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A REVIEW ON PHYSICAL PENETRATION ENHANCERS FOR TRANSDERMAL DRUGDELIVERY SYSTEM

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Abstract:
Novel Drug Delivery System (NDDS) is providing an exceptional improvement in terms of safety, efficacy & quality of conventional drug therapy. Skin is the largest organ present in the body and provides the most convenient route of administration. Transdermal Drug Delivery System (TDDS) is one of the methods introduced under NDDS for providing systemic effect in the body through skin. Although the innovation proves to have maximum patient compliance, it holds limited bioavailability due to the presence of Stratum Corneum, achief protective skin barrier. A lot of novel advanced transdermal technologies in the form of Penetration Enhancers have been developed to increase bioavailability. This review would discuss the active approaches involved for facilitating drug permeability. It includes renowned methods like Iontophoresis, Sonophoresis, Electroporation, Magnetophoresis, Photomechanical waves, and also other new technologies. This review further highlights certain products under transdermal technologies which are approved and currently in the market. We anticipate that in the future, the limitations of the physical approaches would be overcomed and new advancements along with combination techniques will be in the highlights, resulting in better patient compliance and efficient treatment.
Keywords: *drug delivery, novel system, ultrasonic waves, physical transdermal approaches, ultrasound.*

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1. INTRODUCTION

A drug delivery system is a combination of routes of administration and dosage forms of the medication. There are various routes of administration out of which oral and parenteral routes are the most common ones. Although the oral route is the most preferred but there are several drawbacks such as first-pass metabolism by the liver, degradation of proteins and peptide-based compounds by the stomach, and rapid blood level spikes which can be high or low leading to frequent dosing, and the size-dependent absorption issues across the epithelium.[1,2] Hence, the macromolecular substances are administered using injections which have limitations such as reduced patient compliance due to elicitation of injury and pain, the need of trained administrator for the safe administration and non-uniform pharmacokinetic results.[1] These disadvantages can be helped by substitution with Transdermal delivery of medications which aims to improve the therapeutic efficacy along with the safety of drugs.

The transdermal drug delivery system (TDDS) also known as patches is the non-invasive method of administration of medications through the largest organ of the body i.e., the skin, through which it penetrates the circulatory system at controlled rate. It avoids the first pass metabolism, decreases side effects, provides faster systemic effect, and a stable plasma concentration profile.[1,3] The administration of drugs depends on a variety of factors under the physicochemical properties which includes diffusivity, charge, molecular weight, solubility and polarity. The development of TDDS expands into three generations. The first-generation transdermal patches include simple liquid or gel containers containing lipophilic, low-dose drugs. The second-generation ones include common chemical enhancers, iontophoresis, and non-cavitational ultrasound. The third-generation TDDS includes novel chemical enhancers, microdermabrasion, electroporation, and sonophoresis-like methods.[4]

The transdermal patches usually consist of components like- release liner, drug which is placed in an adhesive layer, a rate controlling membrane, a backing layer protecting the patch from the outer environment, and penetration enhancers (PE).[5] The drug release from patches works on the principle of Fick's law of diffusion which states that the molar flux due to diffusion is directly proportional to the concentration gradient. The drugs continue to release till the gradient ceases. Through this passive mechanism, the larger molecules are unable to diffuse because of the physical properties of the stratum corneum (SC) which results in delayed release. For this, active transdermal drug delivery approaches also called physical penetration enhancers are used that enhance the drug absorption, and overcome all the limitations.[1] These are second and third-generation devices that use the electromotive force to transport macromolecular compounds through the skin depending on the nature of the applied electric field, characteristics of the drug molecule and the extent of the skin barrier to be crossed.[6] In this article, we will be discussing the active or physical approaches being applied currently for enhancing transdermal drug absorption.

2. Skin Layers & Physiology

Skin, also known as the cutaneous membrane, is the most accessible, largest multilayered organ which acts as a protective barrier between the body and the external environment. It is exposed to most infections, diseases, and injuries but the protective action of the skin actually safeguards it from various harmful microorganisms, radiations, toxic chemicals, allergens and thereby acts as the first line of defence. Microscopically, skin is divided into three layers namely (1) epidermis, the thinnest superficial layer (2) thicker dermis, and the (3) deepest subcutaneous hypodermis layer.[1] The epidermis layer lacks a vascular system whereas the dermal layer consists of a vascular supply. The hypodermal layer on the other hand consists of large blood vessels which supply to the above layers.

The epidermis is composed of keratinized stratified squamous epithelium and it consists of keratinocytes, melanocytes, langerhans and merkel cells.[7] The uppermost layer of the Epidermis is the Stratum Corneum, also called as non-viable epidermis, consisting of dead keratin cells and corneocytes or keratocytes. The keratocytes are surrounded by an intercellular lipid membrane which consists of 8 different classes of ceramides, fatty acids, cholesterol sulfate, cholesterol and sterol waxes. This layer majorly acts as the principal barrier and protects from all possible injuries and microbial invasions.[2,8] The corneum cells shed to form newer layers of cells from deeper strata. The skin appendages are also present in this layer. Furthermore, layers like stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale are associated with the epidermis. The Stratum basale is the deepest layer consisting of stem cells which undergoes division continuously to form new cells.[2] Usually, for any transdermal or dermal drug, the outer layer acts as a chief barrier for its penetration rate.

Dermis, The dermal layer consists of connective

tissue with collagen and elastic fibres and is responsible to provide nutrients to both the layers of dermis and epidermis. Further divided into the papillary region and deeper reticular layer, it consists of nerve endings, sweat glands, pilosebaceous units, hair follicles, and blood vessels.

The dermis region is mainly responsible for transdermal drug delivery as the permeation of the drug through blood vessels makes the drug show systemic action.[1,2,9]

The hypodermis, also called the subcutaneous layer, consists of areolar and adipose cells. It mainly stores fat. It protects against thermal attacks and physical shocks, it also has a presence of fibroblasts and macrophages.[9,10]

3. Percutaneous Absorption: Routes and Factors

Transdermal drug delivery systems would only be effective when the drug is absorbed into systemic circulation by passing through the skin layers. Percutaneous absorption is defined as the penetration and permeation of drugs through the skin to reach the systemic circulation.[11] It is a 5 step process that includes:

1. Penetration: It is defined as the process by which the drug enters into the first layer of the skin.
2. Drug partitioning from the lipophilic stratum corneum and continuing to the viable epidermis layer.
3. Drug diffusing from the avascular epidermis to the highly perfused dermis layer.
4. Permeation: After entering the first layer of the skin through penetration, permeation ensures the penetration of the drug from one layer to another. These layers are structurally and functionally different.
5. Resorption: It is the final step involving the uptake of drug in the vascular system.[12,13]

The major process, penetration of the drugs, happens across the intact skin mainly through the 2 routes: trans- epidermal - drug enters the circulation by passing through Stratum Corneum and trans-appendageal - hair follicles, sweat ducts & secretary glands.

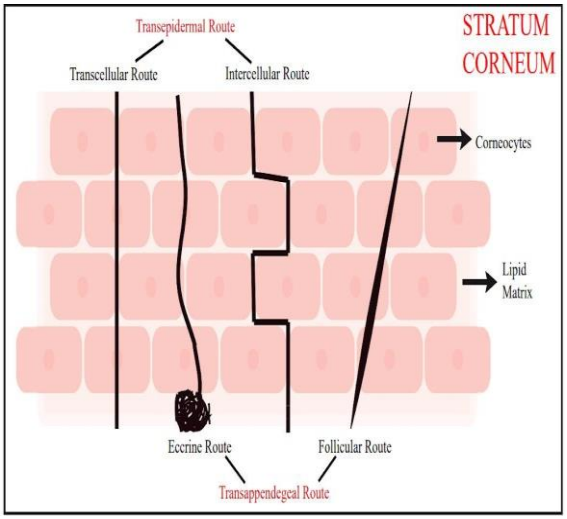


Fig.1 Permeation routes through the skin

When a drug permeates through the trans epidermal pathway, it can follow either an intracellular pathway, also called the transcellular pathway or an intercellular pathway, which is also called the paracellular pathway. The Intracellular pathway is mainly used to transport the hydrophilic or polar molecules wherein the drug passes through the cells with the aid of lipid lamellae and its further absorption in the stratum corneum is enhanced by the hydrophilic nature of keratocytes. The Intercellular route allows the transport of the hydrophobic or lipophilic molecules by facilitating their movement between the keratocytes present in the Stratum corneum. The trans- appendageal route occupies only 0.1% of the whole skin layer, thereby it is considered to be insignificant even if it holds fewer risks and better feasibility.[1][3][12]

Physiological, physicochemical, and pharmacokinetic factors are ideally considered during the infusion of the drugs through the transdermal route. These factors play a significant role in deciding the bioavailability of the drug. Different patches and microneedles-like systems have been formulated by manoeuvring the conditions like skin pH, anatomical site, drugs used in the system, presence of metabolic enzymes, etc. The factors associated majorly are listed below.

1. **Physiological factors**[14,15]: Age, hydration contents, and anatomical site plays a vital role in the effectiveness of the drug. A lot of structural changes are associated with maturity or ageing. As the age progresses towards maturity, the formation of intercellular lipid regions which consist of cholesterol– sulfate, free fatty acids, and ceramides turns out to be a major protective barrier. It is also said that the natural moisturizing factor starts declining with ageing, which results in less absorption of hydrophilic drugs. The epigenital region holds the highest permeability rate for TDDS whereas the skin of the limbs holds the least, thereby the site of the application must be considered accordingly.
2. **Physicochemical properties of the drug**[16]: It should be compatible with the skin barrier properties of the stratum corneum. The molecular weight and transdermal penetration are inverse in the relationship. Therefore, the ideal drug must include low molecular weight resulting in a higher diffusion coefficient. Factors like partition coefficient and distribution coefficient play a key role to exert biological influence. The drugs having log P value below -1 poise hold difficulty in penetration whereas between

-1 to 2 hold a good range of permeability. Similarly, if the pH of the skin is much higher or lower than the normal expected ranges, the topical application may destroy the skin. The melting point of the drugs, if above 150C, shows less aqueous solubility resulting in inverse relation, and decreases the permeation and transport between the skin layers.

3. **Pharmacokinetic factors**[14-16]: The pharmacokinetic factors determine the drug penetration and absorption including skin state, metabolic enzymes presence, and temperature. The presence of damaged or diseased skin increases the drug infusion and reverses the effect in the intact skin, presenceof metabolic enzymes may lead to an increase in the penetration, if the drug is a prodrug whereas may also decrease the penetration if undergoes first pass skin metabolism, and lastly, the temperature can lead to increased flux as of higher fluidization of lipid layers. Though, even after considering the factors, the maximum concentration is not delivered through the conventional ways because of the protective barrier which leads to a need for penetration enhancers.

4. Need of Enhancers & its Classification

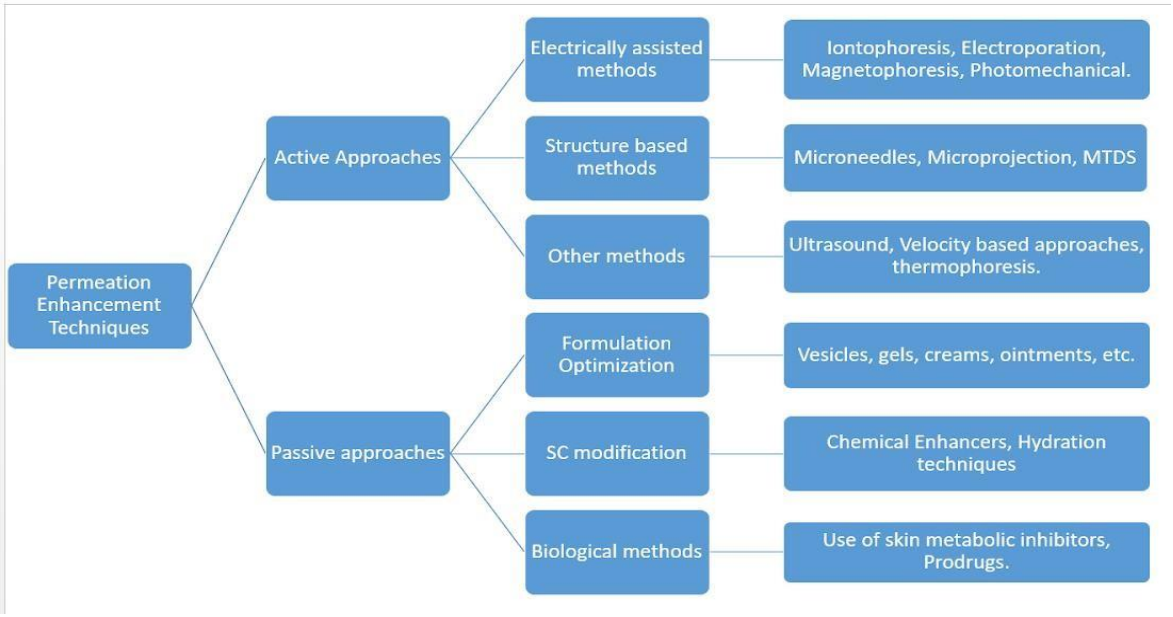
TDDS provides a convenient route for drug delivery, yet it holds several challenges. High cost, molecular size restrictions, slow drug release and low permeability limits are the major limitations. To overcome the low permeability challenge and increase the bioavailability of the drug administered through the transdermal route, penetration enhancers are used widely. Penetration Enhancers also called Permeation enhancers, act to facilitate the permeation through the skin barrier, SC.

The ideal properties of the penetration enhancers include[5,17]:

- It should be able to produce the desired permeation action without causing any pharmacological effect.
- Should be non-reactive, non-toxic, and non-allergenic.
- Compatible and should hold reversible action.
- Should not cause any loss of endogenous substances during drug delivery/storage.

Passive methods and Active methods, also called physical penetration enhancers are the broad classes under PE. The passive delivery method involves the use of Chemical Enhancers (CE), prodrugs, vesicles, polymer nanoparticles, and inclusion complexes like approaches for bringing the action.[18] CE acts by two pathways, one is through bringing fluidization of the lipid lamellae, other is extracting lipids from the skin which paves a way for the drugs to enter. Although skin irritation, followed by a lack of permeability of the chemical enhancers themselves shows huge restrictions on its applications. Active Method employs the use of different forms of energies to increase the permeation. Examples are Sonophoresis, Iontophoresis, Thermal Ablation, Magnetophoresis, Photomechanical waves, lasers, thermophoresis, and many other such methods hold their own drawbacks and advantages.[18] Below figure shows the classification of penetration enhancement techniques.[18,19]

Fig. 2. Classification of Permeation Enhancement Techniques



4.1 ltrasound based approach - Sonophoresis

Sonophoresis, also called Phonophoresis, was discovered as another novel advanced technique to cross the skin protection barrier reversibly using ultrasonic waves. Ultrasound waves (USw) hold a frequency range above that of human hearing, which is above 20KHz. The technique came into existence in the 1950s with the aid of non- invasive ultrasound therapies for neurological disorders. Further, scientists Fellinger and Schmidt successfully attempted to apply hydrocortisone ointment to treat polyarthritis of digital joints using high force sonophoresis (HFS - 0.7 to 16 MHz) as physical force. In the 1980s, McElnay and Benson used the same technique for various therapeutic applications. HFS acted majorly for topical drug therapy with a maximum of 10 times enhanced permeability. Nevertheless, it was just little milestones covered till the 90s. After the 90s, the low- frequency ultrasound (20 to 100 kHz) was invented and proven to show a thousand times more permeability for transdermal drug delivery by Mitragotri scientist.[20,21]

It consists of an ultrasound generator, a transducer to convert one form of energy to another, having a crystal of piezo-electric material.[20] Sonophoresis is associated with 2 broad mechanisms namely, (1) thermal effect and
(2) Acoustic cavitation for enhancing drug delivery through the SC. These mechanisms are based upon hypotheses, and the exact mechanism is not known yet. The thermal effect is based upon the physics of energy absorption and scattering effect in the human body. When the USw falls onto the skin, it is absorbed into the tissues which induce body temperature to rise. And this local temperature increase is dependent on factors such as frequency of waves, area of the beam, duration of

exposure, and heat removal rate, all of which when maintained aptly produce an increase in skin permeability coefficient.[21]

The second mechanism which USw utilizes is Acoustic Cavitation. Acoustic Cavitation can be defined as anything which under the influence of tensile force creates gas bubbles in fluids, or causes already present bubbles to grow, nucleate or just split into parts. It is divided into (1) Stable Cavitation and (2) Inertial Cavitation.[21,22]

Stable Cavitation is defined as the process whereby continuous oscillations of the bubbles occur at wide ranges of pressures without any collapse. The oscillations give rise to microstreaming, a process that is defined by the

unidirectional flow of fluid across membranes because of high-velocity gradients and shear stress. When the bubbles start growing in size as of uneven gas flow, it is known as rectified diffusion. Inertial Cavitation, also called Transient Cavitation is the process whereby uncontrolled and quick growth of bubbles happens at different pressure cycles and may further collapse to form shock waves or form microjets. Both impacts may lead to structural alteration or may induce lipid bilayer disruption for facilitating the drug infusion, respectively. It was observed by Mitragotri, that cavitation occurs widely, within the skin that is in the cavities in the stratum corneum for HFS. The hypothesis it generated was that the pulsating bubbles can disrupt the lipids layers of SC to enhance permeation. Though for low-frequency sonophoresis (LFS), it was concluded that inertial cavitation was a significant method for enhanced permeability, and cavitation outside the skin was the prime mechanism.[21-23]

The sonophoresis approach to facilitate drug penetration to the skin tries to ensure maximum permeability even when combined with different other approaches. Yet it held vital side effects which were observed in the year 1998 by Singer. LFS had caused minor skin reactions whereas HFS resulted in second-degree burns.[21] For future advancements and regular usage, these limitations need to be solved.

4.2 Electrically Assisted techniques

4.2.1 Iontophoresis

Iontophoresis is a process of using electric currents (generally between 0.1–1.0 mA/cm^2) to drive ions across the membrane. The electric current causes ions to move towards the anode and cathode. When the membrane involved is skin, the process is known as Transdermal Iontophoresis.[16,24] This method came into existence by the scientist Pivati in 1747 which was further advanced by Galvani and Vota in the 18th century by stating that electricity can produce dislocation of metal ions and this movement of the ions holds the capability to produce electricity. The term Iontotherapy was then introduced in the 20th century by Leduc who proved that electric current could drive molecules across the skin by conducting experiments on rabbits with strychnine and cyanide ions.[21][24][25]

Transdermal Iontophoresis involves mainly the use of electromigration and electroosmosis or a combination of the methods as the main mechanism for facilitating the transport of ions through the skin. Electrophoresis acts for charged drugs majorly whereas the weakly charged and neutral drugs are facilitated by electroosmosis.[9] Usually, a modified Franz diffusion system is used with an additional change for iontophoretic electrodes.[26]

Electrorepulsion is the principle method that is used under Iontophoresis. To understand this phenomenon, we need to get acquainted with the terminology, active electrode and return electrode. The Active Electrode consists of the same charge as the active therapeutic agent whereas the Return Electrode is the one that contains the opposite charge agents in it. Electrorepulsion, also known as Electromigration is the process wherein the active electrode and return electrode, both when influenced by the electric current, releases the same charged ions towards the skin and attracts the opposite charged endogenous ions towards them. For example, an anode bearing a positive charge will be surrounded by a positive drug/ion (D^+) dissolved in electrolyte solution whereas a cathode with a negative charge will be surrounded by the negative buffer ions in case of Anodal Iontophoresis. As the anode would release cationic drug, as of repulsion effect, the cathode will attract cations, both being placed at different places in the body, and ultimately, would cause an increase in flux, hence drug absorption. The cathodal Iontophoresis is the same just here anions are involved.[21][24][25]

At physiological pH, the skin is negatively charged, and thereby it favors Anodal Iontophoresis. This selectivity towards the cations results in convective solvent flow from anode to cathode leading to the second electrotransport mechanism - Electroosmosis (EO). EO, driven by voltage difference, is then used to transport neutral molecules from the anode and gain endogenous neutral ions at the cathode. The Cathodal Iontophoresis is opposed by the convective solvent flow. The influence of EO is dependent on size of ion as of which, the large size anion from the anode can be delivered more efficiently from the anode rather than the cathode. This is called Reverse Iontophoresis or Wrong-way Iontophoresis.[21][24][25][27]

As it is one of the electrically assisted methods, drugs that are hydrophilic, charged & are poor candidates for passive delivery are majorly optimized for this method. The transdermal drug delivery by Iontophoresis is dependent on various factors like physicochemical properties of the compound, drug formulation (buffers used, pH, viscosity, presence of other ions), the nature of the applied electrical cycle, type of electrode, biological variations, skin temperature and duration of iontophoresis. The major disadvantages associated with the following method remain membrane selectivity, pain and skin irritation which limits maximum drug delivery at a fast rate.[21,25,26]

4.2.2 Electroporation

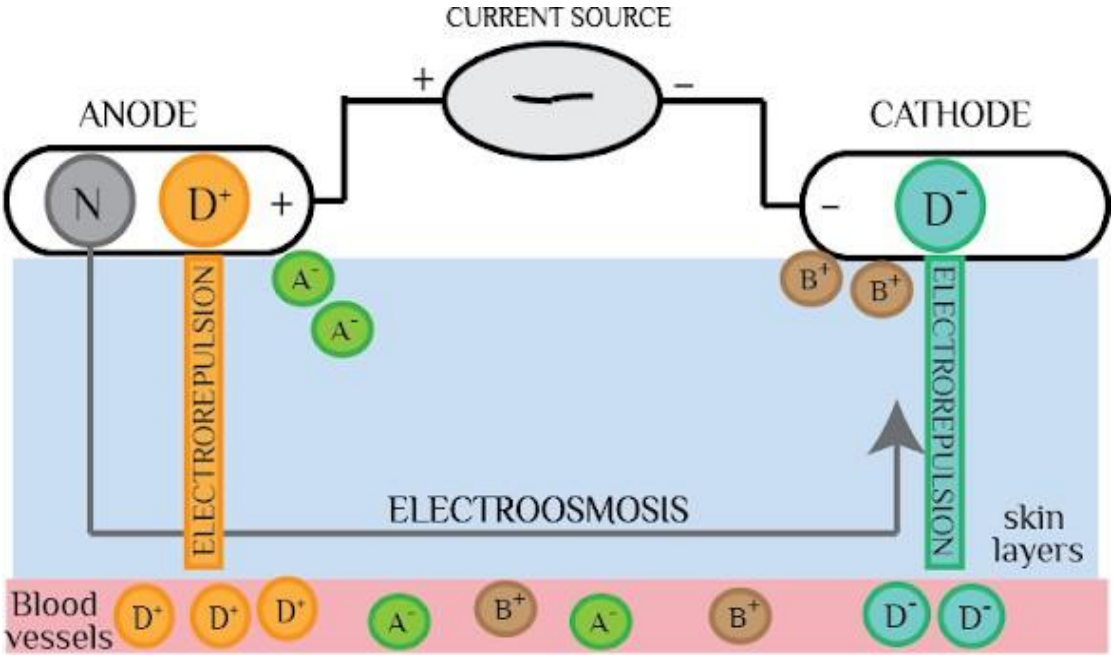


Fig.3. Schematic representation of Iontophoretic drug delivery.

The era of Electroporation was dated to begin in 1754 when its first application came into existence in food sciences by killing the presence of microbes. Followed by 1982, biomedical fields saw its use through the reversible fusion of two cells & insertion of genes through electroporation by Zimmermann & Neumann. However, its transdermal application was studied in 1993 by Prausnitz.[28]

Electro permeabilization refers to the electro-pulsation of the cell membrane above the given threshold which induces cellular modification of the membrane by temporary disruption and formation of pores. The transport of the molecules & ions occurs through the pores which are short-lived. This phenomenon is applied in electroporation where the electric impulse (>100 kV/cm) applied lasts for milliseconds to microseconds, generating aqueous nanosized pores (20 to 200 nm) in the SC thus facilitating the transfer. The efficacy of the technique is generally dependent on the duration, wavelength & number of the impulses produced; however, the formulation parameters seemingly affect it to a considerable extent with respect to the pH, the molecular size of the compound, and the presence of polymers, etc.[29,30,31]

When focusing on the mechanism we reflect on the physical as well as kinetic occurrences in the lipid layer. Physical Mechanism involves:

1) Electroporation of appendageal ducts shows a decrease in the resistance which is inversely proportional to voltage & allows passage of molecules.[21]

2) Formation of intensity-dependent sized pores which can be either numerous small pores with limited permeability or LTRs (local transport regions). The characteristic LTRs allow molecules passage more efficiently and are formed by high voltages due to: 1) Random fluctuations in the lipid

membranes between corneocytes or 2) At previously electroporated sites by high voltages or small voltages.

3) The in-vivo studies mention the LDRS (Localised Dissipation Regions) that are formed around LTRs due to thermal heat generation during the process & it mediates transport indirectly by delaying resealing of the pore with centralised heating, rupture of membrane & increasing passage entry time.[21,32]

Kinetic mechanism estimates the contribution of the following mechanism:

1) Electrophoresis: The movement is facilitated by the current applied and allows the molecule to pass.

2) Molecular diffusion: Diffusion is enhanced with the aid of the voltage however lasts till the duration of the pulse only, the aftermath diffusion occurs mainly due to reverse electrode polarity, neutral molecules, and ejection ofa drug after the pulse.

3) Electro-osmosis: The role of electro-osmosis is limited owing to a time period of seconds. [21][30][33]

Electroporation is generally applied as a reversible/irreversible method. Within reversible mode that involves the application of one volt for 400ns, the resealing of the pores takes place. However, in irreversible mode, the resealing is faltered. This may be a potential drawback for the process which leads to disruption of the skin membrane, mostly observed in the LTRs. Alongside the pain can also be experienced for an extended duration. Some studies also predict the possibility of edema and erythema development. Though one of the reliable techniques, the parameters of physical pain & corresponding alteration of the skin should always be considered while its application.[21][30][34]

4.2.3 Photomechanical Waves

Photomechanical waves (PW) were one of the modern aid techniques deduced to resolve the permeation of drugs by a physical method more effectively. Their occurrence came into the picture after the development of Q-switched Laser (1964), & further its application was boosted after its discovery by Lee in 1996 wherein the studies concluded its action in transport. [34]

PWs are referred to as pressure waves and are generally produced by LASER (Light Amplification by Stimulated Emission of Radiation), a photogenic device that produces unipolar, broadband optical amplitudes with reference to stimulated radiation. PWs' focus on compression force & thereby negative pressure occurring culminates which exist in phonophoresis, ultrasound, etc. PWs are generated for nanoseconds to microseconds with the pressure of about (1000-3000 Pa) as compression force & effortlessly break the surface of the cell membrane. Laser PWs are predicted to be produced by the following mechanism: Ablation (degeneration of the target molecule into smaller parts), optical breakdown & thermoelastic generation (heating of absorbing medium). Achieving enhancement or preferred intensity of activity is estimated to be primarily the effect of the laser-generated modulations with regards to wavelength, pulse, duration, etc., and thereby should be analysed before application. [34-37]

The proposed studies by Massachusetts claim diffusion according to the concentration gradient to be a reliable mechanism of transport. PWs are preferred to be accompanied by a solution medium that allows conduction on the SC. When applied on the SC, they modulate the skin barrier by the expansion of lacunar space and formation of pores which is facilitated more actively with aquaporins, due to their dimension. The transmission of waves causes surface heating in four stages involving heating, coagulation, drying, and vaporization resulting in microchannels. Alteration of the membrane opens various routes for diffusion to occur until the membrane recovers. For further enhancement, the process can be aided with the chemical penetration enhancers like Sodium Lauryl Sulfate (SLS). [36-38]

A single PWS sufficiently permeabilizes the membrane enough, however continuous pulses for increased intensity may cause effects: Sensation of pain for a short time when the depth reaches more than 200µm along with irreversible cell damage and resultant leakage of its contents. With respect to increasing the depth of penetration, we can allow pretreatment by the rise in temperature of skin which causes diffusivity, or use of SLSas mentioned earlier. Photomechanical waves have limited shortcomings that may arise which include better transport of nanoparticle diffusion & should be coupled with other techniques for better efficacy.[33][36-38]

4.3 Magnetophoresis

The allied use of magnetic fields recently gained profound application in the biological drug delivery

field. For several years, they have been used to fasten the thrombosis process & increase wound healing. An experiment conducted by Murthy on lidocaine permeation proved the successful application of magnetic fields for drug passage in the SC.[21] Every molecule has its own magnetic properties that actively respond in the presence of magnetic field: Diamagnetism causes the particles to move in a direction opposite to the applied magnetic field, paramagnetism allows magnetic waves to pass through them, ferromagnetism through which the molecules attract each other, however, each of them allows the molecules to align accordingly under the field.[21,39]

Magnetophoresis is an application of the magnetic property of the molecule in delivery under the influence of magnetic fields. When a magnetic field of 5 to 300 mT is applied the nanoparticles get aligned and move across the membrane which is dependent on the increase in the magnetic flux. Experiments suggest a number of theorized mechanisms however, the most adopted theory insists on magnetokinesis. It is usually observed for diamagnetic molecules that move against the direction of the field and thus may diffuse through the membrane. Magnetokinesis occurs as Magnetorepulsion & Magneto-hydrokinesis. For a clearer perspective of the perceived mechanism, the behaviour of water molecules under the magnetic field is observed. When suspended under the field, water provides a diamagnetic response by deriving itself away from the field. This property of water explains two parameters: 1) Diamagnetic molecules like water will also diffuse through the SC similarly by repulsion (Magnetorepulsion) 2) When water is used as a solubilizing medium, it will enhance the passage as a diamagnetic carrier through the property (Magnetohydrokinesis). Though this can be made more advantageous by either increasing the concentration of the drug or the field strength. Along with this, the magnetic field also improves the partition coefficient of drugs in the octanol phase & may be deduced to allow it to move through the lipophilic layer of skin. Magentophoresis as a technique can be more reliable due to the delivery of drug without damaging the skin structure, however, the drawback for this would include application limited to diamagnetic molecules, dependability on field strength resulting in a weak activity in some cases.[37,39,40]

4.4 Other methods

4.4.1. Structure-based Physical techniques: These involve Microneedles, Microscissuining, Metered Dose Transdermal Systems (MDTS) & Micro-projection approaches. All the methods consist of structural changes in the conventional patches used for transdermal drug delivery.[21,41] Microneedles is an invasive technique that on insertion damages SC or creates pores leading to a shorter path for drug delivery. The MNs may involve drug coating or they may not, depending on the approach used. The MN strategies being applied are: 1) Poke and Patch: Here the skin is first perforated via microneedle, disrupting the skin layers, and then conventional patches, gels, or ointments are applied. 2) Coat & Poke: This strategy involves coating the surface of MN to be utilized and then inserting it into the deep layers of skin for direct delivery 3) Poke & Release: Dissolving MN arrays is a significant change in the poke & release strategy wherein MN are made up of water soluble and biodegradable materials. The MNs is kept inserted until it dissolves completely for efficient delivery. This strategy holds the advantage of the ability to control the dissolution rate. 4) Poke and Flow: This is similar to conventional hypodermic needles with just the change in the size of the needles. The drug solution is filled in the hollow microneedle and is allowed to release after perforation in the skin.[42]

Microprojection incorporates a titanium array that paves a superficial pathway through the skin layers. The titanium disk is often coated with the medicinal agent and it penetrates the dead cell layers of SC creating a microchannel to allow the transport of drug molecules.[16,43]

MDTS involves topical aerosol-like systems that on spraying form a film enhances patient compliance and acceptability. It usually consists of drugs dissolved completely in the vehicle, polymers, and permeation enhancers. The method operates with the mechanism of fluidizing the lipid layers in the SC to increase drug diffusivity.[41]

Skin abrasion, also called microscissuining, employs sharp metal granules to erode the skin's impermeable layers and then creates microchannels to facilitate drug infusion.[43]

4.4.2 Needle Less Injections: Using higher velocities for delivering the drug molecules, is another way to enhance skin permeation. It consists of various designs involving Jet syringe, Mini-ject, Implaject, Cross Jet, and so

on. All of the designs employ supersonic speeds to transport solid or liquids. It forces the compressed gasout, usually helium, via a nozzle resulting in even the release of entrapped drug particles. It has found application in delivering testosterone, lidocaine hydrochloride, and various macromolecules like calcitonin, though, the drawback remains its short duration and possible contamination of devices with interstitial fluids.
[16][43][44]

4.4.3 Thermophoresis: Thermophoresis, also called thermal ablation, is the method wherein the SC is disrupted by providing heat through the microchannels, without affecting the deeper tissues. Efficient drug delivery can be achieved by passing heat for either a long duration with a temperature ≤ 100 °C or a short duration with higher temperatures ≥ 100°C. Methods like Laser, Radiofrequency, chemical heating, and thermoporation are utilized to induce thermophoresis. The biggest advantage of this method is that it delivers small as well as macromolecules and doesn't cause major patient-related problems unless the deeper tissues get affected. It is used to enhance the delivery of various drugs including biomacromolecules. [45,46]

5. Marketed applications

Few of the transdermal technologies which are commercially available, are listed below:[21]

Name of Product	Drug/ Component	Technology used	Company
Ionsys®	Fentanyl	Iontophoresis	Alza Corporation
U-Strip™	Insulin	Ultrasound	Dermisonics, Inc.
Intanza®	Inactivated Virus	Microporation	Sanofi- Aventis
IontoPatch®	dexamethasone	Iontophoresis	Travanti Pharma Inc.
Epiture™ Easytouch	Lidocaine	Laser ablation	Norwood Abbey
Biojector®		Jet injector	BioJect (USA)

Table 1. Marketed applications

6.CONCLUSION:

Increased patient compliance, avoidance of first-pass metabolism, and fast onset of action, all of these remarkable advantages contribute to the demand for TDDS. Though to overcome the skin barrier properties withthe most safety and efficacy remains a challenge that the penetration enhances tends to solve. The physical penetration enhancement techniques tend to facilitate the absorption rate to a greater extent, are completely non-reactive, and doesn't hold any pharmacological effect in the body. Nevertheless, these enhancers yet have the capability to produce toxic and irritant effects.

In the past years, many refinements and upgrades were made on the enhancers yet we lack a device encompassing all the guidelines. The physical techniques including Iontophoresis, Ultrasound, Magnetophoresis, and other similar methods are currently being applied for only few drugs due to certain limitations of every method. Ways to increase the absorption of other drugs along with this active effect where there is cost management along with least side effects yet need to be looked upon.

The research in the further years should focus on the ways with which we can achieve maximum desired activity for TDDS by the application of physical penetration enhancers. Combining Physical penetration enhancers with vesicular enhancers, chemical enhancers, and nanocarrier systems, also developing new methods of physical enhancers which can overcome the existing clinical gaps must be studied and addressed. This method involves great use of technology and the new method thereby can be devised in a way keeping effectiveness, safety, user-friendliness, costs, & portability in mind.

CONFLICT OF INTEREST

None

REFERENCES:

1. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7[4]:438–70.
2. Bala P, Jathar S, Kale S, Pal K. Transdermal Drug Delivery System [TDDS] - A Multifaceted Approach For Drug Delivery. J Pharm Res

[Internet]. 2014;8[12]:1805–35.
3. Hafeez A, Singh J, Maurya A, Rana L, Jain U. Recent Advances in Transdermal Drug Delivery System [TDDS]: An Overview. J Sci Innov Res [Internet]. 2013;2[3]:733–44.
4. Prausnitz MR, Langer R. Transdermal Drug Delivery. Nat Biotechnol. 2009;26[11]:1261–8.
5. Nagdev SA, Agrawal O, Usman MRM. Transdermal Drug Delivery System: An Overview. Res J Pharm Technol. 2022;15[3]:1371–7.
6. Riviere JE, Heit MC. Electrically-assisted transdermal drug delivery. Vol. 14, Pharmaceutical Research. 1997. p. 687–97.
7. Yousef H, Alhajj M, Sharma S. Anatomy, Skin [Integument], Epidermis. [Updated 2021 Nov 19]. In: StatPearls [Internet]. Treasure Island [FL]: StatPearls Publishing; 2022 Jan.
8. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomater Res. 2021;25[1]:1–15.
9. Rodríguez Cruz, Isabel & Domínguez-Delgado, Clara & Escobar-Chávez, José & López-Cervantes, Miriam & Díaz-Torres, Roberto. Physical penetration enhancers: An overview. Current Technologies to Increase the Transdermal Delivery Of Drugs. 2016;:3–34.
10. Kim JY, Dao H. Physiology, Integument. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island [FL]: StatPearls Publishing; 2022 Jan.
11. Sajid Ali, Maryam Shabbir, Nabeel Shahid. The Structure of Skin and Transdermal Drug Delivery System- A Review. Research J. Pharm. and Tech. 8[2]: Feb. 2015; Page 103-109.
12. Holmgaard R, Nielsen JB. Dermal absorption of pesticides – evaluation of variability and prevention. Danish Environ Prot Agency [Internet]. 2009;[124]:116.
13. Ruela ALM, Perissinato AG, Lino ME de S, Mudrik PS, Pereira GR. Evaluation of skin absorption of drugs from topical and transdermal formulations. Brazilian J Pharm Sci. 2016;52[3]:527–44.
14. Singh I, Morris A. Performance of transdermal therapeutic systems: Effects of biological factors. Int JPharm Investig. 2011;1[1]:4.
15. Shabbir M, Ali S, Nabeel Shahid M, Rehman K, Amin M, Raza M. Formulation Considerations And Factors Affecting Transdermal Drug Delivery System-A Review. Int J Pharm Integr Life Sci. 2014;2[October 2016]:20–35.
16. Akhtar N, Singh V, Yusuf M, Khan RA. Non-invasive drug delivery technology: Development and current status of transdermal drug delivery devices, techniques and biomedical applications. Biomed Tech. 2020;65[3]:243–72.
17. Kharat, R., & Bathe, R. S. [2016]. A Comprehensive Review on: Transdermal drug delivery systems. International Journal of Biomedical and Advance Research, 7[4], 147.
18. Karande P, Mitragotri S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochim Biophys Acta - Biomembr [Internet]. 2009;1788[11]:2362–73.
19. Zorec B, Préat V, Miklavčič D, Pavšelj N. Active enhancement methods for intra- and transdermal drug delivery: A review. Zdr Vestn. 2013;82[5].
20. Bhowmick M, Tamizharasi S, Rathi J, Sonkar S, Shivakumar T. Electrically Assisted Transdermal Therapeutic Devices-An Overview. Res J Pharm Dos Forms Technol. 2010;2[4]:264–9.
21. Dragicevic N, Maibach HI. Percutaneous penetration enhancers physical methods in penetration enhancement. Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement. 2017. 1–508 p.
22. Oberli MA, Schoellhammer CM, Langer R, Blankschtein D. Ultrasound-enhanced transdermal delivery: recent advances and future challenges. Ther Deliv. 2014 Jul;5[7]:843-57.
23. Be P, Hart D, Langer R, Blankschtein D, Park D, Ryu H, et al. 19 selected items - PubMed - NCBI Results : 19 Ultrasound -mediated transdermal drug delivery : mechanisms , scope , and emerging trends . experimental study . ultrasound and sodium lauryl sulfate . Perspectives on transdermal ultrasound mediated drug del. 2012;9[4]:8–10.
24. Rawat S, Vengurlekar S, Rakesh B, Jain S, Srikarti G. Transdermal delivery by iontophoresis. Indian JPharm Sci. 2008;70[1]:5–10.
25. Dhote V, Bhatnagar P, Mishra PK, Mahajan SC, Mishra DK. Iontophoresis: A potential emergence of a transdermal drug delivery system. Sci Pharm. 2012;80[1]:1–28.
26. Ita K. Transdermal iontophoretic drug delivery: Advances and challenges. J Drug Target. 2016;24[5]:386–91.
27. Guy RH, Kalia YN, Delgado-Charro MB, Merino V, López A, Marro D. Iontophoresis: Electrorepulsion and electroosmosis. J Control Release. 2000;64[1–3]:129–32.
28. Meijerink MR, Scheffer HJ, Naranayan G. Irreversible electroporation in clinical practice. Irreversible Electroporation Clin Pract. 2017;[April 2020]:1–285.
29. Weaver JC, Chizmadzhev YA. Theory of electroporation: A review. Bioelectrochemistry Bioenerg.1996;41[2]:135–60.

30. Ita K. Perspectives on transdermal electroporation. Pharmaceutics. 2016;8[1].
31. A. Charoo N, Rahman Z, A. Repka M, N. Murthy S. Electroporation: An Avenue for Transdermal Drug Delivery. Curr Drug Deliv. 2010;7[2]:125–36.
32. Vaughan TE, Weaver JC. Mechanism of Transdermal Drug Delivery by Electroporation. Electrochemother Electrogenether Transdermal Drug Deliv. 2003;37[4]:187–211.
33. Escobar-Chávez JJ, Bonilla-Martínez D, Villegas-González MA, Revilla-Vázquez AL. Electroporation as an efficient physical enhancer for skin drug delivery. J Clin Pharmacol. 2009;49[11]:1262–83
34. Kotnik T, Rems L, Tarek M, Miklavcic D. Membrane Electroporation and Electropermeabilization: Mechanisms and Models. Annu Rev Biophys. 2019;48:63–91.
35. Doukas AG, Kollias N. Transdermal drug delivery with a pressure wave. Adv Drug Deliv Rev.2004;56[5]:559–79.
36. Lin CH, Aljuffali IA, Fang JY. Correction to: Lasers as an approach for promoting drug delivery via skin. Expert Opin Drug Deliv. 2014;11[12]:1979.
37. Wong TW. Electrical, magnetic, photomechanical and cavitational waves to overcome skin barrier for transdermal drug delivery. J Control Release [Internet]. 2014;193:257–69.
38. Doukas AG, Lee S, Hospital MG. Photomechanical drug delivery. 2000;3916.
39. Donnelly RF, Singh TRR. Novel Delivery Systems for Transdermal and Intradermal Drug Delivery. Novel Delivery Systems for Transdermal and Intradermal Drug Delivery. 2015. 1–268 p.
40. Murthy SN, Sammeta SM, Bowers C. Magnetophoresis for enhancing transdermal drug delivery: Mechanistic studies and patch design. J Control Release [Internet]. 2010;148[2]:197–203.
41. Bala P, Jathar S, Kale S, Pal K. Transdermal Drug Delivery System [TDDS] - A Multifaceted Approach For Drug Delivery. J Pharm Res [Internet]. 2014;8[12]:1805–35.
42. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7[4]:438–70.
43. Nagdev SA, Agrawal O, Usman MRM. Transdermal Drug Delivery System: An Overview. Res J Pharm Technol. 2022;15[3]:1371–7.
44. Lokhande R, Gedam B, Shah Y, Tandon M, Bansod PY. Rationale for near total thyroidectomy in patients with nodular goitre. Int J Biomed Adv Res IJBAR Int J Biomed Adv Res J [Internet]. 2015;6[605]:427–30. Available from: www.ssjournals.com
45. Parhi R, Mandru A. Enhancement of skin permeability with thermal ablation techniques: concept to commercial products. Drug Deliv Transl Res. 2021;11[3]:817–41.
46. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomater Res. 2021;25[1]:1–15.