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*Review Article*

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ISSN      Print      2231 – 3648  
              Online     2231 – 3656

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**International Journal of  
Pharmacy and Industrial  
Research**

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**TRANSDERMAL THERAPEUTIC SYSTEMS - AN OVER VIEW**

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**Abstract**

The transdermal patch has become a proven technology which offers a variety of significant clinical benefits over other dosage forms. Transdermal drug delivery system has emerged a new era in controlled release of the drug, maintains steady blood level profiles, reducing systemic side effects, avoiding hepatic first pass metabolism and improved efficacy. TDDS is an excellent mode of delivery which has been explored extensively over the last 25 years with therapeutic success and is suited ideally for the diseases which require chronic treatment. The transdermal route of drug delivery has attracted many researchers due to its biomedical applications, but however, excellent impervious nature of skin which acts as a barrier is the greatest challenge that has to be overcome for successful delivery of drug molecules to the systemic circulation. To achieve this, numerous or several approaches are used such as use of prodrugs/lipophilic moiety, permeation enhancers, physical approaches like iontophoresis, electroporation and sonophoresis, stripping of stratum corneum, hydration of stratum corneum, chemical approaches and biological approaches. This article deals with basic components of TDDS, different approaches and methods of preparation of TDDS, and advanced techniques to facilitate the permeation of drug molecules through the skin.

**Key words:** Transdermal drug delivery, Permeation Enhancers, Stratum Corneum, Electroporation, Iontophoresis, Micro Needles.

**Introduction**

Transdermal drug delivery systems which are commonly known as transdermal patches are the dosage forms when applied onto the skin delivers the drug through the skin at a controlled rate into the systemic circulation. The first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness; the FDA has approved more than 3 dozen transdermal products<sup>1</sup>. The clinical benefits, strong market,

interest of industry and regulatory precedence show why transdermal drug delivery has become a successful and viable dosage form.

The main goal of transdermal products design is to maximize the flux through the skin into the systemic circulation and to minimize the retention and metabolism of drug in the skin<sup>2</sup>. This route offers various biomedical advantages over conventional routes.

**Advantages of TDDS<sup>3</sup>**

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- Avoids hepatic first pass metabolism.
- Releases over entire period of medication.
- Low dose and short biological half life drugs.
- Decreases GI side effects.
- Increased patient compliance.
- Self medication is possible.
- Non invasive method.
- Avoids risks of IV therapy.
- Termination of drug action is possible.
- Advantageous in patients who are nauseated or unconscious.
- Play a vital role in regulation of blood pressure
- Disposal of biochemical wastes
- Synthesis and metabolism

Skin is majorly differentiated into 3 layers -

### 1. Epidermis

It composed of polygonal epithelial cells with thickness of about 150 $\mu$ m. Differentiation process occurs frequently which is responsible for the production of horny layer i.e., stratum corneum. Fibrous bundles of keratin are present in between epithelial cells which are proteinous in nature constitutes about 75-85% of protein and the remaining with lipids. Stratum corneum is devoid of vasculature. Following the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, stratum germinativum are present.

### 2. Dermis

It composed of polygonal cells, muco polysaccharides, collagen fibers present in a lucid of muco polysaccharides, rich bed of capillaries, lymphatic, nerves, epidermal appendages such as hair follicles, sebaceous glands, sweat glands.

### 3. Hypodermis

It is a highly vascular layer.

### Limitations of TDDS<sup>4</sup>

- Drug should possess certain specific physicochemical properties for penetration through stratum corneum such as dose should be less(<10mg/day), molecular weight(<500daltons)
- Local irritation at the site of administration such as erythema, itching, local oedema –may be caused by drug/adhesive/other excipients
- Variation in absorption efficiency at different sites of skin
- Cannot deliver ionic drugs

### Structure of skin<sup>5</sup>

Skin is a multilayered organ covers an area of about 2m<sup>2</sup> in an average human adult and it receives 1/3<sup>rd</sup> of all blood circulating through the body.

### Functions of skin

- Acts as a barrier against physical, chemical and microbial attacks
- Acts as a thermostat in maintaining body temperature

### Biochemical nature of skin

- Synthesis of proteins from precursors of amino acids in dermis
- Reduction of P<sub>H</sub> (7 to 6) which affects the absorption of drugs due to the conversion of glucose to lactic acid in epidermis
- Microbial burden on the surface of the skin affects the absorption of drugs

### Mechanism of absorption of drug through skin<sup>6</sup>

Percutaneous absorption of drugs occurs through skin in 2 ways

**Transepithelial absorption pathway:** Drug will partition into stratum corneum and then diffuses through dermis into the tissues. For lipophilic drugs, diffusion is the rate limiting step. For hydrophilic drugs, partitioning is the rate determining step.

**Transfollicular pathway or shunt pathway:** Drug will diffuse through the shunts, hair follicles, eccrine glands and enters directly into dermis. There is no rate limitation by stratum corneum in this pathway.

### Basic Components of TDDS

#### 1) Drug<sup>7,8</sup>

Selection of drug for TDDS is based on two properties

#### Physicochemical properties

- Dose should be less (<10mg/day)
- Molecular weight (<500daltons)
- Melting point (<200<sup>0</sup> C)
- Aqueous solubility (>1mg/ml)
- Log P value (1-3)

#### Biological properties

- Short biological half life
- Should be potent
- Should be non allergic, non irritant
- Narrow therapeutic window
- Should not have any binding capacity to skin proteins
- Extensive first pass metabolism

#### 2) Polymer

It is a vital component in TDDS because these are the agents which control the release of the drug from transdermal device.

#### Properties<sup>8</sup>

- Should be stable
- Should be compatible with drug and other components of TDDS
- Should provide effective and controlled release of drug

Polymer matrix preparation is done by dispersion of drug in solid or liquid state synthetic polymer base.

#### Classification of polymers

**Natural polymers:** cellulose derivatives, natural rubber, zein, gelatin, shellac, waxes, starch, chitosan, gums and its derivatives.

**Synthetic polymers:** polyvinyl alcohol, polyvinyl chloride, polyvinyl pyrrolidene<sup>10</sup>, polyamide, poly ethylene, poly propylene, poly urea, poly acrylate, poly methyl methacrylate.

**Synthetic elastomers:** polybutadiene, polysiloxane, polyisobutylene, neoprene, nitrile, acetonitrile, hydrin rubber, silicon rubber, butyl rubber

Polymers like polyethylene glycol<sup>11</sup>, eudragits<sup>12</sup>, ethyl cellulose and hydroxy propyl methyl cellulose<sup>13</sup> are used as matrix type transdermal drug delivery.

#### 3) Permeation enhancers<sup>14</sup>

These are the agents which enhances the permeability of stratum corneum by interacting with structural components of stratum corneum i.e, proteins or lipids to attain higher therapeutic levels of drug. They alter the

protein and lipid packaging of stratum corneum and chemically modifies the barrier functions leading to increased permeability.

Permeation of drugs across the skin is explained by the equation,

$$J = D \frac{dc}{dx}$$

Where, J = flux

D = diffusion coefficient of the drug

c = concentration of diffusing species

Permeation can be increased by solvents, surface active agents, others like bile salts, urea

**Solvents:** They increase penetration by disturbing the hydrophilic and lipophilic nature of skin which results in swelling of aqueous layer.

Eg: water, alcohols (ethanol, methanol), dimethyl acetamide, alkyl methyl butoxide, dimethyl sulfoxide, propylene glycol, isopropyl myristate, silicone fluids

**Surface active agents:** These agents binds, penetrates and interact with skin strongly which causes larger alterations in the structure of skin resulting in the change of the nature of skin and thus the permeability increases.

They are classified into 3 classes

- a) Anionic: dioctyl sulphosuccinate, sodium lauryl sulphate, dodecyl methyl sulphoxide, sodium dodecyl sulphate, sodium dodeconoate<sup>16</sup>
- b) Cationic: N,N- bis (2- hydroxyl ethyl) oleyl amine
- c) Non ionic: pleuronic F127, pleuronic F68, poly oxy ethylene(20) sorbitan mono oleate

Among the above three categories, non ionic surfactants are preferred widely because they are non irritant.

#### Others

Bile salts- sodium taurocholate, sodium glycocholate, sodium deoxy cholate, sodium tetra glycocholate

Urea - It is a hydrophilic carrier which enhances the permeation by hydrating the skin.

Fatty acids - oleic acid, undecanoic acid

Fatty alcohols - octanol, nonanol

Polyols – poly ethylene glycol, propylene glycol.

N,N- dimethyl toluamide, anti cholinergic drugs, dioctyl methyl-β- cyclodextrin, eucalyptol, menthol, soya bean casein, cardamom oil, lemon oil, caraway oil, d-limonene, linoleic acid.

#### 4) Other excipients

##### Adhesives

##### Examples<sup>16</sup>:

Poly acrylates - These are most widely used which are polar in nature and allows to absorb moisture readily and maintains adhesion to the wet skin.

Polyiso butylenes - These have low solvent capacity for drugs, which are composed of high and low molecular weight polymers that provide cohesion and tackiness. These are commonly used in membrane controlled systems.

Silicone – These are characterized by low allergenicity. They mostly dissolves drug poorly and regulate tackiness and cohesion through polymer size.

Hot melt pressure sensitive adhesives (HMPSA) - They melt to a viscosity suitable

for coating but when cooled they are in flow less state. They are thermoplastic in nature. Compounded HMPSA are ethylene vinyl acetate copolymers, paraffin waxes, low density poly propylene, styrene- butadiene copolymers, ethylene- ethacrylate. Uncompounded HMPSA are poly esters, poly amides, poly urethanes.

### Backing layer laminates

It is a pressure sensitive layer for supporting the transdermal device<sup>17</sup> and prevents loss of drug from the device. It gives perfect geometry to the patch. It should be flexible.

Eg : metallic plastic laminates, plastic baking with adsorbent pad, occlusive base plate with aluminium foil, adhesive foam pad with polyurethane, aluminium foil discs, vinyl, polyesterfilms, polyester-polypropylene films, polypropylene resin, polypropylene resin, polyurethylene, cotrans9722film, ethylene vinyl acetate.

### Release liner<sup>18</sup>

It is a protective liner which is removed and discharged immediately before the application of the patch to the skin. It is called as primary packaging material.

### Properties

It should be chemically inert as it is in intimate contact with the transdermal device. It is composed of base layer which is non occlusive (paper fabric) or occlusive (polyethylene, poly vinyl chloride) and a release coating layer made up of Teflon or silicon. Other materials used as release liner are polyester foil metalized laminates.

### Plasticizers

These are the agents that provide plasticity to the transdermal patch.

Eg : di butyl phthalate, polyethylene glycol, tri ethyl citrate, propylene glycol.

### Kinetics of drug permeation through skin<sup>19</sup>

For a systemically active drug moiety to reach from the site of administration to the target tissues it should possess some properties which are capable of,

- Facilitation of sorption of drug by stratum corneum.
- Passage of drug through epidermis.
- Uptake of drug by capillary network to enter into systemic circulation.

The rate of drug permeation across the skin is given by the equation,

$$\frac{dQ}{dt} = p_s(c_d - c_r)$$

Where,

$dQ/dt$  = rate of drug permeation

$p_s$  = permeability coefficient

$c_d$  = concentration of drug in donar compartment(stratum corneum)

$c_r$  = concentration of drug in receptor compartment(body)

Drug concentration in the donar compartment should always be greater than in the receptor compartment.

Permeability coefficient of skin tissues to the penetrant molecules is given by the equation,

$$P_s = \frac{k_s D_{ss}}{H_s}$$

Where,

$k_s$  = partition coefficient of penetrant

$D_{ss}$  = diffusivity of penetrant at steady state

$H_s$  = thickness of stratum corneum

When  $c_d \gg c_r$ ; the rate of drug permeation becomes,

$$\frac{dQ}{dt} = p_s c_d$$

The rate of drug permeation is maintained constant, if  $c_d$  is made constant. This is achieved when the release of drug from the patch is constant. This condition is observed when  $R_r \gg R_a$ ,

Where,  $R_r$  = rate of release

$R_a$  = rate of absorption

When  $c_d \gg c_s$ , i.e, when the concentration of drug in stratum corneum is much greater than saturation solubility or equilibrium solubility of the drug in stratum corneum, then the maximum rate of permeation  $(dQ/dt)_m$  is given by the equation,

$$\left(\frac{dQ}{dt}\right)_m = p_s c_s$$

Where,  $\left(\frac{dQ}{dt}\right)_m$  = maximum rate of permeation

$P_s$  = permeability coefficient of stratum corneum

$C_s$  = saturation solubility of drug in stratum corneum

**Conclusion:** As the maximum rate of permeation depends upon the permeability coefficient of stratum corneum and saturation solubility of drug in stratum corneum, so the rate of permeation is said to be *stratum corneum limited*.

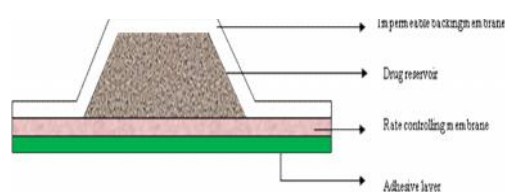
### Different Approaches for Development of TDDS<sup>20</sup>

Four approaches are there for the development of TDDS

1. Membrane moderated controlled TDDS
2. Adhesive diffusion controlled TDDS
3. Matrix dispersion type TDDS
4. Micro reservoir controlled TDDS

### 1. Membrane moderated controlled TDDS

Drug reservoir is sandwiched in between drug impermeable backing membrane and a rate controlling polymeric membrane. In this the drugs are homogeneously dispersed in a solid polymer matrix or suspended in a viscous liquid medium ( eg: silicone fluid). Drug releases through the rate controlling membrane which is micro porous or non porous (eg: ethylene vinyl acetate copolymer). Beneath the rate controlling polymer, a thin layer of drug compatible, pressure sensitive, hypo allergenic adhesive polymer (eg: silicone or poly acrylate adhesive) to achieve an intimate contact of the transdermal patch to the skin. The rate of release of drug from this type of TDDS can be tailored by varying the polymeric composition, permeability coefficient and thickness of rate controlling membrane and adhesive. Fig 1.



**Fig 1: Membrane moderated controlled TDDS**

The rate of drug release from this type of systems is given by

$$\frac{dQ}{dt} = \frac{c_R}{\frac{1}{P_m} + \frac{1}{P_a}}$$

Where,

$c_R$  = concentration of drug in the reservoir compartment

$p_m$  = permeability coefficient of rate controlling membrane

$p_a$  = permeability coefficient of adhesive

But,

$$p_m = \frac{k_{m/r} \cdot D_m}{h_m}$$

$$p_a = \frac{k_{a/m} D_a}{h_a}$$

Substitute  $p_m$  and  $p_a$  in the above equation,

$$p_a = \frac{k_{m/r} k_{a/m} D_m D_a}{k_{m/r} D_m \delta_a + k_{a/m} D_a \delta_m} \cdot C_R$$

Where,

$K_{m/r}$  = partition coefficient for the interfacial partitioning of the drug from reservoir to the membrane

$K_{a/m}$  = partition coefficient for the interfacial partitioning of the drug from membrane to the adhesive

$D_m$  = diffusion coefficient of the rate controlling membrane

$D_a$  = diffusion coefficient of the adhesive

$h_m$  = thickness of the rate controlling membrane

$h_a$  = thickness of the adhesive

## 2. Adhesive diffusion controlled TDDS

Drug release is formulated by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive onto an impervious backing layer. The drug reservoir layer is then covered by a non medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlled drug delivery system. Fig 2.

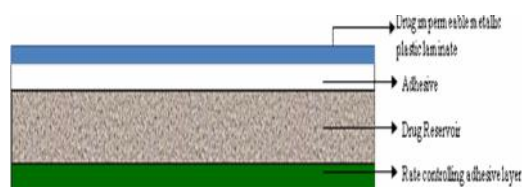


Fig 2: Adhesive diffusion controlled TDDS

The rate of drug release from this type of systems is given by the equation,

$$\frac{dQ}{dt} = \frac{k_{a/r} D_a C_R}{\delta_a}$$

Where,

$k_{a/r}$  = partition coefficient for the interfacial partitioning of drug from the reservoir layer to the adhesive layer.

*Advanced model:*

Multi laminate systems: The rate of release of drug from this system is given by

$$\frac{dQ}{dt} = \frac{k_{a/r} D_a}{h_a t A (h_a)}$$

Where,  $A(h_a)$  = diffusional path length

$t$  = thickness at time  $t$

## 3. Matrix dispersion type TDDS

Drug reservoir is formed by dispersing drug solids in a hydrophilic or lipophilic matrix. This medicated polymer is molded as a disc with certain surface area and thickness. This medicated polymer disc is adhered onto an occlusive base plate in a drug impermeable plastic backing fabricated compartment. The adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc. Fig 3

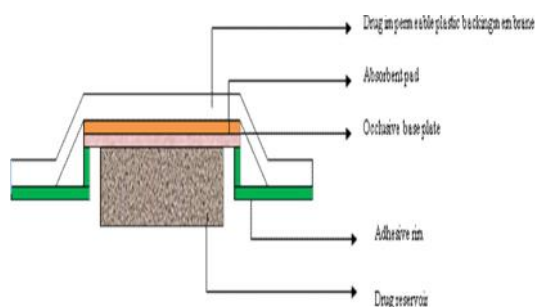


Fig 3: Matrix dispersion type TDDS

The rate of drug release from this type of systems is given by the equation,

$$\frac{dQ}{dt} = \left( \frac{A C_p D_p}{2t} \right)^{\frac{1}{2}}$$

Where,

$A$  = initial loading dose

$C_p$  = solubility of drug in polymer

$D_p$  = diffusibility coefficient in polymer

When  $C_p = C_R$ , then

$$\frac{Q}{t^{\frac{1}{2}}} = [(2A - C_p) C_p D_p]^{\frac{1}{2}}$$

#### 4. Micro reservoir controlled TDDS

It is a combination of matrix and reservoir dispersion systems. Drug reservoir is formed by dispersing the drug in aqueous polymer matrix solution and then transferred into a lipophilic matrix forming polymer in order to form a several thousands of unleachable, microscopic spheres of drug reservoirs. By immediately cross linking the polymer insitu, the thermodynamically unstable dispersion is stabilized. Thus, a transdermal therapeutic system is formed as a disc which is placed at the centre and surrounded by an adhesive rim.

Fig 4

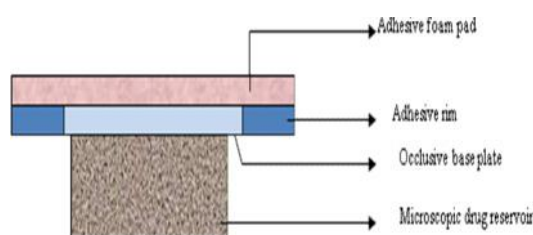


Fig 4: Micro reservoir controlled TDDS

The rate of release of drug from this type of systems is given by the equation,

$$\frac{dQ}{dt} = \frac{D_p D_s \alpha' K_p}{D_p \delta_2 + D_p \delta_p \alpha' K_p} \left[ \beta S_p - \frac{D_1 S_1 (1 - \beta)}{\delta_1} \left( \frac{1}{K_1} - \frac{1}{K_m} \right) \right]$$

Where,

$M = a/b$

$A$  = Ratio of drug concentration in elution medium to the drug solubility.

$B$  = Ratio of drug concentration on the outer edge of polymer coat to the drug solubility.

$N$  = Ratio of drug concentration on the inner layer of interfacial barrier to the solubility of drug in matrix.

$D_l, D_p, D_d$  = Diffusion coefficient of liquid layer, polymer coat membrane, hydrodynamic diffusion layer surrounding the polymer coat.

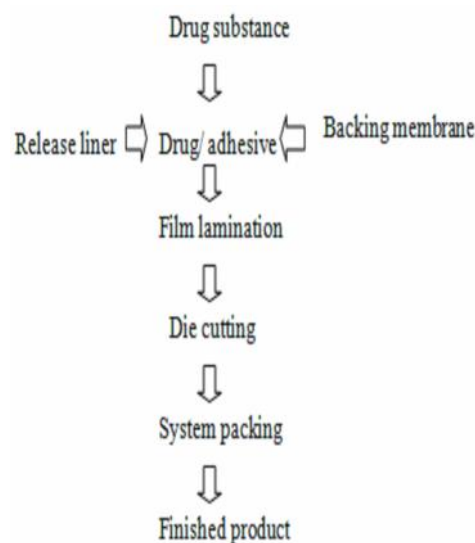
$H_l, h_p, h_d$  = thickness of liquid layer, polymer coat membrane, hydrodynamic diffusion layer surrounding the polymer coat.

$k_l, k_p, k_m$  = Partition coefficient of liquid layer, polymer coat membrane, hydrodynamic diffusion layer surrounding the polymer coat.

$S_l, s_p$  = solubility in liquid layer, polymer coat membrane.

#### Production of Transdermal Therapeutic Systems<sup>21</sup>

##### 1) Membrane moderated controlled TDDS

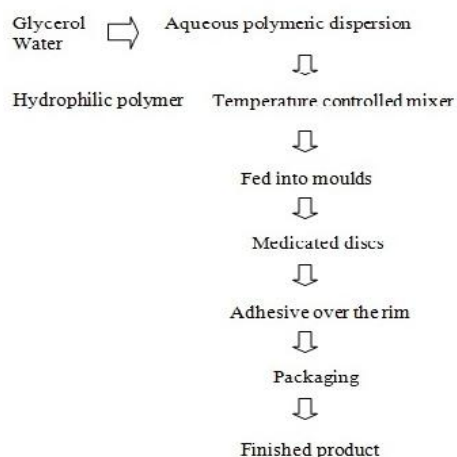


##### 2) Adhesive diffusion controlled TDDS

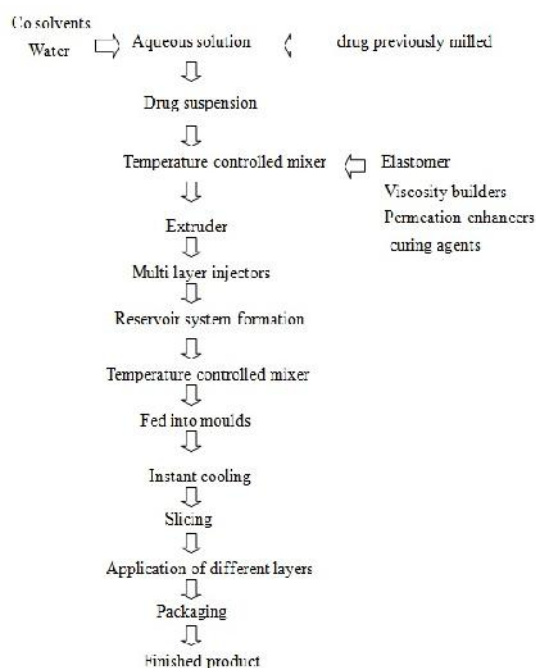
- Preparation of individual matrix solutions.
- Coating the individual matrix layers.
- Building the multilayer laminate.
- Separation of units in multilayer laminate.
- Packaging.



### 3) Matrix dispersion type TDDS



### 4) Micro reservoir controlled TDDS



### Advanced Techniques

To increase the transdermal penetration of drugs, the barrier properties of the skin minimal therapeutic level.

#### 1) Iontophoresis<sup>22</sup>

It is a process of sending the ionic or charged molecules through the skin tissues by using direct current or alternate current by putting in electrolyte solution.

Repulsion occurs by placing same charge of electrode on the same charge of drug molecules which acts as a driving force for the passage of drug molecules. The electrical density used should be less than the pain threshold of the patient which is about 5 milliamperes/ cm<sup>2</sup> of the area. A porous moist pad is present in between the skin and electrode plate.

Eg : water soluble drugs, local anaesthetics, corticosteroids

Various iontophoretic techniques are used for sending local anaesthetics and corticosteroids are PHORESOR II, EMPIDUPEL, LIFE TECH IONTOPHOR. These are manufactured by Alza corporation (USA), Fournier (France), Histamistec(Japan)

#### Factors to be considered

- Electrical density
- Drug related factors – size, charge, dose, lipophilicity, pH, ionic strength
- Biological factors – humidity of skin, erosion of skin which differs with different people

#### Applications

- Delivery of Oligonucleotide in cancer treatment
- Delivery of peptides having shorter biological half life
- Delivery of Fentanyl which has extensive pre systemic metabolism

#### 2) Electroporation<sup>23</sup>

Electroporation is the process of applying voltage pulses which causes dissociation of stratum corneum results in the formation of pores through which small molecules and other

oligonucleotides can pass through the pores in significant amounts.

Eg : Delivery of oligonucleotides, DNA, peptides, other macromolecules

#### Factors to be considered:

- Selection of the pulse voltage i.e, 100 – 300 volts
- Number of pulses applied
- Duration of the pulse
- Gap between the pulses

This method is always used in combination with other therapies *electrochemotherapy* which involves creation of pores by electroporation and then sending the chemotherapeutic drugs to the tumor cells through the pores.

#### 3) Sonophoresis<sup>24</sup>

Sonophoresis is the process of applying high frequency ultrasonic energy helpful in the passage of high molecular weight molecules through the skin.

Ultra sonic energy is of 3 types

- a) **Low frequency sonic energy:** It causes acoustic streaming of stratum corneum and during propagation of sonic energy, some oscillations will develop which will enhance the transport of drugs.
- b) **Therapeutic frequency sonic energy:** It cause some cavitation effects i.e., the air sacs / air bubbles present in viable tissue collapses during application of sonic energy resulting in the alteration of arrangement in the properties of tissues which helps in the passage of drugs through skin.
- c) **High frequency sonic energy:** It causes excessive cavitation effects which are not advisable.

Sonic energy shows synergistic effect along with electroporation and permeation enhancers.

**Limitation:** It increases the temperature of skin which is not advisable

#### Applications

- Delivery of high molecular weight compounds like proteins
- Transdermal topical application of ointments eg hydrocortisone

#### 4) Microneedles<sup>25</sup>

Microneedles are the devices which are prepared with silicon by the process of microfabrication. They are very small in size with diameter of about <1mm, i.e., 1/100<sup>th</sup> of human hair. The tip of microneedle is 3-dimensional, very sharp and narrow shaped consists of a small tiny pump through which the drug enters into the skin in desired quantities.

#### Properties

- Should have sufficient length, such that they can deliver drugs to the target site
- Should not cause pain when they penetrate the skin
- Should have excellent physical hardness, such that they can penetrate the stratum corneum having thickness of 10-20µm.

#### Potential

- To supply microlitre volumes of insulin
- High accuracy, good reproducibility and moderate fabrication cost
- Highly targeted drug administration to individual cells
- Very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in

- a micro volume that can be precisely controlled
- They are used to remove fluids from the body for analysis as blood glucose measurements
- Administration of antidotes in bioterrorism incidents

#### Applications

- Cellular delivery – DNA vaccine delivery, Desmopressin delivery
- Local tissue delivery
- Systemic delivery

#### 5) Microblades<sup>26</sup>

Microblades consists of a cutter having a plurality of microprotrusions having a height chosen with respect to the layer of skin that is to be disrupted and a ‘stop’ for preventing the apparatus from penetrating the skin beyond a predetermined distance. As advancement to the basic technique, a microblade device along with negative pressure was patented for percutaneous sampling of an agent. The use of electrotransport, osmosis or pressure along with protrusions for withdrawing body fluids via a hydrogel medium increased the permeation of decapeptide over the transport period as compared to an ordinary electrotransport device.

#### Studies carried out on Transdermal drug delivery system

Drug	Purpose	Reference
Aceclofenac	NSAID	Rakesh P.Patel etal <sup>27</sup>
Amlodipine Besilate	Antihypertensive	Hemangi J.Patel etal <sup>28</sup>
Budesonide	Non halogenated corticosteroid	Rupesh V.Chikale etal <sup>29</sup>
Carvedilol	Antihypertensive	Mandal Sonjoy etal <sup>30</sup>
Ketoprofen	NSAID	Shasikant D.Barhate etal <sup>31</sup>
Fulvestrant	Estrogen receptor antagonist	Vinod K.R etal <sup>32</sup>
Indapamide	Antihypertensive, diuretic	G S Sanap etal <sup>33</sup>
Isoxsuprine	Uterine relaxant	K.Subramanian etal <sup>34</sup>
Lovastatin	Antilipedemic	Shinde Anil Kumar etal <sup>35</sup>
Glibenclamide	Antidiabetic	J.R.Patel etal <sup>36</sup>
Metoprolol Tartrate	Cardioselective $\beta$ -blocker	Meenakshi Bharkatiya etal <sup>37</sup>
Sinomenine	Antirheumatic	Yuje Ye etal <sup>38</sup>
Repaglinide	Antidiabetic	Shailesh.T.Prajapati etal <sup>39</sup>
Ampicillin sodium	Antibiotic	Janardhanan Bagyalakshmi etal <sup>40</sup>
Diclofenac sodium	NSAID	Gattani S.G etal <sup>41</sup>
Indomethacin	NSAID	Liang Fang etal <sup>42</sup>
Nifedipine	Antianginal	Mohammed Gulzar Ahmed etal <sup>43</sup>
Nitrendipine	Calcium channel blocker	Y. Madhusudan Rao etal <sup>44</sup>
Propranolol	$\beta$ -blocker	Nirav S Sheth etal <sup>45</sup>
Rotigotine	Antiparkinsonian	Sanford etal <sup>46</sup>
Tolterodine	Antimuscarinic	Vinay Pandit etal <sup>47</sup>
Valsartan	Antihypertensive	Gulam Irfani etal <sup>48</sup>

**6) Needleless syringe<sup>26</sup>**

Needleless syringe consists of an elongate, tubular duct having a lumen for delivering the particles towards the target tissue. It has a membrane which is ruptured by gas pressure to generate a supersonic gas flow in which therapeutic agent is injected.

**7) Increase in local temperature<sup>26</sup>**

Increase in local temperature increases blood flow which in turn increases the rate of permeation / transport of active substance into the skin. This method is non-invasive and is advantageous of not using a chemical. Koch et al (2004) used an effective component Opraflux to increase the local skin temperature and observed an increase in transdermal absorption rate of morphine base from 5.7 to 26.4%

Eg: insulin, nicotine, dexamethasone, nitroglycerine, sufentanil.

**8) Mechanical vibrations<sup>26</sup>**

Mechanical vibrations can be used for increasing drug absorption through skin. Bernabei (2004) used electric pulses to increase the absorption of substances in conjunction with the mechanical vibrations. In order to increase the absorption effect, the frequency and phase of electrical and mechanical vibrations were synchronized.

**Conclusion**

The Transdermal route of drug delivery system has attracted many researchers due to its biomedical applications, but however, excellent impervious nature of the skin which acts as a barrier is the greatest challenge that has to be overcome for successful delivery of drug molecules to systemic circulation. This article delivers valuable information regarding

the transdermal drug delivery system and its evaluation details as an excellent reference for the research scientists who are involved in TDDS. Due to the excessive benefits of TDDS, many new research scientists are enthusiastic in the development of newer drugs in our future days. With the wide range of polymers that are being used in the transdermal drug delivery systems, there are still issues faced in terms of skin side effects like rashes, inflammation, burn; crystallization of the drug in the rate controlling membrane altering the rate of permeation of drug in the skin. All these disadvantages suggest the more research and intensity of materials being employed is required before they are put out for commercial use.

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