs via diffusion through skin. The concentration gradient between two compartments i.e. hydrogel reservoir and the ventral surface of skin. In such systems hydrogel act as biocompatible drug reservoir.

The unique physical properties of hydrogels have stimulated particular interest in their use in drug delivery applications [54]:

1. Hydrogels are also known to be generally highly biocompatible, as obvious from their use in peritoneum [55] and other sites in *in vivo* systems. This attribute of biocompatibility is due to the high-water content of hydrogels. Furthermore, hydrogel have physicochemical properties mimicking that of native extracellular matrix, both compositionally (particularly in the case of carbohydrate-based hydrogels) and mechanically.

2. Porous nature of hydrogels permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network (**Figure 4**).

3. Their highly porous structure can easily be tuned by controlling the amount of cross-linker and the affinity of the hydrogels for the aqueous environment in which they are swollen.

4. Hydrogels for drug delivery exhibit pharmacokinetic benefits – by allowing the sustained and controlled delivery of drug in the surrounding tissues over an extended period.

5. Biodegradability or dissolution of hydrogels may be tuned via enzymatic, hydrolytic, or

environmental (e.g. p^H, temperature, or electric field) pathways.

6. Hydrogels are deformable due to their sol-gel nature. Hence, they take the shape of the surface to which they are applied. This distinguishing trait of hydrogels is accountable for the muco- or bio-adhesive properties which is profitable in immobilizing them at the site of application.

The term hydrogel was originally introduced by Wichterle and Lim in 1960s and its biological application was put forward. The first paper sighted was by DuPont scientist in 1936 for medical applications, which introduced the spark that was enlightened in 1960 by Wichlerte and Lim who worked on poly (2- hydroxyethylmethacrylate) poly (HEMA).1 It highlighted the properties of this brittle polymer as a highly water swollen, soft and elastic gel. This led to the keen interest in hydrogels as a class of biomaterials and their application as drug delivery systems. Furthermore, because of their high-water content, swollen hydrogels can provide a better feeling for the skin in comparison to conventional ointments and patches. Versatile hydrogel-based devices for transdermal delivery have been proposed so far. The topical application of hydrogels can effectively be used to deliver drugs that can help to alleviate the symptoms of many pathological conditions.

For instance, Nho *et al*. [56] reported a therapeutic hydrogel made of poly (vinyl alcohol) or poly (vinylpyrrolidone) for the treatment of a topic dermatitis.

Peppas and group [104] have reviewed the applications of hydrogels in the pharmaceutical field, hydrogel characterization and analysis of drug release from such devices.

Sun *et al*. [94] have reported the composite membranes comprising of cross linked PHEMA with a nonwoven polyester support. Permeation flux of 4 to 68 mg/cm^2 per h for nitroglycerin can be managed by adjusting the preparation conditions.

Kim *et al*. [95] have reported the preparation of a Carbopol 934w-based formulation containing phosphatidylcholine liposomes (liposome-gel). In their study, the skin absorption behavior of hydrocortisone containing liposome- gel was assessed. Gayet and Fortier have reported bovine serum albumin (BSA) and PEG copolymerized hydrogels [96]. This hydrogel allows the release of hydrophilic and hydrophobic drugs due to their high-water content. Hence this hydrogel has potential application as controlled release devices in the field of wound dressing. Hubbell [97] have reported in-situ photopolymerizable hydrogels made from terminally diacrylated ABA block copolymers of lactic acid oligomers (A) and PEG (B) for barriers and local drug delivery in the control of wound healing.

Currently research in transdermal applications is focusing on electrically assisted delivery, using skin permeation techniques such as iontophoresis and electroporation [98]. For

instance several hydrogel-based formulations are being investigated as medium for transdermal iontophoresis to obtain the enhanced permeation of luteinizing hormone [99] releasing hormone, sodium nonivamide acetate [100], nicotine [101] and enoxacin [102]. On the other hand, a methyl cellulose-based hydrogel was used as a viscous ultrasonic coupling medium for transdermal sonophoresis assisted with an AC current, resulting in an enhanced permeation of insulin and vasopressin across human skin in vitro [103].

10.1. Hydrogel in Transdermal Iontophoretic Delivery

European Patent Application EP 0 524 718 A1 demonstrated hydrogels are suitable for transdermal iontophoretic delivery of drugs [58]. This invention used polyurethane hydrogel matrices as monolithic drug reservoirs.

Transdermal iontophoresis is defined as the transport of ionic drugs through the skin, driven by a very weak electric current as described in previous section. The applied current helps to transfer the ionized drugs through the stratum corneum into the dermis, in which the active ingredient can diffuse into capillaries and then into the systemic circulation.

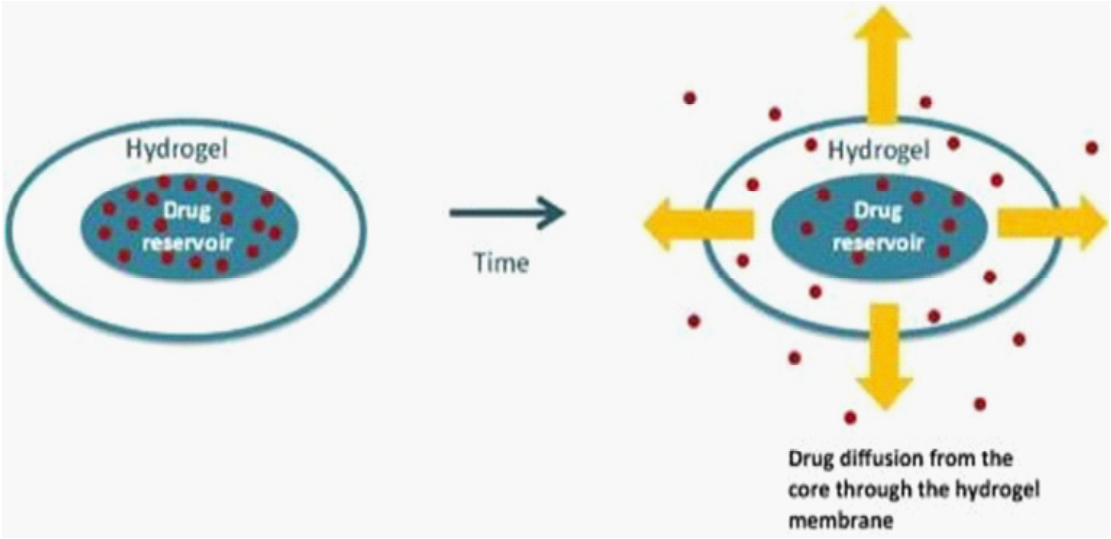

Figure 4: Scheme of drug release through a hydrogel membrane in a reservoir system [57].

Alternatively, hydrogel compositions can be employed as passive transdermal reservoirs. The hydrogels used in the forementioned work showed a high swelling ratio, good flexibility, strength and transparency [58]. Hydrogel-based iontotherapeutic devices as drug reservoir matrices for peptide-based pharmaceuticals have been investigated for transdermal delivery of three model peptides, insulin, calcitonin, and vasopressin [59].

Hydrogels are an ideal candidate for developing the transdermal drug delivery system with dual-functions of moisture and drug delivery. Wang et al. [60] have reported the development of a thermo-sensitive Poloxamer 407/Carboxymethyl cellulose sodium (P407/CMCs) composite hydrogel formulation with twin functions of moisture and drug supply for acute dermatitis treatment. It was found that the presence of CMCs can appreciably improve the

physical properties of P407 hydrogel, which makes it more suitable for tailored drug loading. Transdermal drug delivery behavior revealed that P407/CMCs showed desirable percutaneous performance.

Hydrogels are hydrophilic three-dimensional polymeric networks capable of absorbing a large amount of water or biological fluids [61]. The high moisture content makes hydrogels compatible with most living tissues and thus facilitates widespread application in biomedical and pharmaceutical areas [62,63]. Thermo-sensitive hydrogel exhibits a free-flowing sol form of hydrogel at low temperatures but becomes a gel at body temperature, which facilitates administration and accessibility when applied in drug delivery systems [64,65]. Poloxamer 407 (Pluronic F127) is one of the most typical thermosensitive polymers and has been approved by the FDA. Poloxamer 407 self-assembles into micellar structures and form hydrogels under certain condition. The micellization results from the dehydration of hydrophobic PO blocks and the resultant micelles are spherical with a dehydrated polyPO core and an outer shell of hydrated swollen polyEO chains [66,67]. A high drug loading can therefore be achieved simply by incorporating hydrophilic drugs into the micellar structures. Bioadhesive polymers such as cellulose derivatives are normally added to enhance the bioadhesive property of poloxamer-based hydrogels [68].

High doses cannot be delivered transdermally from a patch of reasonable size, even for molecules whose physicochemical properties are ideal for passive diffusion across the skin's stratum corneum barrier. Therefore, transdermal delivery has traditionally been limited to fairly lipophilic, low molecular weight, high potency drug substances. Since most drugs do not possess these properties, the transdermal delivery market has not expanded beyond around 20 drugs.

Marketed MN-based patches are likely to increase this number of transdermally deliverable drugs in the coming years. However, this increase will only be maximized if high dose molecules can be delivered in therapeutic doses using MN.

12. Hydrogel for Transdermal Delivery Using Miconeedles (MN)

Microneedles are used to pierce the skin to overcome this barrier. Microneedles can be divided into several categories, for instance, solid microneedles, coated microneedles, and hollow microneedles and so on. However, all these types have their weak points related to corresponding mechanisms. In recent years, pioneering scientists have been working on these issues and some possible solutions have been investigated [69]. There are several kinds of MNs [70], namely, solid MNs [71] for skin pretreatment to increase skin permeability, MNs coated with drugs, hollow MNs [72] for drug infusion into the skin, polymeric or polysaccharide MNs [73] that encapsulate drugs and partially or fully dissolve in the skin.

11.1. Solid Microneedles (MNs)

Solid MNs are also called as first generation of MNs. They do not contain drugs themselves and enhance the permeability of skin for drugs, by creating pores into the skin [74]. They are generally made up of silicon or metals [75]. Drawbacks associated with Solid MNs:

- Solid MNs requires a two-step application, which is not convenient for patients.
- Moreover, some of the needles happen to break and are left in the skin, irritation is inevitable, such incidences are not appreciable.
- The fabrication cost is high and the disposition of wastes is also a question.
- Some materials, for example, silicon, require clean room processing and are not FDAapproved biomaterials.

11.2. Hollow Microneedles

- Just like Solid MNs, hollow MNs usually require very specific manufacturing technology and have high production cost, hence massive production is not very feasible [76].
- In case of breakage of hollow MNs in the skin, significant leakage or uncontrolled drug release may occur [77], which may be associated with further complications associated with high dose administration.
- There are also risks that the body tissue blocks the narrow channels which interfares with the drug dosage.

11.3. Polymer Microneedles

Polymer microneedles offer solutions to all above mentioned drawbacks associated with microneedles. The polymer MNs have benefits of ease of fabrication, cost-effectiveness, and the capacity for mass production, as well as controlled drug release with the help of water solubility and degradation properties of polymers [78]. Hydrogel MNs are one kind of polymeric or polysaccharide MNs which are fabricated with polymers or the hydrogel coated on the surfaces of solid MNs. There are three kinds of drug-loading methods (**Figure 5**), some MNs only have drugs in the tips; some in the patches; others have drugs in both.

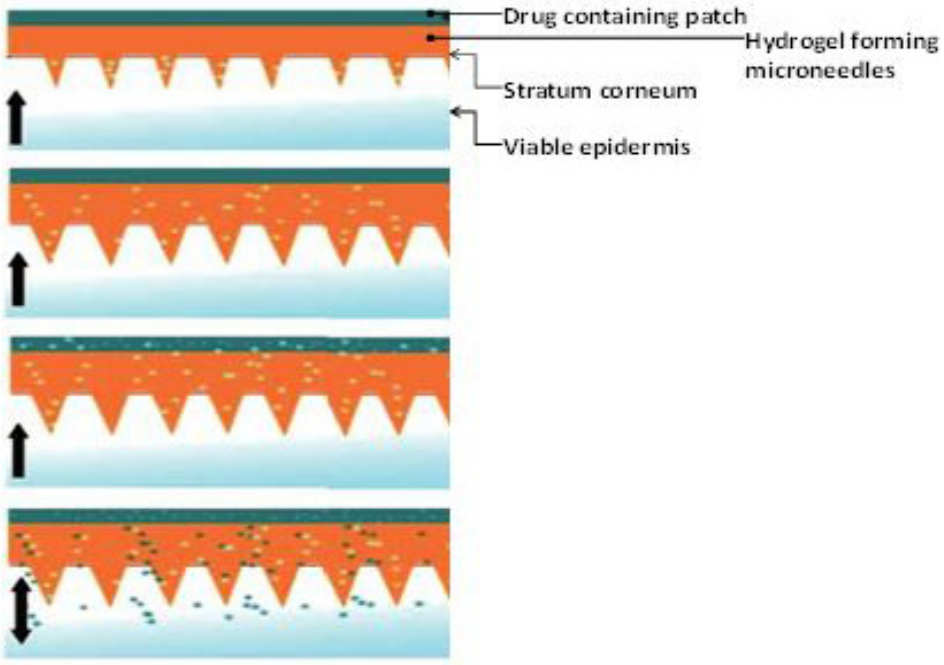

Figure 5: The design of hydrogel MNs [79].

11.4. Advantages of polymer/Hydrogel MNs

- Hydrogel microneedles provide large spaces for drugs to be loaded. The drug loading amount is better than the solid MNs and drug coated MNs as well as the hollow MNs.

- Polymer microneedles also offer the benefits of ease of fabrication, cost-effectiveness, and the capacity for mass production, as well as controlled drug release with the help of water solubility and degradation properties of polymers [79]

- Polymers and hydrogels have excellent biocompatibility, degradability, and nontoxicity [80,81].

- Hydrogel MNs are overall easier and more FDA approvals. The fabrication methods often include the photolithographic process and micro-molding process [78].

According to the function mechanism of hydrogel MNs, they are divided into two categories.

1. Dissolving or degradable MNs

2. Phase transition MNs

11.3.1. Dissolving or degradable MNs:

The dissolution or degradation of the MN matrix, i.e. the polymer or polysaccharide themselves [78,82,83] lead to the drug release. These MNs dissolve or degrade in the skin and release the loaded drugs in a short time leaving no sharp medical waste after use [84-86].

An example of dissolving MNs is reported by Ming-Hung Ling *et al*. [88]. This group

presented a dissolving microneedle patch, made up of starch and gelatin and used insulin as the model drug. An important report by Chin Chen *et al*. [87,89] confirms that drugs loaded in chitosan carriers can be released through swelling and degradation of the chitosan matrix, leading to a clear sustained-release effect. Chitosan with suitable molecular weight is readily biodegradable in *in vivo* systems.

Another way to exploit the biodegradable MNs is to leave the needles in skin to deliver bolus drugs or sustained release of drugs for longer durations by separating the needles from the patches in the skin. Min Kim *et al*. [90] demonstrated one such use of MN, by separation of hydrogel MNs, mediated by hydrogel swelling in response to absorption of fluids on contact with body fluid. In such cases, the tips of biodegradable polymeric MNs are separated because of hydrogel microparticles, which were fabricated between the needle tips and the patches, expand quickly and lose mechanical strength rapidly by swelling and absorbing body fluid. Leonard Y. Chu *et al*. [91] investigated separable arrowhead MNs which upon insertion in the skin, the sharp-tipped polymer arrowheads induced hydrogel part which contained drugs to separate from their metal shafts.

11.3.2. Phase transition MNs

This type of MNs, exhibit phase transition upon in absorption of body fluids by polymer leading to swelling mediated drug release. This kind of MNs leaves few or no residuals after application. These MNs preserve the advantages of other MNs, such as the drug permeating amount, rate improvement, large drug loading amount and relatively easy to be fabricated. They also have the potential to be daily used since few non-drug residuals will be left in the skin, which may increase the patients' compliance. They are so far very promising MN technologies.

Ryan F. Donnelly *et al*. [92,93] developed MNs made of Gantrez AN-139, a copolymer of methyl vinyl ether and maleic anhydride, which could be removed completely and intact from the skin. The needle tips swell in skin to produce continuous, unblockable conduits from patch-type drug reservoirs to the dermal microcirculation, thus allowing prolonged transdermal drug administration. According to their findings, delivery of macromolecules was no longer limited to what can be loaded into the MNs themselves and transdermal delivery drug was controlled by using the crosslink density of the hydrogel system rather than the stratum corneum. The MNs can be fabricated in a wide range of patch sizes and MN geometries by adjusting the molds used.

So far it has become evident that, the hydrogel microneedles are more promising compared with their solid or hollow counterparts. There are also some weaknesses related to the dissolving or biodegradable mechanisms. The most prospective MN type is the hydrogel MN which does not dissolve or degrade in skin but with a controlled or sustained release of drugs.

The application of other methods, for skin permeation, may enhance the drug release rate, but they also increase the costs of MNs while lower the patients' compliance.

12. Conclusion

However, TDDS is very promising drug delivery method with a number of advantages over existing conventional drug delivery methods. But there are some disadvantages associated with TDDS such as high cost, limited drug repertoire that can be administered through skin, allergic response or contact dermatitis due to transdermal patches which can be patient specific.

In conclusion, the TDD sector continues to grow and develop with rapid expansion in fundamental knowledge feeding industrial development. There is a massive potential in this type of drug delivery systems that needs to be exploited for better. In coming time, it is expected that technological advancements in TDD will lead to enhanced disease diagnosis and control, with concomitant improvement in health-related quality of life for patients worldwide

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