



## Transdermal drug delivery an emerging approach for antipsychotics

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### ABSTRACT

Transdermal drug delivery system is one of the leading technology which gives extensive benefits compared to other dosage forms. In the case of drugs having a first-pass metabolism problem, small doses of drugs can be delivered. Oral drug delivery is associated with several problems like pain interrelated with the use of injections, needles, and the researchers mainly focus on the development of the transdermal route. The aim is to provide a rationale for improvement of the transdermal system of antipsychotics by highlighting the antipsychotic formulation and safely delivering medications across the skin. The present review emphasis on the latest advances in a transdermal delivery system which acts as a platform for effective transdermal delivery of antipsychotic. By using this technique, the pharmacotherapy of patients who have psychosis can be improved. There are numeral physical methods, and the skin penetration enhancement techniques have been developed that helps in delivering drugs through the skin. This technique helps to alter the barrier properties of skin and improves the penetration of the drug. It majorly highlights the possible role of microneedle in the transdermal system and acts as a different carrier in delivering several therapeutic agents effectively. This article summarizes the novel transdermal delivery approaches, advantages, and the choice of antipsychotropic drugs.



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### INTRODUCTION

Transdermal drug delivery system (TDDS) is a trouble-free technique for delivering drugs systemically by applying a medication onto unbroken & well skin. The penetration of the drug through stratum corneum and passes through deeper epidermis and dermis without increasing the drug level

in the dermal layer (Alkilani *et al.*, 2015). Transdermal patchwork in a pretty simple way. Patches are a drug in the adhesive (DIA) system in which drug is distributed in pressure-sensitive adhesive (PSA) matrix. The transdermal patch includes constituents like PSA, the release liner, backing membrane, and few excipients (Nandgude and Ganapathy, 2017). The transdermal system was first introduced in the mid-1990s, and this technology made great interest for researchers and pharmaceutical companies. This review article describes various components of the transdermal patch and its application, advantages disadvantages, and few recent advancements in this field. Innovations in novel technology occur at a positive rate, which leads to a productive and pulsating area of innovation for research and product development. Numerous physical, chemical, biochemical strategies are used to disrupt the stratum corneum to enhance transdermal drug delivery, with physical procedures

like thermal ablation, electrically assisted methods, e.g. electroporation, iontophoresis (ITP) and currently developed strategies like microneedles. Microneedle is a sub-millimetre device that creates a microchannel (Earle and Subramanyam, 2014). It is a minimally invasive method that evades the stratum corneum without exciting the dermal nerves or bleeding. Small molecules to nanoparticles can be transported through the skin by microneedle. The present review mainly focuses on the use and development of microneedle, its type, and application, which significantly enhances drug delivery through the transdermal route. All across the world, the transdermal patch market has risen to 2 billion dollars. In 1979 the first FDA approved the transdermal system for motion sickness was “SCOP-Transderm” (Mehta, 2004).

### Structure of skin

The human skin is the external covering of the body and largest organ of the integumentary system, having a surface area of 1.7 m<sup>2</sup> comprising of 15-16 % of total body form. The major function of the skin is a defensive barrier between the drug and external environment against UV radiations, allergens, microorganisms, and chemicals. Skin is divided into three major regions: (1) Epidermis- the outmost layer comprises stratum corneum (2) Hypodermis- the innermost layer (3) Dermis- the middle layer. The stratum corneum is around 10-20 micrometer thick and it acts as an obstruction for drug penetration, it allows only lipophilic molecules to diffuse through the skin. The removal of stratum corneum and viable epidermis leads to a rise in drug delivery (Patole et al., 2013; Alkilani et al., 2015).

### Principles of Transdermal Permeation

The drug enters the bloodstream through the skin through the process of diffusion. Earlier the skin was considered as an impervious protective barrier, but a future investigation was accepted which showed the effectiveness of skin as a route for systemic administration. Penetration through viable epidermis and sorption by stratum corneum (Tiwari, 2013).

### Components of TDDS

The transdermal system is made up of Drugs, Polymer matrix, Penetration enhancers, Adhesives, Backing laminates, Release liner.

Figure 1 depicts the essential components of Tdds (Prabhakar and Sreekanth, 2013; Sudam and Suresh, 2016).

### Drug

There is direct contact of Drug Solution with release liner. The drug parameter considered is as below.

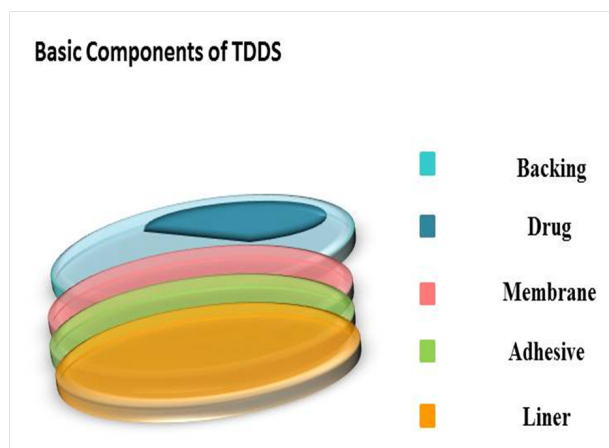


Figure 1: Basic components of TDDS

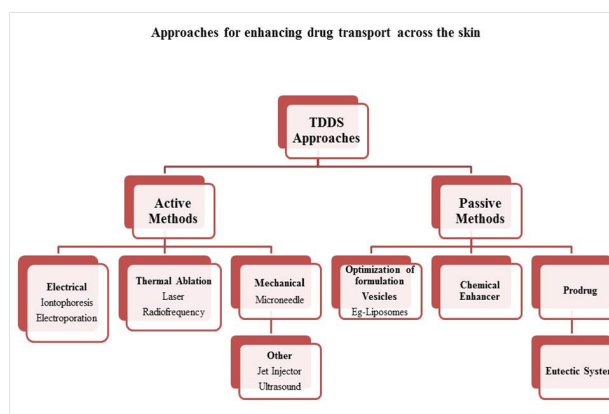


Figure 2: Approaches for enhancing drug transport across the skin

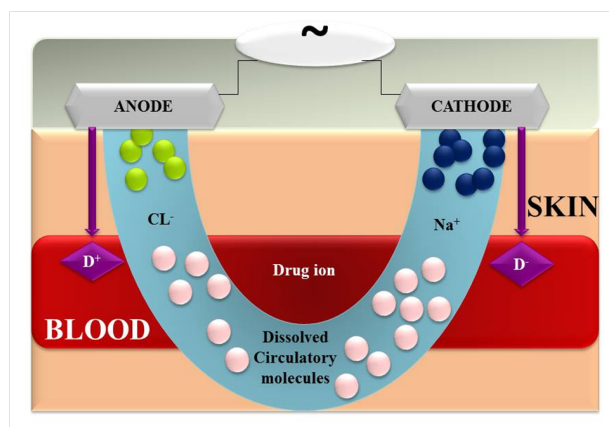


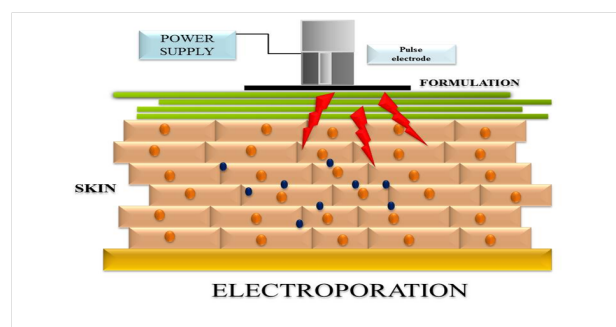
Figure 3: Schematic representation of an iontophoresis patch

**Table 1: List of Marketed TDDS Products**

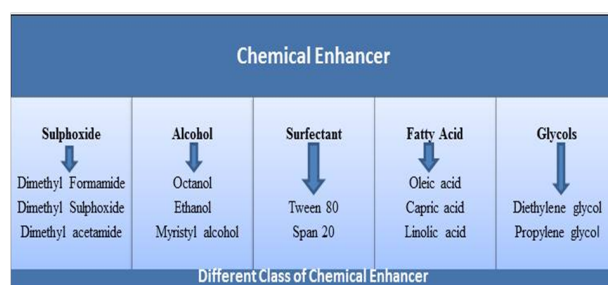
Drug	Product Name	Uses	Manufacturer
Nitroglycerin	Minitran	Angina Pectoris	3 M Pharmaceuticals
	Nitrodisc		Roberts Pharmaceuticals
	Nitro-Dur		Key Pharmaceuticals
	Deponit		Schwarz-Pharma
Fentanyl	Duragesic	Severe/Moderate pain	Alza/Janssen Pharmaceuticals
Estradiol	Alora	Postmenstrual Syndrome	TheraTech / P & G
	Climara		3M Pharmaceuticals
	Climaderm		Ethical Holdings
	Estraderm		Alza/Novartis
	Fempatch		Parke-Davis
Nicotine	Habitraol	Smoking Cessation	Novartis
	Nicoderm		Alza /Gsk
	Prostep		Elan Corp/ Lederle Labs
Estrogen	Fematrix	Postmenstrual Syndrome	Solvay Healthcare Ltd / Ethical Holdings
Progesterone	Nuvelle TS	Hormone replacement therapy	Schering/Ethical Holdings

**Table 2: List of Antipsychotic Drugs in TDDS**

Medication	Class/Category	Target Area	FDA Approval	MHRA Approval	EMA Approval
Rotigotine	Dopamine agonist	Parkinson's disease	Approved	No	Approved
Methylphenidate	CNS stimulant	ADHD	Approved	No	No
Selegiline	MADI	Depression	Approved	No	No
Nicotine	-	Smoking	Approved	Approved	Approved
Fluoxetine	SSRI	Depression	Preclinical Phase	No	No
Rivastigmine	ACE Inhibitor	Dementia	Approved	Approved	Approved
Haloperidol	Antipsychotic	Psychosis	Preclinical Phase	No	No



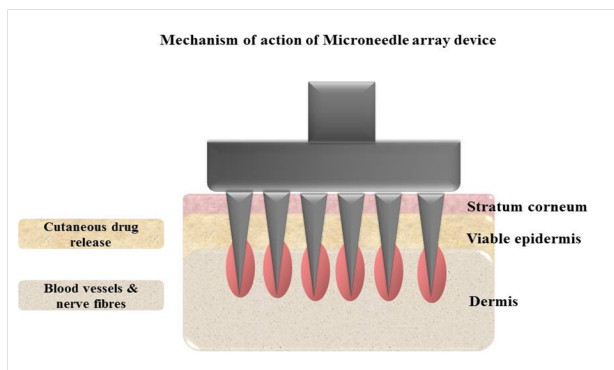
**Figure 4: The basic principle of electroporation**



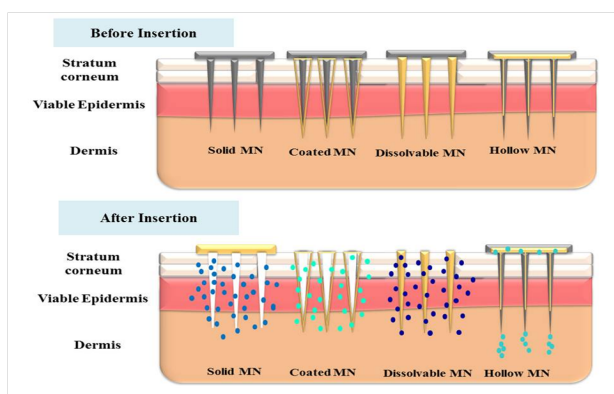
**Figure 5: Class of chemical enhancer**

**Physiochemical Properties**

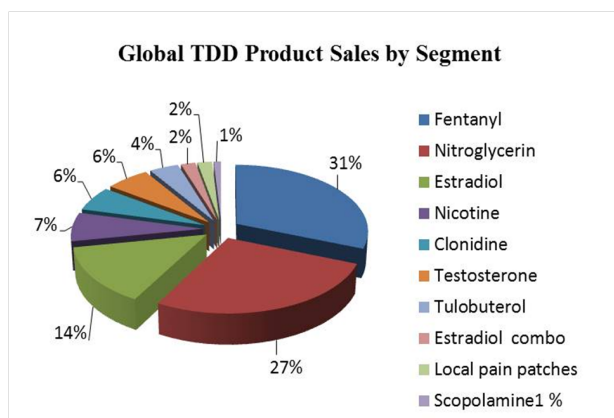
1. The molecular weight of the drug should be less than 1000 daltons.
2. The drug must be similar for both hydrophilic and lipophilic phases.
3. Must have a low melting point of the drug (Nandgude and Ganapathy, 2017).



**Figure 6: Schematic representation of the mechanism of action of a microneedle array**



**Figure 7: A schematic representation of four different MN**



**Figure 8: Representation of four different MN**

### Biological Properties

1. Drug half-life ( $t^{1/2}$ ) must be short.
2. The drug should not show allergic reactions.
3. A daily dose of the drug must be a few mg/day.

### Polymer Matrix

Polymer Matrix acts as a backbone for the transdermal drug delivery system. Change in polymer composition leads to a change in the release rate from TDS. Hence polymer selection is important in designing a variety of membrane perme-

ation (Hejase *et al.*, 2011; Nandgude and Ganapathy, 2017).

Basic criteria for polymer selection are:

1. The polymer must be non-toxic.
2. The polymer must be stable.
3. The polymer should be an inert drug carrier.
4. It must be biocompatible with the skin surface.
5. The polymer should be non-toxic and non-antagonistic to the host.
6. The polymer must be in-expensive

### Types of polymer

Synthetic Polymer: Polyvinyl chloride, polyethene, polypropylene, polyuria, epoxy, polyvinyl alcohol.

Natural Polymers: Gelatin, gum, waxes, protein, cellulose derivative, shellac, natural rubber, starch.

Synthetic Elastomers: Silicone rubber, nitrile, hydrin rubber, neoprene (Hejase *et al.*, 2011).

### Penetration Enhancer

Penetration enhancer is a combination that supports the permeability of the skin by modifying the skin as a barrier. When penetration enhancer is mixed with the formulation, it improves the A) Diffusivity B) Solubility of Drug through the skin. Penetration enhancers finally allow the drug to penetrate from the viable tissue and move in systemic circulations.

### Pathways of Drug Penetration

Transportation of penetrant through skin barrier by three significant pathways such as intercellular penetration from the stratum corneum, trans-appendageal penetration through hair follicles and sweat and sebaceous gland, the transcellular /intra-cellular permeation takes place through the stratum corneum (Ramesh and Velraj, 2018).

Ideal Penetration enhancers must have the following properties

1. It must be non-irritant, non-toxic, and non-allergic
2. No pharmacological activity within the body
3. Penetration enhancers must work unifacial.
4. It should be pharmacologically inert.

### Adhesive

Adhesive it acts as a vital component by forming the contact between the delivery system and with skin. Pressure-sensitive adhesive is placed outside of the device or at the posterior of the device (Prabhakar and Sreekanth, 2013).

Adhesion is the net effect of three phenomena mainly,

1. Peel: It has resistance against the cracking of the adhesive bond
2. Tack: Polymer can adhere to the substrate with small contact pressure
3. Creep: There is tacky relaxation of the adhesive bond upon shear

#### Adhesive Material and its Ideal Characters

1. It must be able to remove it easily.
2. It must have good contact with the skin surface.
3. It must be non-irritant
4. Should not produce washable residue on the skin
5. The drug must have physical & chemical compatibility (Nandgude and Ganapathy, 2017).

#### Antipsychotic

“Psychosis” disorder is severe mental disorders that affect abnormal thinking and disturbs brain function. Psychiatric illness such as schizophrenia leads to a condition of psychosis. Significant symptoms include: (Gardner, 2005) Hallucinations, delusions, talking illogically. The patient isn't aware of his or her behaviour. Antipsychotics are the medications that are used to alter mental conditions like psychosis. It is also called major tranquilizers or neuroleptics (Cipollina, 1992). Based on the extrapyramidal effect, the drugs are classified as typical and atypical antipsychotics, which are used to treat bipolar disorder like (mixed episodes and acute mania) (Tandon, 2011). The atypical antipsychotic is favoured as it has a more favourable adverse effect profile and has a low charge for causing transformation from mania to depression. The use of antipsychotic drugs achieves the blocking of the D2 receptor. Antipsychotic drugs are useful in monitoring symptoms of acute schizophrenia (Cummings, 1992; Nussbaum and Ellis, 2003; Björkelund *et al.*, 2006). The list of marketed TDDS products are mentioned in Table 1 (Kumar and Philip, 2007; Saroha *et al.*, 2011).

#### Novel Enhancement Techniques for Skin Permeation

Various technology has been used for modification in barrier properties of stratum corneum, and this is divided into passive/chemical or active/physical methods.

Chemical penetration enhancer is the most widely used passive approach. Various mechanism of action for penetration enhancers are as follows:

1. The stratum corneum lipid bilayers fluidity is increased.

2. Interruption or extraction of intercellular lipids
3. Contact with intercellular proteins
4. The thermodynamic activity of drug increases which leads to an increase in stratum corneum hydration

The most widely used penetration enhancers are alcohol, azone, essential oils, sulphoxides, urea, fatty acids, and water. Penetration enhancers are associated with limitations such as reduced efficacy and safety (Alkilani *et al.*, 2015).

A practical method for skin penetration includes:

1. Ultrasound
2. Methods which are electrically assisted (electroporation and Iontophoresis)
3. Devices based on velocity such as (jet injector, powder injection)
4. Mechanical methods like (Microneedle and tape stripping)
5. Thermal approach (Laser and Radiofrequency Heating)

Through these approaches, a wide range of drugs can be delivered across the skin. The active method can provide a wide range of medications which overwhelms lag time. Figure 2 depicts the approaches for enhancing drug transport across the skin (Alkilani *et al.*, 2015).

Few active methods involve the use of the following methods,

#### Ultrasound devices

Ultrasound is known as an oscillating sound pressure wave which has a wide application in the field of chemistry, biology, physics, and engineering. By applying a Frequency of 20 kHz-16 MHz, there is a transport of drugs across the skin (Han and Das, 2015). Diverse categories and types of drugs can be effectively delivered by applying ultrasound (Schoellhammer *et al.*, 2014). Mechanism of ultrasound which affects tissue and cells includes cavitation effect and thermal effect. The mechanism involves the oscillation of cavitation bubbles in the ultrasound field (Seah and Teo, 2018).

#### Physical Enhancement Approaches

It includes major two types a) Indirect physical method and b) Direct physical method

#### Indirect Physical Method

For enhancement, Several new approaches are involved in the application of electrical (Iontophoresis, sonophoresis, electroporation, and innovative methods such as magnetic energy and laser energy for commercial purposes) (Benson *et al.*, 2019).

## Iontophoresis

In Iontophoresis, a milliampere of current is applied to a specific area of skin. The mechanism involves the use of an electrode, which is in contact with the medication which needs to be administered. By potential gradient, the charged drugs are passed from the skin and into the body. For the enhancement of a wide range of drugs, Iontophoresis has been widely studied (Benson *et al.*, 2019). In September 2015 the security patch was introduced, but its sales were ceased in June 2016 as it showed burns at the application site. Three Iontophoretic delivery systems developed to include a) Phoresor b) Lidosite c) E-trans. Lidosite is used for fast dermal anaesthesia, and it delivers Lidocaine which is the first approved commercial iontophoretic patch.

Iontophoresis has a wide application in diagnosis and therapeutic use. This process can enhance the permeation of topically applied therapeutic agents. Figure 3 depicts the representation of an iontophoresis patch.

The following mechanism can enhance drug permeation: a) Electro-osmosis (for uncharged solutes) b) Electro-repulsion used (for similar charged Solutes) c) Electro-perturbation (both charged & non charged Solutes) (Stanekzai *et al.*, 2019).

Micro iontophoresis is a system that is used to study cellular function, by using a small size capillary probe, that releases particular quantities of active substances (Nanda *et al.*, 2006).

## Electroporation

In this approach, the high intensity of the electric pulse is applied which leads to the creation of aqueous openings in the lipid bilayer of stratum corneum and permits diffusion of drug diagonally to the skin (Alkilani *et al.*, 2015). A voltage of 50-500V is used, which increases the passage across the skin. The electrical parameters and physicochemical properties of drugs lead to an increase in the transport of drugs. This expertise has been used to enhance skin penetrability of different molecules with different sizes (i.e. proteins, peptides, oligonucleotides). The principle of electroporation is shown in Figure 4 (Nanda *et al.*, 2006).

## Sonophoresis

Sonophoresis involves a blend of ultrasound treatment and topical drug treatment to reach therapeutic drug concentration at specific places of the skin. The system which uses ultrasound to increase the absorption of topical medication onto the skin is called as sonophoresis. A low-frequency pressure wave of not more than 100 kHz is applied, because of this, the molecules get to penetrate through the

skin easily (Park *et al.*, 2014; Seah and Teo, 2018). Sonophoresis is used in the treatment of muscle soreness and tendonitis. The mechanism involved in this technique is

a) Cavitation (generation and oscillation of gas bubbles)

b) Thermal Effect (Increase in Temperature)

Sonophoretically enhanced transdermal drug delivery system has a wide application in gene therapy and tissue engineering (Stanekzai *et al.*, 2019). Sonophoresis transdermal drug transport can be used in the field of biotechnology and genetic engineering (Bhatt and Aqil, 2010).

## Magnetophoresis

In this technique, the magnetic field is applied, which acts as an energetic force to upsurge the dispersion of diamagnetic solute across the skin (Kumar and Philip, 2007).

## Velocity based Devices

Devices that are dependent on velocity includes the powder or liquid jet injection, which uses a high-velocity jet having velocity 100 to 200m/s for puncturing the skin, and by using power sources such as compressed gas or spring, it delivers the drug. Liquid jet injectors are of two types:

1. The single-dose jet injector (disposable cartridge jet injectors)
2. Multi-use-nozzle jet injectors (MUNJIs)

A jet injector is a useful device that helps to deliver drugs in an electronically controlled manner and is a needle-free device which results in enhanced uniformity and reduces pain in the patient.

Liquid jet injector pushes the liquid from the nozzle having a diameter of 50 to 350um, which is smaller than the hypodermic needles (800um). Delivery of drugs to different layers of the skin can be achieved by using a jet of different orifice diameter and velocity the drug is delivered. The significant benefit of this method is secure and safe needle disposable without any accidental needle injury. Therefore multi-nozzle jet injectors are limited to provide only multi-dose drugs to an individual. E.g., Tjet device delivers somatropin, i.e. (human growth hormone) (Kumar and Philip, 2007).

The advantage of a powder jet injector over liquid jet injector is it can deliver reliable drugs or vaccines to the skin. Eg-DNA vaccination has a particle size between 0.5um to 3 um (Arora *et al.*, 2008).

## Thermal Approach

In the thermal ablation approach, systemic delivery of drugs across the skin by warming the surface

of the skin, which exhausts the stratum corneum at specific sites of heating only without affecting the deeper tissue. By using ohmic microheaters and radio-frequency, ablation skin heating can be achieved (Bhatt and Aqil, 2010).

Methods used for thermal ablation includes- “laser and radiofrequency”.

### Laser Thermal Ablation

Laser ablation is used for the treatment of dermatological situations like pigmented skin. The mechanism involved in laser thermal ablation is the removal of stratum corneum without damaging the deeper tissue. Thus it improves the supply of lipophilic and hydrophilic drugs into the skin surface (Baron, 2003). By the installation of light energy, the laser removes the stratum corneum leading to loss of water and the development of microchannels in the skin (Saravanakumar, 2015).

### Radiofrequency Thermal Ablation

Radiofrequency thermal ablation is a technique that is used to reduce pain. The microscopic pathway in stratum corneum is produced by applying a high-frequency irregular current of (~100 kHz) by which the drug gets penetrated.

This method permits the transdermal delivery of an extensive range of hydrophilic drugs and macromolecules (Bala, 2014).

### Other Approaches

#### Biochemical Enhancer

Proteins/peptides are used instead of chemical as a chemical enhancer. E.g, Natural pore-forming peptide, i.e., magainin. When a surfactant and chemical enhancer is used in combination, magainin, it acts as an effective enhancer. Figure 5 depicts the different classes of chemical enhancers (Pathan and Setty, 2009; Das and Ahmed, 2017).

#### Mechanical approach

Some of the innovative approaches are used to overcome the difficulties and novel methods like MN and tape stripping methods are useful. These are a few advanced methods that have a wide application in the transdermal drug delivery system (Prabhakar and Sreekanth, 2013; Alkilani *et al.*, 2015).

#### Tape Stripping

In this system repeated applications of an adhesive tape that eradicates the skin layer, SC. The amount of stratum corneum removed by a single adhesive factors such as the patient's age, the thickness of stratum corneum and the extent of lipid should be considered. The pH and transepidermal water loss are the skin parameters that need to be

measured (Akhtar *et al.*, 2020).

It is a technique that can be used in ecological research – dermatopharma for selectively removing the skin (Lademann *et al.*, 2009).

### Microneedle

It is the most recently developed drug delivery system which is similar to the conventional needle. Still, the difference is they are fabricated in a micron size range of 1-100 micron in length and of a diameter of 1 micron (Akhtar, 2014). MN array is a good alternative for hypodermic and subcutaneous needles. Other than pain-free delivery it has various advantages such as MN does not cause bleeding, it eliminates the dosing unevenness of small molecules, potential for self-administration, it avoids needle stick injuries and ease of MN waste disposal. MN approach provides tremendous amplification potential for a preferred immune response (Giannos, 2014). Figure 6 depicts the image of the mechanism of action of a microneedle array

Marketed Micro needle products are Intanzia and Micronjet which are prepared for metals and silicon respectively. Intanzia was the first influenza vaccine that targets the dermis. Sanofi Pasteur MSD Ltd developed the intanzia. During the designing as well as fabrication of MN, the shape and geometry are very much critical.

### Methods of Microneedle Application (4 Methods)

1. Solid MN
2. Coated MN
3. Dissolvable MN
4. Hollow MN (Arora *et al.*, 2008)

#### Solid microneedle

It creates microholes across the skin, which increases the permeability of the drug formulations. After insertion of the microneedle, there is the formation of micro-channels that helps in the transport of drugs to viable epidermis. Solid MN consist of the “Poke and patch” approach. Metals, silicon, and polymers can be used for the fabrication of solid MN (Benson *et al.*, 2019).

#### Coated microneedle

It is used for the fast dissolution of coated drugs into the skin. It is a one-step application process, but the dosage is limited to the amount of coating.

Coated MN has a wide application in the field of vaccines. Coated MN consist of the “Coat and poke” approach (Gill and Prausnitz, 2007).

### **Dissolvable microneedle**

Materials used in Dissolvable MN it forms a sharp estimate with the payload dissolved or suspended within, allowing it to poke into and then dissolved within the skin to release the payload. Dissolvable MN involves encapsulation of the drug inside the biodegradable polymeric microneedles. Polymers used in dissolvable MN are PLA, PGA, PLGA, PVP, Polycarbonate (Ito *et al.*, 2012).

### **Hollow microneedle**

Hollow MN is used to rupture the skin surface and in-turn discharge the liquefied drug (Arora *et al.*, 2008). Hollow MN contains a deep bore at the centre of the needle. It works by the mechanism of diffusion or active infusion of the preparation over the needle bores. The approach involved in hollow MN is the "Poke and flow" approach. By diffusion process, it carries the drug continuously into the body. It can also be used to remove the fluid from the body for analysis purposes. The representation of four different MN is shown in Figure 7 (Martanto *et al.*, 2006).

### **Characteristics of Microneedle**

#### **Ruggedness**

To resist the inclusion force deprived of being fractured.

#### **Penetration**

It is Essential to pierce the medication to deepness in the tissues.

#### **Dimensions**

The distance between 100-900microns; Base width of 50-300 microns and Tip diameter of 1-50 microns (Caffarel-Salvador and Donnelly, 2016).

### **Advantages of Microneedles**

1. Trouble-free System
2. Easy to handle
3. First pass effect is evaded
4. It is potentially Biodegradable
5. Low cost-effective
6. Good stability
7. Patient compliance is improved (Hong *et al.*, 2014)

### **Application of Microneedles**

#### **Cellular delivery**

MN has a wide application in cellular delivery.

The Membrane impermeable molecules can be delivered into the cells by this method.

### **Systemic delivery**

The use of MN overcomes the restrictions of injections.

#### **Biopharmaceuticals**

Microneedles can deliver insulin, heparin, growth hormones and human growth hormone.

#### **Immunobiologicals**

Microneedles have an advantage over other methods due to the absence of pain. E.g., influenza vaccine, hepatitis B vaccine, etc.

#### **Cosmetics**

The main stream dermatological products are imparted through the microneedle tools and are used for non-surgical action. eg: used in the management of Ageing (wrinkles) (Patole *et al.*, 2013).

### **Evaluation of MN**

#### **Microneedle Geometry characterization**

The tip radius, base, and thickness of MN are determined by scanning electron microscopy. These values measure interfacial interaction between the skin and the needle.

#### **Safety margin**

The proportion between the force essential for penetrating the stratum corneum and the power where the microneedles brakes are called a margin of safety. For biomedical application microneedle array of a ratio, less than 1 (<1) can be used.

#### **Diffusion Test**

For evaluating the penetration of model drug, Franz diffusion cell is used.

#### **Trans Epidermal Water Loss (TEWL)**

When water is passed from dermis through the epidermis, and it gets evaporate from the skin surface, it is known as TEWL. It is used to characterize the skin barrier function. The principal involved in this process is diffusion and evaporation. The probes are positioned in the wheel clamp beyond the application site. At several times interims earlier and later the application of microneedle the estimates were measured for about three minutes. In humans, the TEWL is about 300-400mL/day.

#### **Biological Safety Test**

From microneedle, the chemicals were pulled out by dipping them in physiological saline solution at 37°C for 72 hours. the extract obtained was applied on shaved intact human skin. If dermal irritation is absent, then it is proved that the biological safety of



microneedle (Mathur *et al.*, 2010; Earle and Subramanyam, 2014).

### Future of the transdermal system

TDDS is best for delivering oral and injected drugs. Because of low skin permeability, various types of drugs do not pass across the skin. Iontophoresis, as well as Sonophoresis, are two recently developed methods for improving the skin penetration. Iontophoresis involves the use of electrical current along the dual electrodes on the skin surface. Sonophoresis works by the mechanism of ultrasonic energy, which transfers drugs of high molecular weight over the skin. Most advanced, as well as favourable technology is microneedle enhanced drug delivery. The most interesting & new concept, i.e. microneedle, has a generous value in the future (Caffarel-Salvador and Donnelly, 2016).

### Global TDDS Market

The world wide TDDS (percutaneous) has a market value of USD 5400.2 million till 2017 and is predicted to reach a CAGR of 4.6% in the coming years. The international transdermal market is estimated to touch 81.4 billion USD by 2024 as per the report of grand view research. The advancement includes third-generation TDDS includes ultrasound, Iontophoresis, and microneedle (Gowthaman *et al.*, 2015). In 2015, in North America, the overall TDDS market had increased by more than 50.0 %. The list of antipsychotic drugs in TDDS is mentioned in Table 2 (Isaac and Holvey, 2012; Ita, 2017; Abruzzo *et al.*, 2019).

Figure 8 depicts the Global TDDS Product Outlook (revenue from 2013-2024) includes the following (Hafeez, 2013).

Radio frequency, Electroporation, Iontophoresis, Microporation, Thermal, Ultrasound, Mechanical Arrays, Others

### CONCLUSION

TDDS is one of the leading sectors in the field of the pharmaceutical industry. Ever since 1981, the TDDS is used for delivering drugs safely. A lot of development is done in the area of transdermal patches. Nowadays, many researchers are working on innovative medicines to be given via TDDS, and it offers excellent therapeutic response. It is expected that technological development in TDDS leads to improvement in the prevention of disease, diagnosis, and upgrading of the life of the patient. In this review, several new TDDS approach needs to be established to overcome the limitation of the conventional method. In this review, we advise using innovative methods of the microneedle. A

wide range of materials can be utilized for fabrication. Microneedle has extensive use in the field of medicine for drug delivery, diagnosis, and vaccination. Other practices like Iontophoresis and electroporation are combined with microneedle to boost penetration into the skin. Due to exponential development in investment and attention in the MN approach have a wide application. This article offers valuable data regarding the transdermal drug delivery system and different novel approaches in TDDS.

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### Authors Contributions

All authors contributed equally to this work.

### Conflicts of Interest

The authors declare that they have no conflict of interest for this study.

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