

## A REVIEW ON TRANSDERMAL DRUG DELIVERY

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<p><b>* For Correspondence:</b>  <b>Rajbala Singh</b>  E-mail- singhrajbala44@gmail.com  Siddhartha Institute of Pharmacy,  Dehradun, Uttarakhand</p>	<p><b>ABSTRACT</b></p> <p>Transdermal delivery is constantly challenging system for the drug molecule to encroach appearance of its therapeutic action because of many features of skin. In this review we cover different aspect of transdermal delivery along with its evaluation as well as current advancement in transdermal drug delivery system. We also try to cover different generation of transdermal delivery as like iontophoresis, sonophoresis, electroporation, microneedles, magnetophoresis, photomechanical waves, electron beam irradiation, Chemical–iontophoresis, chemical–electroporation, chemical–ultrasound, iontophoresis–ultrasound, electroporation–iontophoresis, electroporation–ultrasound, pressure waves–chemicals and reported the synergistic effect of the same for safe, effective and practical use of TDDS.</p> <p><b>KEY WORDS:</b> Transdermal drug delivery, Evaluation, Advancement.</p>
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## INTRODUCTION

Our ancestors have applied a lot of substances to their body as ritualistic painting using natural products, through which small lipophilic molecules entered (Jett, et al., 2011). Transdermal drug delivery is an important delivery among controlled release mode in modern century because one third of drugs under clinical evaluation involve delivery into or via the skin as well as about two third of drugs are taken orally (Prausnitz, et al., 2008), but these are not as effective as required as it is minimize and avoids the limitations allied with conventional as well as parenteral route of drug administration such as peak and valley phenomenon (Matteucci, et al., 2008) i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options (Shingade, et al., 2012). The challenges include the considerable effectiveness of the skin barrier (particularly its uppermost layer, the stratum corneum) in limiting drug penetration, the significant variability in penetration between people, and between sites on an individual (Schaefer, et al., 2011).

## 2. Skin as a site for drug infusion:

Skin is largest organ of the body, cover about 20 square feet in an adult, received about one third of total available blood. The skin is multi-layered organ composed of three histological tissues namely the outermost layer of skin, epidermis; beneath epidermis, dermis contains tough connective tissue, hair follicles, and sweat glands; and deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue (Arunachalam, et. at., 2010; Kapoor, et al., 2011). The SC is the outermost layer of the epidermis. Desquamation is approximately 2 weeks process in which Cells migrate from the dermal–epidermal junction to the base of epidermis. The main motto of desquamation involve the differentiation of epidermal keratinocytes into flat, closely packed interdigitated corneocytes, embedded in a highly organized, dense lipid matrix (Bouwstra, et al., 1997; Roberts, et al., 2008). The viable epidermis (VE) is an avascular environment, mainly composed of keratinocytes and comprised of approximately 40% water, 40% protein and 15–20% lipids. The papilla is present at epidermal–dermal junction that project into the dermis cells in the

basal layer of the epidermis (Vanbever, et al., 1999; Jakubovic, et al., 1992). Immediately beneath the epidermis, the dermis is the thickest component of the skin, which is about 4 mm in depth. Its upper layer, the 100–200 μm thick papillary dermis, consists of thin collagen bundles, elastin fibers, fibrocytes and ground substance comprising mainly water, electrolytes, plasma proteins and polysaccharides–polypeptide complexes. Below this layer is the reticular dermis, made up predominantly of thick collagen bundles and coarse elastic fibres (Jakubovic, et al., 1992) (Fig. 1).

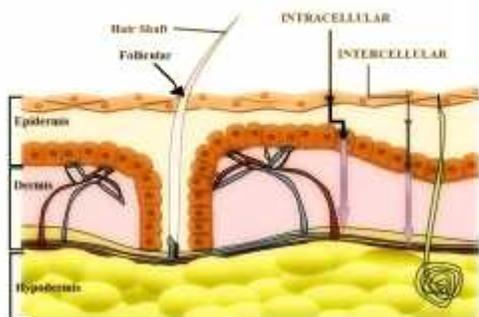


Fig. 1- Figure showing the various main part of skin and drug delivery pathway

From a global perspective, we propose that advances in transdermal delivery systems can be categorized as undergoing three generations of development from the first generation of systems that produced many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancement; through the second generation that has yielded additional advances for small molecule delivery by increasing skin permeability and driving forces for transdermal transport; to the third generation that will enable transdermal delivery of small molecule drugs, macromolecules (including proteins and DNA) and virus-based/other vaccines through targeted permeabilization of the skin's stratum corneum (Prausnitz, et al., 2008).

### 2.1 Pathways through skin

There are main three pathways namely, transcellular/Intracellular permeation through the stratum corneum; intercellular permeation through the stratum corneum and transappendageal permeation via the hair follicles, sweat and sebaceous gland through which foreign particles diffused or penetrate in to skin. The first step in permeation is the sorption by stratum corneum followed by permeation of drug through viable epidermis and then uptake of drug moiety by the capillary network in the dermal papillary layer. The drug must possess some physicochemical properties to reach target site via systemically through stratum corneum. The rate of permeation of drug moiety across the skin is governed by following equation:  $\frac{dQ}{dT} = P_s (C_d - C_r)$

Where,  $C_d$ = concentration of penetrate in the donor phase (on the surface of skin);  $C_r$ = concentration of penetrate in the receptor phase (body);  $P_s$  is the overall permeability coefficient of the skin:  $P_s = \frac{KsD_{ss}}{hs}$

Where, K = Partition coefficient of the penetrant;  $D_{ss}$ = Apparent diffusivity of penetrant;  $h_s$ = Thickness of skin. A constant rate of drug permeation achieved, if  $C_d > C_r$ , then the equation reduced as  $dQ/dT = P_s C_d$

The rate of skin permeation ( $dQ/dt$ ) becomes a constant, if the  $C$  value remains fairly constant throughout the course of skin permeation. To maintain the  $C_d$  at a constant value, it is critical to make the drug to be released at a rate ( $R_r$ ) which is always greater than the rate of skin uptake ( $R_a$ ), i. e.,  $R_r \gg R_a$  as shown in figure

By doing so, the drug concentration on the skin surface ( $C_d$ ) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum ( $C_s^e$ ), i.e.,  $C_d \gg C_s^e$ ; and maximum rate of skin permeation ( $dQ/dt$ )<sub>m</sub> as expressed by equation  $(dQ/dt)_m = P_s C_s^e$

Apparently, the magnitude of ( $dQ/dt$ )<sub>m</sub> is determined by the skin permeability coefficient ( $P_s$ ) of the drug and its equilibrium solubility in the stratum corneum ( $C_s^e$ ).

### 3. Transdermal Patches

A transdermal patch is defined as medicated adhesive patch which is placed above the surface of skin to deliver a specific dose of medication in to systemic circulation. There are different division in transdermal patches (Prausnitz, et al., 2008) (Fig. 2).

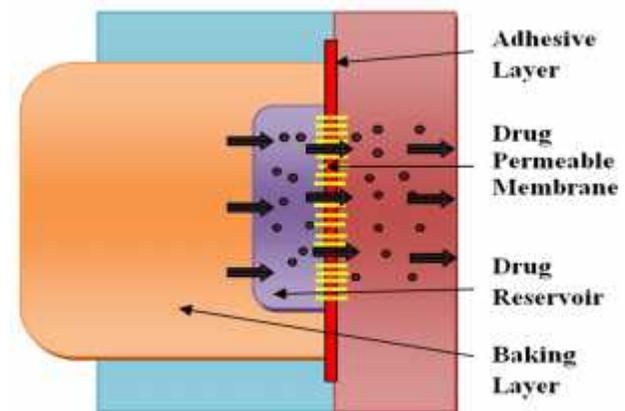


Fig. 2- Figure showing the transdermal drug delivery patches and drug delivery pathway

#### 3.1. Basic components of transdermal system:

3.1.1. Polymer matrix or matrices: Polymers are the foundation of transdermal system, it important to select the accurate of polymer and design. Considerations for polymer selection in transdermal delivery system; Should be stable and non-reactive with the drug moiety, easily available, fabricated and manufactured in to

desired formulations, molecular weight glass transition temp, melting point and chemical functionality etc. so that the drug can easily diffused through it and with other components of system; mechanical properties should not change if large amount of drug is incorporate; should provide consistent release of drug throughout the life of system (Dwivedi, et al., 2012). The polymers used in transdermal system are: Natural Polymers (zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes and chitosan); Synthetic Elastomers (hydrin rubber, polyisobutylene, polybutadiene, silicon rubber, nitrile, neoprene, butylrubber, acrylonitrile); Synthetic Polymers (polyvinylchloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethacrylate) (Chien, et a., 2009). Polymers used in transdermal system in versatile manner such as:

**3.1.1.1. Rate controlling membrane:** It control the release of drug by disperses through an inert polymer matrix. The polymer powder blended with drug moiety by physical manner and then moulded in to desired shape with required thickness and surface area (Dwivedi, et al., 2012).

**3.1.1.2. Adhesive:** make an intimate contact between the skin and transdermal system. It carries the drug which is dissolved or dispersed in solution or suspension form. The quality of drug diffused in to skin depending on the holding power (Chien, et al., 2009).

**3.1.1.3. Pressure sensitive adhesive:** Hitherto the rapidity of transdermal system can be done by pressure sensitive adhesive. The three most commonly used adhesives are polyisobutylene, polyacrylate and silicones in TDD devices (Dwivedi, et al., 2012).

**3.1.1.4. Release liners:** The patch is covered by protective liner during storage until it is used .The release liner removed and discarded just before the application of patch over the skin since release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert. The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used as release liner in transdermal patches include polyester foil and metalized laminate (Chien, et al., 2009).

**3.1.1.5. Backing laminate:** While design the baking layer following points: must be flexible; having low water vapour transmission rate so as to promote skin hydration and thus greater skin permeability of drug; should be compatible with transdermal system as remain in use while applying; should be chemical resistance; having good tensile strength must be in considered; non-irritant, Examples of backings laminate

are polyethylene film, polyester film, and polyolefin film, and aluminum vapor coated layer (Chien, et al., 2009).

**3.1.1.6. Drug:** Transdermal delivery of drugs has taken a surge of popularity nowadays. Various physicochemical, pharmacokinetic and pharmacological properties of the drug should be considered for transdermal system development. Because of the limited permeability of the skin, drugs have to be transdermal delivered by passive diffusion through the skin, and are limited by several substantial constraints. The drug moiety for transdermal system should be potent (dose in mg), having molecular weight  $\leq 1000$  Da, adequate solubility in the vehicle, log P value of  $< 5$ , melting point of  $200\text{ }^{\circ}\text{C}$  approx lipophilicity, undergo extensive pre-systemic metabolism, non-ionic and non-irritant are considered as suitable candidates for delivery via this route (Arunachalam, et al., 2010; Hanumanaik, et al., 2012; Sharma, et al., 2011).

**3.1.1.7. Penetration enhancers:** Compounds which promote the penetration of topically applied drugs are commonly referred as absorption promoters, accelerants, or penetration enhancers. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allow the drug to penetrate to the viable tissues and enter the systemic circulation (Dwivedi, et al., 2012).

**3.1.1.7.1. Desired properties for penetration enhancers:** It should be non-irritant, non-sensitizing, non-phototoxic, and non-comedogenic; Onset of action should be rapid and duration of activity should be predictable and reproducible; Have no pharmacological activity in the body i.e. should not bind to the receptor site; Upon removal of the enhancer, the upper layer should immediately and fully recover its normal barrier property; The barrier function of the skin should reduce in one direction only; Endogenous material should not be lost to the environment by diffusion out of the skin; The accelerants should be chemically and physically compatible with all drugs and adjuvants to be formulated in topical preparations and devices; should be inexpensive, tasteless and colourless; readily formulated in to dermatological preparations; have a desired solubility parameter that approximates that of skin; should adhere and spread well on the skin with a suitable skin feel (Sinha, et al., 2000). Some of the examples of the widely used classical enhancers involve various classes that include water, hydrocarbons alcohols, acids amines, amides, esters, surfactant terpenes, terpenoids and essential oil, sulfoxides, lipids and miscellaneous such as cyclodextrin derivatives, chitosan etc (Matteucci, et al., 2008).

**3.1.1.8. Plasticizers:** Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry

basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surfaces or membranes and improvement in strength of film. Some of its examples are glycerol or sorbitol, at 15%,w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400 (Sharma , et al., 2011; Sinha, et al., 2000).

**3.1.1.9. Solvents:** Various solvents such as methanol, chloroform, acetone, isopropanol and dichloromethane etc. are used to prepare drug reservoir (Dwivedi, et al., 2012).

#### 4. Approaches in the development of transdermal therapeutic system:

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies are as follows:

##### 4.1 Adhesive dispersion type system:

In this system the drug reservoir is prepared by directly dispersing the drug in an adhesive polymer which spread on flat sheet of drug impermeable baking membrane through solvent casting or hot melting to obtain a thin drug reservoir layer. A layer of rate-controlling adhesive polymer (non-medicated) of constant thickness is dispersing over it with detachable release liner which is removed when applied over the required area. This type of system is illustrated by one day medication transdermal therapeutic system of Valsartan as angiotensin II type 1 selective blocker for angina pectoris (Fig. 3) (Matteucci, et al., 2008; Sharma, et al., 2011; Rastogi, et al., 2012; Keleb, et al., 2010).

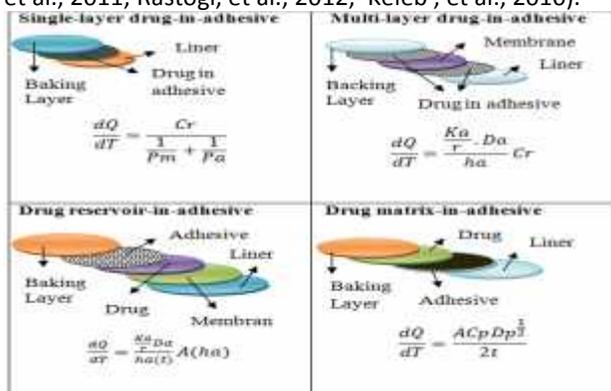


Fig. 3-Figure showing different type of transdermal drug delivery

Where  $C_r$  = drug concentration in reservoir compartment;  $P_a$  = Permeability coefficient of adhesive layer;  $P_m$  = Permeability coefficient of rate controlling membrane,  $K_a/r$  = partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer,  $h_a$  = thickness of adhesive layer;  $A$  = thickness of diffusional path,  $A$  = the initial drug loading dose dispersed in the polymer

matrix;  $C_p$  = solubility of the drug;  $D$  = diffusivity of the drug in the polymer

##### 4.2 Membrane permeation controlled system:

In this approach the drug reservoir is fabricated by dispersed homogenously in a solid polymeric matrix (e.g. polyisobutylene) suspended in the unleachable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution and then totally incased in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane. The drug molecules were released across the rate controlling membrane (microporous or non-porous polymeric membrane) simply by diffusion process (Dwivedi, et al., 2012). On the top surface of the polymeric membrane a thin layer of drug compatible adhesive polymer, for example-silicone adhesives can be applied, to provide intimate contact of the transdermal system with the skin surface. The release rate from this transdermal system can be tailored by varying the polymer composition, thickness of the rate controlling membrane, permeability coefficient and adhesive this type of system is illustrated by Transderm-Scop (Scopolamine- 3 days protection) of motion sickness and Transderm-Nitro (Nitroglycerine-once a day) of angina pectoris (Fig. 3) (Dwivedi, et al., 2012, Rastogi, et al., 2012; Keleb, et al., 2010).

##### 4.3 Matrix diffusion controlled system:

In this system, the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilicity polymer matrix or combination of both. The resultant medicated polymer is then mold into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature and/or under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is then spread to form a strip of rim along the medicated disc. This matrix type of transdermal system is best example by the nitroglycerine releasing transdermal therapeutic system. The advantage of matrix dispersion type transdermal systemic the absence of the dose dumping since the polymer cannot rupture (Fig. 3) (Dwivedi, et al., 2012; Chien, et al., 2009; Rastogi, et al., 2012; Anne, et al., 2000).

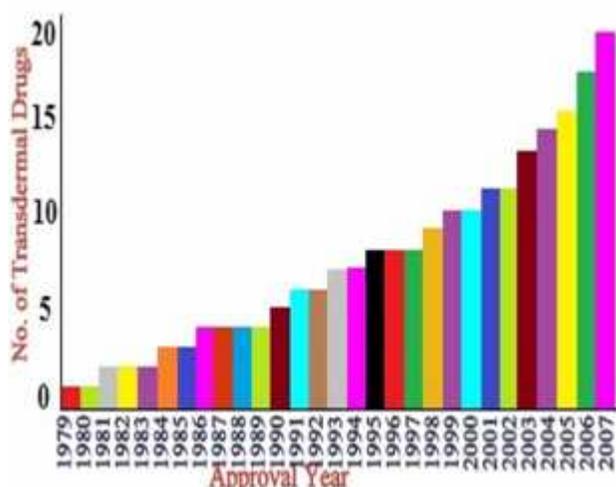
##### 4.4 Micro-reservoir type controlled system:

This system is mainly mixture of reservoir and matrix-dispersion type of drug delivery system. In this system,

drug reservoir is formed by suspending the drug in an aqueous solution containing liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer e.g. silicone elastomers by high energy dispersion technique by shear mechanical force to form thousands of unreachable, and microscopic spheres of drug reservoirs. Release of a drug from a micro reservoir-type system can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix. This technology has been utilized in the development of Nitro disc (**Fig. 3**) (Dwivedi, et al., 2012; Chien, et al., 2009; Keleb, et al., 2010).

### 5. Transdermal Market Product:

An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. Over the past 5 years (2003–2007), that rate has more than tripled to a new transdermal delivery system every 8 months (Prausnitz, et al., 2008). It is assumed that more than one billion transdermal patches are currently produced every year. Advancement in transdermal drug delivery from a global view, advancement occurs in transdermal delivery systems can be categorized in to three generations of development. in the first generation of systems that produced many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancement; through the second generation that has yielded additional advances for small molecule delivery by increasing skin permeability and driving forces for transdermal transport; to the third generation that will enable transdermal delivery of small molecule drugs, macromolecules (including proteins and DNA) and virus-based/other vaccines through targeted permeabilization of the skin's stratum corneum (**Fig. 4**).



**Fig. 4- Figure showing the no of Transdermal drugs globally from 1979 to 2007**

## 6. Recent Advancement in transdermal delivery system:

### 6.1 First-generation transdermal delivery system

With first-generation transdermal delivery system, almost all transdermal patch designs, the drug is stored in a reservoir which is enclosed on one side with an impermeable backing membrane and has an adhesive layer on other side that contacts the skin (Arunachalam, et al., 2010). Some designs involve drug dissolved in a liquid or gel-based reservoir, which permit the use of liquid chemical enhancers. These patches characteristically composed of four layers: an impermeable backing membrane; a drug reservoir; a semi-permeable membrane that may serve as a rate-limiting barrier; and an adhesive layer. Other designs include the drug into a solid polymer matrix. Matrix systems composed of three layers, by eliminating the semi-permeable membrane or two layers, incorporating the drug directly into the adhesive. To extent transdermal patches has replaced by metered liquid spray, gel or other topical formulation which when applied to the skin, upon evaporation or absorption, leave small lipophilicity drugs into the stratum corneum, which in turn serves as the drug reservoir for extended release into the viable epidermis over hours. For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery (Prausnitz, et al., 2008).

### 6.2 Second-generation transdermal delivery system

The second generation of transdermal delivery systems recognizes the importance of skin permeability enhancement to explore the scope of transdermal drugs. However, enhancement methods developed in this generation, like conventional chemical enhancers, non-cavitational ultrasound, and iontophoresis and still struggled with the balance between achieving increased delivery across stratum corneum, and protecting deeper tissues from damage. Conventional chemical enhancers enhanced the skin permeability, second-generation delivery strategies had turned largely towards chemical enhancers. One challenge of this approach is to increased permeation enhancement of small molecules, yet it increased skin irritation. A numbers of these enhancers which increased skin permeability without irritations had been used successfully to deliver small molecules, but have had show limited delivery of hydrophilic compounds or macromolecules while Iontophoresis, approach mainly based on electrical driving force for transport of drug molecules across stratum corneum (Anne, et al., 2000).

### 6.3 Electrophoresis

Electrophoresis can moved charged drug molecule while electro-osmotic flow of water generated by the preferential movement of mobile cations (e.g., Na<sup>+</sup>) instead of fixed anions (e.g., keratin) in the stratum

corneum can move weakly charged and uncharged compounds (Denet, et al., 2004). The strongest point of iontophoresis is that the rate of drug delivery associated with the electrical current, (Vanbever, et al., 1999) which can be easily controlled by a microprocessor and Ultrasound was recognized as a skin permeation enhancer when it was discovered that massaging anti-inflammatory agents into the skin using ultrasonic heating probes increased efficacy (Anne, et al., 1999). Although it was hypothesized that the pressure gradients and oscillation associated with ultrasound act as a driving force to move drug molecules into the skin. It appears that in this approach, the main effect was to disrupt stratum corneum structure and thereby enhance permeability.

#### **6.4 Third- generation transdermal delivery systems**

Third-generation transdermal delivery systems were poised to make significant impact on drug delivery because it mainly targets its effects to the stratum corneum. This approach enables almost complete disruption of the stratum corneum wall and thereby more effective transdermal drug delivery, while protecting deeper tissues together. In this way, novel chemical enhancers, cavitation ultrasound, electroporation and more recently micro-needles, thermal ablation and micro-dermabrasion have been shown to deliver macromolecules, including vaccines and therapeutic proteins, across the stratum corneum in human clinical trials (Prausnitz, et al., 2008; Mukherjee, et al., 2005).

#### **6.5 Chemical enhancers**

Combinations of chemical enhancers suitably designed combinations of chemical enhancers can balance between enhancement and irritation. This approach enables a strategy to target effects that not only enhance skin permeability in the stratum corneum, (Walker, et al., 2004) but also avoid irritation in deeper tissues where the formulation composition becomes diluted or otherwise altered for example- a combination of sodium lauryl sulphate (an anionic surfactant) and phenyl piperazine (a compound with aromatic nitrogen) at concentrations of 0.35 and 0.15 wt%, respectively, in a 1:1 mixture of phosphate-buffered saline and ethanol. In vitro screening results were validated with in vivo delivery of a peptide (leuprolide acetate) to hairless rats (Prausnitz, et al., 2008).

#### **6.6 Biochemical enhancers**

Biochemical enhancers, currently the peptides have been examined as enhancers of skin permeability. Experiment showed that natural pore-forming peptide (magainin), can be used to enhance skin permeability by a mechanism proposed to target bilayer disruption in stratum corneum lipids but not in deeper tissue (Denet, et al., 2004).

#### **6.7 Electroporation**

Electroporation is a well-known method; in the short, high-voltage pulses used to reversibly disrupt cell membranes for gene transfection and for other applications. Electroporation also used to disrupt lipid bilayer structures in the skin. Recently, electroporation was shown to deliver a model peptide vaccine into the skin of mice to generate a strong cytotoxic T lymphocyte response (Denet, et al., 2004; Li, et al., 2008).

#### **6.8 Cavitation ultrasound**

In addition to generate heat, ultrasound is also generate cavitation, which is the oscillation, formation, and, collapse of bubbles in an ultrasonic pressure field (Machet, et al., 2002; Wu, et al., 2006). It is generated only under specific conditions (e.g., low-frequency ultrasound). The opportunity for transdermal drug delivery is that cavitation bubbles collect the energy of ultrasound and thereby enable targeted effects at the site of bubble activity. The expected mechanism of cavitation ultrasound is that bubbles oscillate and collapse at the surface of skin, which generates localized shock waves and liquid micro jets directed at the stratum corneum. This disrupts stratum corneum lipid structure and thereby increases skin permeability for up to many hours without damaging deeper tissues (Suja, et al., 2012).

#### **6.9 Micro-needles**

Micro-needles developed as a means to deliver drugs into the skin by invasive manner. Solid micro-needles have been shown to painlessly pierce the skin to increase skin permeability to a variety of small molecules, nanoparticles and proteins from an extended-release patch. It has been dip coated with a variety of compounds such as small molecules, DNA, proteins, and virus particles (Yeu-Chun, et al., 2012). In a recent study, naltrexone was administered to healthy volunteers whose skin was pre-treated with microneedles<sup>51</sup>. After applying the naltrexone patch, therapeutic levels of naltrexone achieved (Eric, et al., 2013).

Thermal ablation approach mainly based on, heating the skin surface to generation of micron-scale perforations in the stratum corneum. Animal studies have revealed the ability of thermal ablation to deliver a number of compounds, such as interferon  $\alpha$ -2b and human growth hormone. Skin heating has been achieved using ohmic microheaters and radio-frequency ablation (Bramson, et al., 2003; Levin, et al., 2005).

Micro-dermabrasion is way to remove the stratum corneum barrier employs abrasion by simply using sandpaper or micro-dermabrasion; it is a widely used method to alter and remove skin tissues for cosmetic purposes (Herndon, et al., 2004).

7. Evaluation Parameter of Transdermal Drug delivery: (Table no. 1)

S. No	Evaluation Parameter	Method of Evaluation	Reference
1	Interaction studies	The drug and polymer compatibility was characterized by means of FTIR spectroscopy in ratio of drug and polymer (1:1).	Shingade, et al., 2012; Prabhakara, et al., 2010; Adhyapak , et al., 2011; Shankar, et al., 2011.
2	Patch thickness	Thickness is measured at five different points on the film and average of five readings is taken by using micro meter, electronic vernier callipers, with a least count of 0.01mm, dial gauge, or screw gauge.	Shingade, et al., 2012; Prabhakara, et al., 2010; Adhyapak , et al., 2011; Shankar, et al., 2011; Suja, et al., 2012
3	Percentage flatness	Film is cut in to strips, two from either end or one from the center & % constriction is calculated by $\% \text{ Constriction} = \frac{(\text{Initial length} - \text{Final length})}{\text{Initial length}} \times 100$	Shingade, et al., 2012; Adhyapak , et al., 2011; Shankar, et al., 2011
4	Folding endurance	It can be determined by repeatedly folding a small strip of film (2 x 2 cm) at the same place till it breaks. The number of time folded at the same place without breaking represent folding endurance value.	Shingade, et al., 2012; Adhyapak , et al., 2011; Shankar, et al., 2011
5	Tensile strength	It determined by using pulley system in which weight is gradually added till the patch breaks represent tensile strength. $\text{Tensile Strength} = \frac{\text{Tensile Load}}{\text{Cross section Area}}$	Adhyapak , et al., 2011; Shankar, et al., 2011
6	Elongation break test	It determined by noting the length just before the break point by using formula $\text{Elongation break} = \frac{(\text{Final length} - \text{Initial length})}{\text{Initial length}}$	Adhyapak , et al., 2011; Shankar, et al., 2011
7	Weight uniformity	It randomly selected patches about 10 in number cut specified area in different parts of the patch and weighed in a digital balance; calculate average weight and standard deviation value from the individual weights.	Adhyapak , et al., 2011; Shankar, et al., 2011
8	Drug content	The film of required area placed in to 100 ml buffer ( pH 7.4 or 6.8 or as prescribed) and shaken continuously for 24 hours, ultrasonicated for 15 minute, filtered and estimated spectrophotometrically.	Prabhakara, et al., 2010; Adhyapak , et al., 2011; Shankar, et al., 2011
9	Percentage of moisture content	The films are weight individually and left in a desiccators containing anhydrous calcium chloride or activated silica at room temperature for 24 hours, weight individually until showing a constant weight and calculation is done by $\% \text{ Moisture Content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$	Shingade, et al., 2012; Prabhakara, et al., 2010; Adhyapak , et al., 2011; Shankar, et al., 2011
10	Percentage of moisture uptake	weight film kept in a desiccators at room temperature for 24 hours and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccators until a constant weight is shown and calculation is done by $\% \text{ Moisture Uptake} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial Weight}} \times 100$	Shingade, et al., 2012, Prabhakara, et al., 2010, Adhyapak , et al., 2011; Shankar, et al., 2011
11	Water vapour transmission rate	1 gm of anhydrous/fused calcium chloride kept in completely dried vials, fix the films on the brim of vials and weigh individually, kept in closed desiccators containing saturated solution of potassium chloride to maintain humidity approx. 84%, vials were weighed in 6 , 12 , 24 ,36 , 48 , and 72 hours respectively and calculation is done by $\text{Transmission rate} = \frac{(\text{Final Weight} - \text{Initial Weight})}{\text{Area} \times \text{Time}} \times 100$	Shingade, et al., 2012, Adhyapak , et al., 2011; Shankar, et al., 2011

12	<b>Content uniformity test</b>	In selected 10 patches, if 9 out of 10 showed content between 85-115% of the specified value, and no one has shown 75-125% of the specified value, the test has been passed but if 3 patches shown the content between 75-125% then taken 20 additional patches and further test performed.	Prabhakara, et al., 2010, Adhyapak , et al., 2011; Shankar, et al., 2011
13	<b>Uniformity of dosage unit test</b>	It accurately weigh patch is cutted in to small pieces, transferred to specific volume of suitable solvent for dissolution of drug and then sonicated for complete extraction of drug, solution obtained kept untouched for 1 hour, then supernatant obtained dilute as required, analyzed with suitable analytical (HPLC / UV) technique.	Hanumanaik, et al., 2012, Adhyapak , et al., 2011; Shankar, et al., 2011
14	<b>Polaris cope examination</b>	It studies the crystal structure of drug in a patch.	Shingade, et al., 2012, Hanumanaik, et al., 2012,, Adhyapak , et al., 2011; Shankar, et al., 2011
15	<b>Shear adhesion test</b>	It adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch parallel to this plate. The time taken to pull off the patch from the plate determines the cohesive strength.	Shingade, et al., 2012, Hanumanaik, et al., 2012,, Adhyapak , et al., 2011; Shankar, et al., 2011
16	<b>Peel adhesion test</b>	The single patch is adhering to test substrate (Steel) and it pulled from the substrate at 180° angle.	Shingade, et al., 2012, Hanumanaik, et al., 2012,, Adhyapak , et al., 2011; Shankar, et al., 2011
17	<b>Thumb tack test</b>	It evaluation is done by pressing the thumb in to the adhesive.	Shingade, et al., 2012, Hanumanaik, et al., 2012,, Adhyapak , et al., 2011; Shankar, et al., 2011
18	<b>Rolling ball tack test</b>	The distance travelled by a stainless steel of diameter 7/16° on inclined track having angle 22.5°, determine the tackiness of polymer.	Shingade, et al., 2012, Hanumanaik, et al., 2012, Adhyapak , et al., 2011; Shankar, et al., 2011
19	<b>Peel tack or quick stick test</b>	The patch is pulled away from the substrate at 90° with speed 12 inches/minute to break the bond between the adhesive and the test substrate.	Shingade, et al., 2012, Hanumanaik, et al., 2012, Adhyapak , et al., 2011; Shankar, et al., 2011
20	<b>Probe tack test</b>	The tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive and probe, removal of probe at a fixed rate away from the adhesive which break the bond.	Shingade, et al., 2012, Hanumanaik, et al., 2012, Adhyapak , et al., 2011;
21	<b>Skin irritancy studies</b>	can be performed on healthy rabbits / mice albino / rats by applying the transdermal formulation over the clean surface for 24 hour, and potential can be evaluated by modified Draize test by giving score from 0 to 4 [zero point given for no erythema, 1 point for slight erythema (barely perceptible-light pink), 2 points for moderate erythema (dark pink), 3 points for moderate to severe erythema (dark pink) and 4 points for severe erythema (extreme redness)].	Shingade, et al., 2012, Prabhakara, et al., 2010, Hanumanaik, et al., 2012; Adhyapak , et al., 2011; Shankar, et al., 2011
22	<b>Confocal laser scanning microscopy (clsm)</b>	Depth of skin penetration of a patch can be assessed by applied formulation for 8 hours to the dorsal skin, excised and washed with distilled water, cover in aluminium foil, cut in to pieces of 1mm <sup>2</sup> and thickness is optically scanned at different increments through the z-axis of a CLS microscope.	Hanumanaik, et al., 2012

23	<b>Stability studies</b>	according to ICH guidelines, as at different temperature and relative humidity 25-30°C (60% relative humidity) and 45-50°C (75% relative humidity) over a period of 60 days, samples were withdrawn at 0,3,6, and 9 weeks respectively and were analyzed for their physical appearance, drug content and in-vitro diffusion studies.	Shingade, et al., 2012, Prabhakara, et al., 2010, Hanumanaik, et al., 2012,
24	<b>In-vitro release studies</b>	The quantitatively assure about the biological availability of a drug from its formulation by Paddle over disc apparatus (USP apparatus 5), Cylindrical apparatus (USP apparatus 6) and Reciprocating disc	Prabhakara, et al., 2010, Hanumanaik, et al., 2012
25	<b>In-vitro skin permeation</b>	It greatly help in investigating the route of skin permeation and the rate of transfer through skin by which drug entered in to systemic circulation, studies can easily performed through Franz Diffusion Cell, Horizontal-type skin permeation system and Flow Diffusion Cell	Hanumanaik, et al., 2012
26	<b>In-vivo Studies</b>	the true depiction of formulation performance by using following model like Animal Models, Human volunteers, Biophysical Model (Reservoir Technique, Mass Balance Technique)	Hanumanaik, et al., 2012

**Table: 1-Table showing the various evaluation parameters for transdermal delivery of drugs.**

## CONCLUSION

Transdermal drug delivery system has a great impact for research of a many drug molecules with several advantages over other drug delivery particularly on oral and parenteral drug delivery. The alluring feature of this delivery system is more acceptances in patient, withdrawal of patch at any time and control drug delivery; A number of formulation of lie under various clinical phases for different diseases like hypertension,

angina, motion sickness, female menopause etc. For the patient compliance Liu et al., has developed novel insulin-loaded micro-needle arrays (MNs) fabricated from hyaluronic acid, for their applicability in the transdermal delivery of insulin (Liu, et al., 2012). The future of Transdermal drug delivery system is very bright and this portion of medical system need to more focused so that patient suffers with disorders like Diabetes and asthma will get their medication with painfully.

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