



## Transdermal approaches in drug delivery

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### Abstract

The authors have advocated the basics and applications of transdermal drug delivery – an approach used to deliver drugs through the skin for therapeutic use as an alternative to oral, intravascular, subcutaneous, and transmucosal routes. Various transdermal drug delivery technologies are described including the scientific basics for the design and use of suitable formulations, carriers and penetration enhancers. The established and contingent technological frameworks with construction components and kinetic principles for the most commonly used devices for the transdermal delivery of therapeutic molecules are detailed.

**Key words:** Drug delivery, transdermal systems, noninvasive drug delivery systems

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### Introduction

Management of illness through medication has entered an era of rapid growth. A variety of means by which drugs are delivered to the human body for the therapy such as tablets, capsules, injections, aerosols, creams, ointments, suppositories, liquids etc. are referred as a conventional drug formulations. Therapy with such formulations involves attainments and maintenance of drug concentration in the body within a therapeutically effective range by introduction of fixed doses of drug, at regular interval, into the body [1, 2]. The molecular structure of the drugs which are responsible for their intrinsic pharmacological activities, are never used as pure chemical substance. Drugs are always put into delivery systems which may be mechanical or electromechanical devices or formulated dosage forms. The dynamics of drugs release from a dosage form in the site of its action in the body is equally important in determining the safety and effectiveness of the course of drug therapy as in intrinsic pharmacological activity of chemical substances that the drug product contain. The formulation and manufacture of drug dosage forms, as well as how drug delivery devices are designed and operated has a profound influence on the manner in which drug access their site(s) of action.

Among many pharmaceutical dosage forms, continuous intravenous infusion at programmed rate has been recognized as a superior mode of drug delivery not only to bypass the hepatic 'First Pass' elimination, but also to maintain a constant, prolonged and therapeutically effective drug level in the body. A closely monitored intravenous infusion can provide both advantages of direct entry of drug into systemic circulation and also control to circulating drug levels. However, such mode of drug delivery entails certain risks and therefore necessitates hospitalization of the patients and close medical supervision of the medication. Now it is known that the benefits of intravenous drug infusion can be closely duplicated without its potential hazards, by continuous Transdermal drug administration through an intact skin. In response to this new idea, several Transdermal drug delivery systems have recently been developed aiming to achieve the objective of systemic medication through topical application on the intact skin surface [3]. Transdermal drug delivery systems are pharmaceutical preparations intended to be applied on the unbroken skin in order to achieve ingredients(s) to the systemic circulation after passing through the skin barrier. They are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through skin at a controlled rate to systemic circulation [4]. Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. The mustard plaster, applied as a home remedy for severe chest congestion, may be considered an example. Perhaps the most remarkable forerunner of modern transdermal medication was Stronger Mercurial Ointment, used as a treatment for syphilis when Salvarsan and other arsenicals were in use, before the discovery of penicillin. The transdermal patches can be exemplified by first with development of scopolamine releasing TDDS (Transdermal- scop by Alza corporation USA in 1980), provides controlled delivery of scopolamine over a 3-days wearing period. Now, FlectorPatch (diclofenac), an approved new drug, is commercially available with "...improved pain relief at a variety of sites, including back, knee, ankle, shoulder, upper and lower leg, and hip". The promotional material goes on to say and even emphasize, "Minimal steady-state plasma concentrations. Range: 1.3 ng/mL to 8.8 ng/mL). The transdermal devices are successful because they overcome some of the pharmacokinetically undesirable property of nitroglycerin e.g. (a) its rapid plasma elimination half life and (b) very high plasma clearance. In addition, its high first pass metabolism which would prevent any pure drug from reaching the general circulation after oral administration is avoided [3].

### **Advantages and limitations of transdermal**

#### *1.1.1. The potential advantages which have been described including the following:*

- i) Dosage intervals not limited by gastric transit time.*
- ii) Elimination of vagaries of gastro intestinal absorption that normally affect drugs after taken orally.*
- iii) Elimination of pulse entry of drugs into the systemic circulation, thereby reducing side effects.*
- iv) Reduction of drug metabolism, due to initial bypass of the liver.*
- v) Utilization of drugs with short half life, which can not be successfully delivered by conventional dosage forms to maintain the therapy.*

- vi) Elimination of hazards and difficulties to intravenous infusion or intramuscular injections.
- vii) Improved control of the concentrations of drugs with small therapeutic indices.
- viii) Single application has capacity for multi-day therapy, thereby improving patient compliance.
- ix) Immediate termination of drug effect is possible by removal of the delivery system whenever required.
- x) Medication can be identified quickly in case of emergencies, in case of non-responsive, unconscious or comatose patient.
- xi) Easy to prepare and easy to transport.
- xii) Self medication is possible with these systems.

1.1.2. *These systems are however, having some limitations these include the following:*

- i) It is required to have some optimum physicochemical properties for the drug to penetrate through stratum corneum and the drug dose required for therapeutic value should be  $\leq 10\text{mg/day}$ , otherwise the delivery through Transdermal route will be very difficult and some time it may not be possible. Normally, drugs with therapeutic dose less than  $5\text{ mg/day}$  are preferred to be delivered through Transdermal route.
- ii) Skin irritation and contact dermatitis reported some times due to some of the excipients are penetration enhancers are another limitation for such delivery.
- iii) Clinical is also an area that has to be examined carefully before a decision is made to develop a Transdermal product.
- iv) The barrier function of the skin for penetration of the drug is found to vary between subjects and some times within subjects too and with age [5].

## **Skin as a platform for drug delivery**

### **2.1. The skin**

The skin is one of the most extensive organs of the human body covering an area of about  $2\text{m}^2$  in an average human adult. This multilayered organ receives approximately one-third of all blood circulating through the body [6]. It has varied functions and properties. With a thickness of only a millimeter, the skin separates the underlying blood circulation network from the outside environment, serves as a barrier against physical, chemical and microbial attacks, acts as a thermostat in maintaining body temperature, protects against harmful ultraviolet rays of the sun and plays a role in the regulation of blood pressure. Anatomically, the skin has many histological layers but in general, it is described in terms of three major tissue layers: the epidermis, dermis and hypodermis. The epidermis results from an active epithelial basal cell population and its approximately 150 micrometer thick. It is the outermost layer of the skin and the process of differentiation of results in migration of the cell from basal layer towards the skin surface [7]. The end of this process is the formation of a thin stratified and extremely resilient layer (stratum corneum) at the skin surface. Below this layer are the layers of the epidermis – the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinative. Together these other layers constitute the viable epidermis.

The stratum corneum or horny layer is the rate-limiting barrier that restricts the inward and outward movement of chemical substances. Over most of the body, the stratum corneum composed of 15 to 25 layers of acutely flattened, metabolically inactive, somewhat polygonal cells having a dry weight density of 1.3-1.4 g/cm<sup>3</sup> the thickness of individual cell layers varies from 0.2-0.5 μm depending to their location. The interior of crisscrossed with densely packed bundles of keratin fibres. Due to this, the dry composition of the horny layer is 75-85% protein, most of which is the intracellular keratin and a part being associated with a network of cell membranes. The bulk of remainder of the substance of stratum corneum is a complicated mixture of lipid which lies between the cells. It appears to be organized into bilayers. The stratum corneum has two distinct chemical regions, the mass of intracellular protein and the intracellular lipoidal medium. These phases are isolated from one another by cell membranes, which are themselves knit together by desmosomes adding a tough infrastructure to the horny mass [8]. The epidermis rest on the much thicker (2000μm) dermis which essentially consist of about 80% of protein (collagen fibres) in a matrix of mucopolysaccharide 'ground substance' [9]. A rich bed of capillaries is encountered 20μm or so into the dermal field. Also contained within the dermis are lymphatic, nerves and the epidermal appendages such as hair follicles, sebaceous glands and sweat glands. Expecting the soles of the feet, the palms of the hand, the red portion of the lips and selected portion of sex organ, the entire skin surface contains hair follicles. Each hair follicle is associated with one or more sebaceous glands, which are out growth of epithelial cells. The duct of the sebaceous glands is filled with a soft, slowly extruded lipoidal medium – sebum. About 1/1000 of the total skin surface is occupied by hair follicles. The sweat glands are divided into the eccrine and apocrine types and are widely distributed over the surfaces of the body. Eccrine glands are particularly concentrated in palm and soles (400 glands/cm<sup>2</sup>). The apocrine glands are found in the axillae (armpits), anogenital region and around nipples. These are coiled tubular glands, about ten times larger than eccrine glands and extends entirely through the dermis and well in to the subcutaneous layer. The sweat glands serve to control the body heat by secretion of a dilute salt solution.

## **2.2. Biochemistry of skin:**

Like other tissue of body, the skin has two metabolic requirements, small molecular weight building block and chemical energy [10]. Dissimilarities peculiar to the skin are discussed here, as it might affect transdermal drug delivery system.

**2.2.1. Dermis:** Protein synthesis (from amino acid precursors) is a key factor in dermal metabolism. Fibroblasts produce and extracellularly, huge quantity of collagen and elastin. This becomes more important in repair/ turnover or dermal protein altered by environmental sunlight. Extensive protein synthesis also occurs in hair follicle where hairs, consisting of approximately 95% protein originate. The sebaceous glands produce large quantity of lipid (from the two carbon precursor's acetate). The energy derived from the intracellular aerobic carbohydrate (glucose) metabolism is used for cellular synthetic processes.

**2.2.2. Epidermis:** The sources of energy for the lower portions of the epidermis is also glucose and the end product of metabolism, lactic acid accumulates in skin, which results in a drop in tissue pH from the usual 7.0 to less than 6.0. The cells rely primarily to fatty acids (lipids) for cellular functions. These fatty acids are derived from the degradation of phospholipids from membranes. The energy derived is used in synthesis of protein and lipids for construction of stratum corneum. During differentiation from basal cells to stratum corneum by degradation of the existing cellular components, the entire cellular make-up changes. Specialized cellular organelles called lysosomes contain a host of lytic enzymes which they release for intracellular lysis. The epidermis is reservoir of such lytic enzymes. Many of these enzymes are in activated (probably by auto catalytic processes) in upper granular layer, however many also survive into the stratum corneum. The stratum corneum also has proteolytic enzymes involve in these desquamation.

**2.2.3. Skin surface:** The surface has a population of microorganism. They can contribute to skin enzymology. Their diversity and abundance can vary considerably among individual and body sites. They can also effect skin surface lipid composition via hydrolysis of secreted sebum.

### **Kinetics of transdermal permeation:**

The knowledge of skin permeation kinetics is vital to the successful development of the Transdermal therapeutic system. Transdermal permeation of a drug involves three major steps (1) sorption by stratum corneum (2) penetration of drug through viable epidermis (3) uptake of drug by capillary network in the dermal papillary layer. This permeation can possible only if the drug processes certain physicochemical properties, the rate of permeation across skin ( $dQ/dt$ ) is given by,  $[dQ/dt = P_s(C_d - C_r)]$  where  $C_d$  and  $C_r$  are the concentration of skin penetrant in the donor compartment (e.g. on the surface of stratum corneum) and receptor compartment (e.g. body) respectively.  $P_s$  is over all permeation coefficient of skin tissue to the penetrant and is governed by the partition coefficient ( $K_s$ ) and apparent diffusivity ( $D_{ss}$ ) as:  $[P_s = K_s D_{ss} / h_s]$ . The  $K_s$  as stated above is partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum [11]. The  $h_s$  represent thickness of tissue which offers an apparent diffusivity ( $D_{ss}$ ) for the steady state diffusion of the penetrant molecule through a thickness skin tissue. Since the tissue thickness and partition coefficient are constant under given condition, the permeability coefficient ( $P_s$ ) for a skin penetrant can be considered to be constant.

From the equation above, it is clear that a constant rate of drug permeation can be obtained only when  $C_d \gg C_r$  that means, the drug concentration at the surface of the stratum corneum ( $C_d$ ) is consistently and substantially greater than the drug concentration in the body ( $C_r$ ). Then equation (1) can be reduced to  $dQ/dt = P_s C_d$ , and the rate of skin penetration ( $dQ/dt$ ) is constant provided the magnitude of  $C_d$  remains fairly constant throughout the course of skin permeation. For keeping of  $C_d$  constant, the drug should be released from the device at rate ( $R_r$ ) that is either constant or greater than the rate of skin uptake ( $R_a$ ) i.e.  $R_r \gg R_a$ . The drug release rate from the device remain higher than it is absorbed providing a greater drug concentration ( $C_d$ ) on to the skin surface in equilibrium

with saturation solubility of medicament in the stratum corneum, *i.e.*  $C_d \gg C_s$ , therefore a maximum rate of skin penetration  $[(dQ/dt)_m]$  by a medicament can be described as  $[(dQ/dt)_m = P_s C_s]$ , to be dependent on the permeability coefficient of the medicament and its equilibrium solubility in the stratum corneum.

## Basic components of transdermal therapeutic systems

### 4.1. Polymer matrix:

A polymeric backbone governs the drug release from device. A polymer matrix, to qualify its use in transdermal drug delivery systems has to comply with some general requirements, which include (1) Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug could diffuse properly and get release through it, (2) The polymer should be stable enough, non-reactive with drug, and should support easy manufacturing and fabrication into the desired product, (3) The polymer and its degradation product must be non-toxic or non-antagonistic to the body tissues in general and to the skin in particular, (4) The mechanical properties of the polymer should not deteriorate excessively when large amount of active agents are incorporated into it, (5) it is desired to be economically sound. Possibly useful polymers for transdermal devices are:

**4.1.1. Natural polymers:** Cellulose derivatives, Zein, Gelatin, Shellac, Proteins, Gums and their derivatives, natural rubber and starch *etc.* Recently some natural polymer latex like jackfruit latex, plum latex and other semisynthetic polymers have undertaken for research to be utilized in TDDS.

**4.1.2. Synthetic elastomers:** Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Buty rubber, Styrenebutadiene rubber, Neoprene *etc.*

**4.1.3. Synthetic polymers:** Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethacrylate, Epoxy *etc.*

The permeation enhancers and some other additives like plasticizers, adhesives *etc.* are often required to be added with the polymer matrix as per the formulation requirements.

### 4.2. The Drug

Most drugs are not suitable candidate for Transdermal drug delivery for one or more reasons: the 'easy to deliver' drugs have already been commercialized into TDDS. To date only 10 drugs out of 100 listed in the USP or 'Physician Desk Reference' (PDR) have been commercialized into TDD products. Since the Transdermal patches was approved in 1981 to prevent nausea and vomiting associated with motion sickness, the FDA has approved through the past 22 years, more than 35 Transdermal patch products spanning 13 molecules [12]. In general the desired physico-chemical; biopharmaceutical Pharmacokinetic attributes of drug for passive TDD include (1) low daily dose ordinarily, less than 20mg/day (2) short half life *i.e.* 10 hr or less (3) molecular weight less than 400 Dalton (4) low melting point,  $>200^\circ\text{C}$  (5) high lipid solubility, should have octanol-water partition coefficient ( $\log P$ ) value in range of 1.0 – 4.0 (6) skin permeability coefficient

greater than  $0.5 \times 10$  cm/hr (7) non-irritating and non-sensitizing to skin (8) low oral bioavailability *e.g.* preclude oral delivery (9) low therapeutic index *i.e.* required tight control of plasma levels. The listed parameters are by no means all-inclusive and there are many other desirable attributes for selecting drug for transdermal drug delivery system. A single drug could meet only a few of desirable attribute and an acceptable balance between them needs to be established. The high oral dose, large patch size, skin irritation and/or sensitization are often the main barriers that preclude the most candidate drug from being commercialized for transdermal delivery [13]. A careful preformulation investigation is carried out for selection and optimization of drug candidate and formulation to have an acceptable compromise in desired and practical properties of a promising drug for which transdermal delivery is sought.

## Types of devices

### 5.1. According to drug release mechanism:

The transdermal devices based on their technological construction for drug release can be of four types, *viz.* matrix diffusion controlled, membrane permeation controlled, micro-sealed dissolution controlled, and adhesive dispersion type systems.

**5.1.1. Matrix diffusion controlled TDDS:** These are also called as monolithic drug delivery systems. These devices consist of solid drug particles in a polymer backbone governing the diffusion from self contained reservoir. The drug is released from this system by dissolution and followed by diffusion. Parameters are dependent upon the structural and molecular factors of the polymer drug matrix *i.e.* polarity, hydrogen bonding, glass transition temperature of the polymer, solvating or plasticizer effect of excipients and drug upon the polymer chains the concentration of the different drugs also has significant effect upon its release [14, 15]. The matrix diffusion type drug delivery systems offer several advantages which include the ease of fabrication, sustained release of macromolecules *etc* [16]. The one major drawback in matrix diffusion controlled drug delivery system is that it generally does not display the desired zero order kinetics *e.g.* *Nitrop-Dur* transdermal infusion system [14].

**5.1.2. Membrane permeation controlled TDDS:** This type of systems are composed of a drug reservoir in the form core of pure solid drug particles or a suspension of drug solid particles in a liquid medium, encapsulated in a compartment walled by a constant surface of permeation controlled polymeric membrane, for monitoring the rate of drug release from the system. The membrane permeation controlled drug delivery system provide a constant zero-order drug release profile, while it is more difficult to fabricate and has a potential risk of dose dumping due to membrane breakage *e.g.* Scopolamine releasing *Transderm V* system and nitro glycerine releasing *Transderm-nitro* system [15, 16, 17].

**5.1.3. Micro reservoir type or microsealed dissolution controlled TDDS:** These systems are manufactured by homogenously dispersing the drug in reservoir or a liquid suspension of solid drug particles in water soluble liquid type polymers or in a silicone elastomer, before cross linking the elastomer to form a stable dispersion. This is then molded into any shape of device, walled with impermeable membrane laminates with an

opening of constant surface which can be covered with a permeation controlling polymeric membrane to provide an additional controlling step on the release of the drug molecules. The system is a hybrid type system with homogenous, microscopic diffusion of drug reservoir in polymer matrix to maximize the advantages and to minimize the disadvantages of both matrix diffusion controlled and membrane permeation controlled drug delivery system [18]. It is a matrix in physical appearance and delivers the drug at a rate, which follows either zero-order or square root of time kinetics, depending upon the physicochemical properties of drug in the system [19].

**5.1.4. Adhesive dispersion type system:** This is the simplified form of the membrane permeation controlled systems. The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. poly(isobutylene) or poly (acrylic) adhesive and then spreading the medicated adhesive by solvent casting or hot melt in to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the reservoir layer, thin layers of non-medicated rate-controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion controlled delivery system. For example, *isosorbide dinitrate* transdermal therapeutic system.

## **5.2. According to rate controlling step:**

The transdermal devices, based on rate controlling step may be of two types, the first those they control the rate of drug delivery to the skin and, second those that allow the skin to control the rate of drug absorption. The former is for drugs, which are potent, for which it is important to control the rate of drug derive in order to maintain the minimum effective concentration while the later type is useful for the drugs having wide range of plasma concentration over which the drug is effective but not toxic.

## **5.3. According to polymer:**

**5.3.1. Hydrophilic or hydrogel systems:** In this type hydrophilic polymer are used for preparation of transdermal patches e.g. hydrogel, which releases the drug by swelling mechanism therefore patch of this type absorb the water of skin and skin appendages then swell and release the drug to the skin surface. Hydrogel type of transdermal patches can overcome the side effect like skin irritation and other problem associated with TDDS. Hydrogel have high skin compatibility, probably due to water exchange with the skin, and many therefore are suitable for skin complaint transdermal drug delivery system.

**5.3.2. Hydrophobic or occlusion systems:** The hydrophobic polymers are used for preparation of such transdermal patches. The release of drug involves occluding the skin with impermeable hydrophobic film, preventing from losing the surface water from skin etc. The concomitant swelling of horny layer extensively decrease the protein network density and diffusional path length to drug. Also the occlusion of skin surface increases skin temperature (-2 to 30°) resulting in increasing molecular motion and skin permeation. However, long application of this occlusive TDDS may evoke number of unwanted side effects like, clogging of sweat ducts resulting in sweat retention syndrome,

accumulation of harmful bacteria in accumulated water and sweat that may infect the skin, and risk of allergies or irritation reaction.

### **Technological framework of transdermal patches:**

#### **6.1. Backing support:**

It is used to provide a base on to which the drug incorporated polymers are casted. This may act as occlusive as well as non-occlusive. The backing support also provides an unidirectional flow of drug from transdermal patch to skin only and prevent from any loss to external environment. Examples are, Aluminized plastic, Aluminized polyester *etc.*

#### **6.2. Drug reservoir:**

The drug reservoir consist of the medicament to be delivered, it may be in the form of dispersion of single drug in liquid state embedded into polymer matrix or may be a drug core enveloped with permeation controlled polymeric membrane. The reservoir compartment may also have core of the drug covered with impermeable cover having window for drug release provided with a controlling membrane.

#### **6.3. Adhesive film:**

It is used to provide an intimate contact of drug releasing liver of Transdermal patch with skin. In some cases drug is incorporated in it and act as a reservoir for drugs. Adhesives are used sometimes for delivering of loading dose initially followed by maintenance dose of matrices. These are three classes of pressure sensitive adhesives, which are biocompatible; they are silicones, polyisobutylenes and polyacrylates.

#### **6.4. Release liner:**

It is an occlusive *i.e.* drug impermeable plastic film or metallic plastic laminate. It is used to control the release of drug to a particular surface area of the skin. A protective peel strip of siliconized polyester which cover the above mentioned layer which should be served for the prevention of the contamination of the Transdermal patches from the dust and foreign matter, which should be peeled out before administration.

#### **6.5. Penetration Enhancers:**

A popular approach is the use of penetration enhances, which reduce reversibly the permeability barrier of the stratum corneum (SC) [20]. Such materials known also as accelerant or sorption promoters, if they are safe and non-toxic can be used clinically enhance the penetration rate of co-administered drug or even to treat patient systematically by the dermal route. These agents partition into, and interact with SC constituents to induce a temporary, reversible increase in skin permeability. In this way many compounds such as isopropyl myristates, hydrogenated soya phospholipids, essential oils, butanol, n-octanol, and decanol, terpens, and surfactant have been reported to enhance the permeability of drugs by various researchers [21-26].

*The attribute of the ideal penetration enhances are:*

- i) The material should be pharmacologically inert.*
- ii) It should be non-toxic, non-irritant and non-allergenic.*

- iii) The action should be immediate and effect should be suitable and predictable.
- iv) Upon removal of the material and skin should immediately and fully recover its normal barrier property.
- v) The enhancers should not cause loss of body fluid, electrolytes and other endogenous materials.
- vi) It should be compatible with all drugs and excipients.
- vii) The substance should be a good solvent for drugs.
- viii) The material should be cosmetically acceptable (good spreadability and skin 'feel')
- ix) The chemical should formulate into all the variety of preparations used topically.
- x) It should be odorless, tasteless, preferably colorless and inexpensive.

No single material possesses all desirable properties. However, very few substances exhibit several of these attributes and they have been investigated clinically or in laboratory. Examples are, water, sulphoxides (especially dimethylsulphoxide) and their analogues, pyrrolidones, fatty acid and alcohols, azone and its derivatives, surfactants, urea and its derivatives, alcohols and glycols, essential oils, terpenes and derivatives, and synergistic mixtures. For safety and effectiveness, the best penetration enhancers of water. Most substance penetrates better through hydrated stratum corneum than through the dry tissue. Thus, any chemical which is pharmacologically inactive, non-damaging and which promotes horny layer hydration, can be considered as penetration enhancer.

### **Potential advancements in TDDS**

During recent years there has been immense progress in the field of transdermal delivery devices; several new and more efficient methodologies providing better control, faster onset and larger dose to be delivered, have been developed by technological integration through various physical, chemical or biological means. At first glance, using small electric current to push medication through their skin may not appeal to many patients. But specialist transdermal drug delivery scientists across the globe are confident that within five to 10 years electricity, ultrasound, radiofrequencies, and micro-needles will be widely used to get many commonly used products into the blood stream quickly and efficiently through the skin. Some of these technologies are exemplified as below:

- a) Physically enhanced TDDS: Iontophoresis, Sonophoresis, Electroporation etc.
- b) Chemically improved TDDS: Drug-in-adhesive, Chemical enhancers, Vasodilators etc.
- c) Vesicular Systems: Liposomes, Ethosomes and Transfersomes etc.

#### **7.1. Iontophoresis:**

This technique is used to enhance the transdermal flux of drugs across the skin by applying a small electric current which forces ionized species of drug into the skin. If the drug is polar or ionic, then its delivery by Transdermal route is very difficult (without use of any physical means). The process involving the placing of electrodes patch containing the drug on the skin, which acts by the working electrode (can be negative or positive depending upon the characteristics of drugs). Another electrode placed at a short distance away from the body to complete the circuit and the electrodes are connected to

the power supply. The operator then selects a current intensity below the pain threshold level of the patient (current density less than  $0.5\text{mA}/\text{cm}^2$ ). Iontophoresis enhances the transdermal drug delivery by three ways, (1) Drugs are forced across the skin by simple electronic repulsion of similar charges. An ionic drug can cross the skin by using a negatively charged working electrode vice-versa, (2) Electric current enhanced permeation by inhibiting the skin's ability to perform its protective barrier function, (3) Iontophoresis causes the water to enter the stratum corneum by electro-osmosis. Dissolved drug can be carried across the skin along with the penetrating water during Iontophoresis. Iontophoresis allow high control of delivery rate to achieve successful drug delivery. The drawback associated with technology include: the possibility of skin irritation, sensitization, burns and cost of the treatment.

### **7.2. Electroporation:**

Electroporation is derived from the word 'electric' and 'pore'. The drawback associated with Iontophoresis can be overcome to a certain extent by 'Electroporation technology' developed in recent years. The process involves the application of transient high voltage electric pulse to create small pores in phospholipids by layer of the cell membrane which can assist in the Transdermal delivery of the drugs. Drug encapsulated in the vesicles or particles is delivered into the skin through the channels, which are created by disruption in lipid bilayers in stratum corneum. These changes have been shown to be reversible and pore usually closed within 30 min without significant damage to the exposed cell. In future Electroporation may facilitate the delivery of large and small peptides, oligonucleotides and other hydrophilic drugs that are poor candidate for traditional transdermal drug delivery. There is the problem of instrumentation for home use for this potent technique.

### **7.3. Sonophoresis or Phonophoresis:**

Ultrasound has long been established as a therapeutic agent in the treatment of a wide range of clinical conditions used by physical therapeutics. The application of 'low frequency ultrasound' shown to increase the permeability of human skin through disruption of lipid bilayers of stratum corneum [27]. Low frequency sonophoresis causes cavitations or production of extremely small bubbles in the skin that create small hydrophilic channels through the stratum corneum [28]. Propagation of the sound waves through the skin also causes heating, which has the similar effect. Low frequency ultrasound thus a low potential, noninvasive technology for transdermal drug delivery. Further more the optimal parameters such as frequency, pulse, length and intensity should be observed carefully to ensure a safe and efficacious application. Ultrasound energy of the order of 1.0 MHz and  $0.5$  to  $1.0\text{ W}/\text{cm}^2$  is traditionally used. Enhance skin permeation by ultrasound application may be used for delivery of various proteins such as insulin, interferon and erythropoietin. It can also be used for several other drugs including low molecular weight heparin and leutinizing hormone releasing hormone (LHRH). A problem with this technique is, of course, the need of ultrasonic probe, correctly focused on the work of stratum corneum.

**7.4. Microporation:**

A new area of intense transdermal research and development is the technology that creates micro pores in that stratum corneum. The microfabricated, microneedle technology employ micron sized needle made from silicon that, when applied to the skin, painlessly (nerves located deeper in the skin are not stimulated) creates micropores have lower resistance to drug diffusion than normal skin [27]. The microneedle are usually drug-coated projection of solid silicon or hollow, drug filled metal needles. Each microneedle is about 1 micrometer in diameter or 100<sup>th</sup> of the diameter of a human hair and can be seen only under microscope. A microprocessor is attached to a tiny pump for automatically inject the right dose of the drug continuously or in response of body needs. The microfabrication technique can be easily modified to make larger or shorter needle according to the requirement. Microneedle after insertion into skin, found to be mechanically strong be removed without difficulty as well as reinserted into skin multiple times. These systems have been reported to greatly enhance (upto 100000 folds) the permeation of micromolecules through the skin.

**7.5. Needle-less jet ejectors:**

Needleless jet ejectors combine the advantages the Transdermal and parenterals drug delivery methods. The best known technology, powder ject, fires fine, solid particles through the stratum corneum using high pressure helium gas. The Makers of powder ject claim because of ejector use particles that are too small to trigger pain receptors, drug delivery is painless, making it suitable for patient who fears traditional injections. Additionally powder ject significantly lowers the risk of infections because no sharps are contaminated and no blood exposure occurs through its use. The pulse of *powder ject* can reportedly tailored to a specific depth within the skin. *Powder ject pharmaceutical* claims that their technology can be used to deliver any drug that can be produced in the particles of proper size, mass, and strength, regardless of chemical structure [29].

**7.6. Heat as a means of increasing skin permeation:**

Heat or thermal energy, applied to skin increasing skin permeation by several mechanisms. Heating force or during topical application of drug dilates penetration pathways in the skin and increase kinetic energy. Higher temperature increases microcirculation and blood vessel permeation thus facilitating drug transfer to the systemic circulation. Drug solubility, both in patch formulation and within the skin, may increase with a rise in temperature [29].

**7.7. Other active transport technologies:**

Other techniques like laser assisted delivery and megnetophoresis are also getting some interest in the field of Transdermal drug delivery. Laser technology is design to painlessly and temporarily after the stratum corneum. Or outer layer of skin, to enable a wide range of drug to be delivered effectively and without the gastric side effect associated with oral drug administration. Megnetophoresis is a novel approach in enhancing drug delivery across biological barriers. Benzoic acid, a diamagnetic substance, was selected as a drug candidate. The influence of magnetic field strength on diffusion flux was determined and was found to increase with increasing applied field strength [30].

**Conclusion**

In conclusion, the delivery of drugs to systemic circulation through the skin is recognized as an alternative to taking it orally as it provides better patient compliance, bypass the GI tract and provide much steady absorption of drugs over hours. There have been several advancements on both the molecular and energetic enhancement of Transdermal penetration of drugs that could result in new products with better therapeutic potential. The underlying principles, technological advancements and potential in the field of Transdermal drug delivery is discussed in this paper.

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