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A Review on Current Approaches Used to enhance permeation in Transdermal Drug Delivery System

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ABSTRACT-
The review focuses on different current approaches used in transdermal drug delivery system. Transdermal drug delivery is non invasive, safe and efficient delivery system. In TDDS delivery of drug across the skin barrier to the systemic circulation have been one of the most challenging delivery options hence, recent advances have been made to facilitate permeation of drug.Continous upgrade and improvements in approaches to deliver drug across the skin have been made like new approaches involves iontophoresis, sonophoresis, nanocarriers, micro needles, etc. Recently liposomes, transferosomes and jet injections are also included in TDDS. All of these techniques are proven fortunate substitute to other dosage form like oral, parenteral, intravenous, intramuscular, hypodermal shots, and other invasive delivery modes as it delivers lipophillic, hydrophilic and amphiphilic drugs molecules. These TDDS techniques will help to reduce dose, escalate bioavailability, enhance therapeutic efficacy of drug and evade the problem of drug toxicity. This review summarizes about the physiochemical approaches used in transdermal drug delivery to enhance the permeation of drug across the skin.
Keywords - Transdermal drug delivery, non invasive, iontophoresis, sonophoresis

INTRODUCTION

Historically after fortunate research of first transdermal patch of scopolamine and nicotine its acceptance has became more due to its use in several therapies like hormonal disorder, diabetes, mental disorders, etc. [(1)] Market of transdermal patches or TDDS has been escalated globally and expected rise annually by 7% up to 2024. Microneedles, thermal ablation, electroporation, radiofrequency usage, use of thermal techniques, micro and radio waves, electro-mechanical devices, nano deliveries, cavitational ultrasound and some other techniques have immensely contributed toward making the TDDS more user-friendly, competitive in dose delivery levels, cost-effective, and feasible to use.[(2)]

The continuous upgrade and improvements in new approaches for permeation of drug has made the TDDS today a top contender for drug delivery modes preferences. Currently transdermal route is most promising drug delivery system as it escalates bioavailability by avoiding first pass metabolism, provides control or sustain release of drug and evades drug toxicity, allows constant input of drug with short biological half-life and eliminates pulsed entry of drug into systemic circulation.[(3)] Drug delivery from skin to systemic circulation and drug permeation to different layers of skin is challenging hence to overcome these problems new methods iontophoresis, sonophoresis, and thermal ablation are used. Recently to deliver both lipophillic and hydrophilic drug some nanocarriers like liposomes, transferosomes, polymeric nanoparticles, microneedles are used. [(4)]

Mechanism of drug permeation in TDDS its routes and factors

Drug is absorbed in skin transdermally by percutaneous absorption. Percutaneous absorption refers to permeation of drug molecules through various layers of skin and systemic circulation. It is crucial for transdermal drug delivery because drug has to be absorbed in adequate amount with uniform rate in order to reach therapeutic level throughout the duration of use. Once the drug crosses stratum coreneum it is systemically taken up in blood circulation quickly. [(5)]

Drug release from skin and transportation to systemic circulation involves various stages.

- Dissolution of components and drug within formulation and their release.
- Partitioning from stratum corneum.
- Diffusion from stratum corneum via intracellular pathway.
- Partitioning from stratum corneum to aqueous viable epidermis, diffusion fromepidermis to dermis, uptake into capillary system and microcirculation. (6)

Routes of drug permeation in TDDS

Two routes of permeation are followed like

- **Transepidermal Route** It involves intracellular and intercellular pathways of drug permeation.
- **Transfollicular Route** In this transport of drug take place through sweat glands and hair follicles. (7)

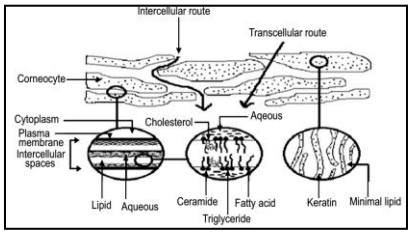

Fig-1 Routes of drug permeation(7)

Factors affecting permeation of drug in TDDS

- **Physiochemical factors**

1. Diffusion coefficient - Permeation of drug to different layers of skin depends upon diffusion coefficient of drug. At constant temperature diffusion coefficient of drug and its medium is observed.

2. Drug concentration - Flux is directly proportional to concentration gradient which depends upon concentration of drug.

3. Partition coefficient - Optimum log K is required for drug to permeate through different layers of skin. If value of log K is more drugs will adhere to lipid membrane of skin while drugs with low log K will not permeate inside the layers of skin.

4. Molecular size- Molecular size of drug should be less than 1000dalton to permeate.

5. Temperature and pH - If temperature variation occurs permeation of drug increases ten folds. Diffusion coefficient is directly proportional to temperature. Unionized drug determines drug concentration in skin. (8)

- **Environmental factors**

1. Sunlight - Sunlight makes blood vessels of skin thinner which lead to difficulty in drug permeation.

2. Air pollution - Dust and dirt can clog pores of skin and can lead to bacterial or fungal infections which can interfere with drug permeation.

3. Cold season - Cold season leads to dry skin that will generate oil pores in skin that causes difficulty in permeation of drug.

4. Air pollution - Dust particles can clog pores and increase bacteria that can affect permeation of drug molecules to different layers of skin. Pollutants that enter to skin can act as barrier for permeation of drug.(9)

- **Biological factors**

1. Skin condition - Skin itself act as barrier for molecules to permeate but acids, alkali, methanol and chloroform help molecules to permeate through skin remove lipid fraction by forming shunt.

2. Skin age - It is observed that adults and young ones skin is more permeable as compare to older people. Toxic effects are observed in children due to use f steroids, boric acid etc because of greater surface area per unit body weight.

3. Blood supply - Transdermal absorption is affected by changes in peripheral circulation.

4. Regional skin site - Few factors like thickness of skin, nature of stratum corneum and density of appendages can affect the permeation of drug molecule.

5.Skin metabolism - Some substances like steroids, hormones, chemical carcinogens andeven some drugs are metabolize by skinthat cause difficulty in permeation. Therefore there are various substances that get metabolized in skin and cause difficulty in permeation through different layers of skin. [10]

CURRENT APPROACHES USED IN TRANSDERMAL DRUG DELIVERY SYSTEM

There are two approaches used in transdermal drug delivery for permeation of drug like active and passive approaches.

- **Active approaches**
  Involve iontophoresis, sonophoresis, electroporation and thermal ablation.
- **Passive approaches**
  They involve vesicles that help to deliver drug like liposomes, transferosomes, ethosomes, and polymeric nanoparticles. [11]

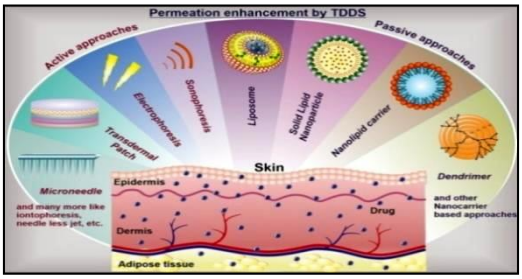

Fig-2 Current approaches used in TDDS for drug permeation [11]

1. Iontophoresis

Ionic and non-ionic drugs permeate by means of electrochemical potential gradient in this method. Drug molecules prefer routes of least electrical resistance.[11] The efficacy of this method depends upon polarity, valency, nature of electrical cycle applied, mobility of drug molecule and formulation containing drug. It generally involves movement of drug across the membrane under the influence of applied electrical potential difference. [12] The potential difference that is applied to transport drug molecule is 0.5 mA/cm^2. [13]

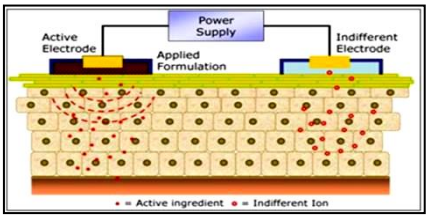

Fig-3 Iontophoresis approach of drug permeation [13]

2. Sonophoresis

In this technique the ultrasound waves with energy of 20 kHz-16 kHz is used to transport drug molecules in transdermal drug delivery. These ultrasound waves increases temperature of skin which disturbs the skin layer and make molecule to permeate inside different layers of skin. Before permeation of drug it is coupled with specific coupler such as gel, or cream. The basic principal of this method is thermal effect of drug molecules that takes place due to ultrasound waves. Ultrasounds used in sonophoresis penetrate the drug molecules up to 4-6 cm. Sonophoresis is used in treatments of muscle soreness, tendonitis, and bursitis. [14]

2. Electroporation

High voltage electric pulse ranging from 5 to 500 volts is used to permeate the drug molecules through skin. These electric pulse help to create pores in stratum coreneum through which drug molecules rapidly get penetrate in skin. This technique is used for low molecular weight drugs like doxorubicin; it generally works on principle of transcutaneous flux. [15]

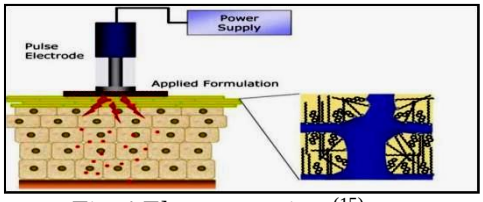

Fig-4 Electroporation [15]

3. **Photomechanical waves**
   Photodynamic waves of energy ranging from 5-7 J/cm^2 is used to increase the depth of 50-400um of stratum coreneum that will permeate the drug efficiently. Transiently created channel are used to deliver the drug. Photodynamic waves are used to deliver drug at depth of stratum coreneum. It can be used to deliver macromolecules such as dextran and can deliver drug within few minutes. [16]

4. **Thermal ablation**
   Thermal ablation, also called as thermophoresis, is a promising technique that disrupts the stratum corneum structure by localized heat that provides enhanced drug delivery through micro channels created in the different layers of skin. A high temperature above 100 °C is required and that leads to heating and vaporization of keratin and ruptures thin layer of stratum coreneum that efficiently delivers the drug. The thermal exposure is created for short period of time of few microseconds to avoid potential pain, bleeding and irritation. Thermal ablation is created by using radiofrequency and laser. [17]

5. **Liposomes, transferosomes, and ethosomes**
   Vesicles involve use of liposomes, transferosomes, and ethosomes to deliver both lipophillic and hydrophilic drug. They control rate of absorption by multilayered structure. [18]**Liposomes** are lipid colloidal vesicles that help to retain drug molecule on skin. It also helps to provide sustain release of drug and prolong activity of drug at particular local site. **Transferosomes** are deformable liposomes that penetrate drug inside skin by creating pores. They allow drugs of 1000kDa to penetrate inside tissues and skin layers. They mainly help in transportation of macromolecules like peptides and proteins. **Ethosomes** are phospholipids containing vesicles that contain high concentration of alcohol. This formulation helps to improve release of drug in circulating blood. Moreover, ethosomes are most stable and have long retention period. [19]

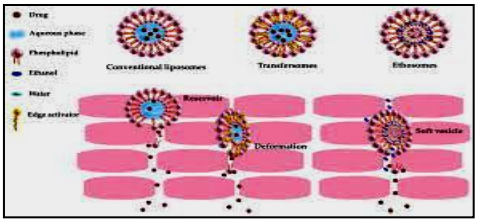

Fig-5 Vesicles used in TDDS for drug permeation [18]

6. **Polymeric nanoparticles**
   Nanoparticles are nanocarriers of size 1 to 1000nm. They also increase the residence time of drug inside the blood circulation which helps to escalate the bioavailability, reduce drug toxicity and side effects. Nanoparticles have advantage that it protects drug against denaturation and destruction. NP's help to achieve continuous release of drug. They are mainly made of polymers hence are highly structured and flexible molecules that allow high molecular weight drugs to penetrate deep inside the skin layers.[20]

7. **Microneedles**
   In this micro sized needle are placed over skin superficially which result in diffusion of drug across the epidermis layer of skin. They lead to active absorption of drug by directly delivering drug in blood capillaries. Microneedles have major advantages that they do not cause pain, help in faster healing at site of injection, and specific area can be targeted. [21]

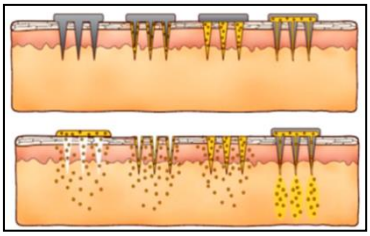

Fig-6 Permeation of drug in TDDS by microneedles [21]

8. Jet Injectors

They are micro devices in which compressed air is filled and are injected on skin. They create micro channels in skin and delivers mainly hydrophilic drugs, peptides and proteins. Single or multiple dose of drug can be given by these devices. The first jet injector that was commercially available in market is Biojector 2000 that delivers drug subcutaneously and intravenously. [22]

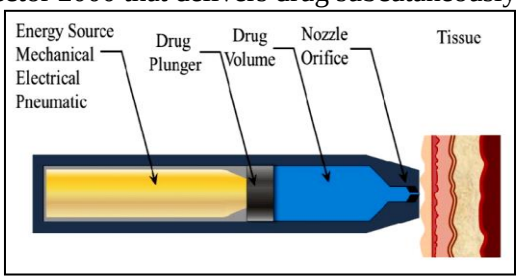

Fig-7 Permeation of drug in TDDS by jet injectors [22]

9. Powderject devices

These devices work at high speed of 600-900 m/s to deliver powder drug across the skin. Generally high speed helium gas is filled inside the ject that pushes the powdered drug deep inside the layers of skin. The advantage of this method is that it causes least damage to skin and its layers, is site specific and provide sustain release of drug molecules. [23]

10. Chemical enhancer

These enhancers work by modifying stratum coreneum. They usually rupture the lipid bilayer of stratum coreneum and collaborate with proteins and permeate the drug molecules through skin by altering the partition coefficient. Examples of such chemical enhancers include fatty acid, alcohol, azones, surfactants etc. They mainly functions by improving permeation of drug molecules by skin. Following chemical enhancers can be used in TDDS as shown below. [24]

Table -1 Different chemical enhancers used in TDDS [24]

CHEMICAL ENHANCERS	EXAMPLES
Solvents	water,ethanol, methanol
Fatty acid	Oleic acid, capric acid, lauric acid
Surfactants	non ionic surfactant, SLS, sulphonamide, Pluronic F68
Terpenes	Menthol, carvone
Amides	dimethyl amide, dimethyl formamide

ADVANTAGES OF CURRENT APPROACHES USED IN TDDS

1. Helps to permeate both lipophillic and hydrophilic drugs.
2. These approaches are used to provide control release of drug.
3. Reduces toxicity and side effects of drug.
4. Continuous release of drug in blood circulation can be achieved via these approaches.
5. Vesicles helps to accomplish sustain release of drug.
6. They can remove stratum coreneum selectively without damaging deeper tissues.

7. Do not cause pain.
8. Microneedles help in faster healing at injection site. (25, 26, 27)

MARKETED EXAMPLES OF DRUGS THAT USES CURRENT APPROACHES TO PERMEATE DRUG ACROSS THE SKIN

Marketed examples of different transdermal patches that uses current approaches to deliver drug across skin are given below. (28-34)

Table 02- Marketed example of transdermal patch that uses current approaches to deliver drug

Techniques used in transdermal drug delivery	**Marketed examples of drug that uses current approaches to permeate drug across skin**	**Uses of marketed transdermal patch**
Iontophoresis	Dexamethasone transdermal patch	Used for Knee pain. (29)
sonophoresis	Rivastigmine and scopolamine patch	Used to treat dementia. (30)
Electroporation	ep – patch	Used to deliver DNA & RNA. (31)
Microneedles	Serum albumin and peptide patch	Used for peptide delivery. (32)
Jet injectors	Jet injector patch	For insulin delivery. (33)
Powderject	Lidocanine patch	For anaesthetic purpose. (34)

CONCLUSION

Many formulations in industries are in process to increase its bioavailability via easy route of administration therefore transdermal drug delivery is non invasive safe and effective system to deliver drug across the skin that undergo high metabolism and have low bioavailability. Current approaches like iontophoresis, sonophoresis, jet injectors, Powderject, microneedles and use of vesicles are developed in TDDS to permeate drug through skin to systemic circulation which are growing fast and providing commercialized market product that delivers the drug by transdermal route in safe, effective and control manner. Moreover in recent year use of these techniques in TDDS majorly use of microneedles has attended great domestic market globally.

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