AI ASSISTED ELECTROPORATION FOR EFFECTIVE TRANSDERMAL DRUG DELIVERY SYSTEMS; CHALLENGES AND OPPORTUNITIES: AN OUTLOOK

Er. Sumanpreet Kaur,

Assistant Professor, College of Engineering & Management, Neighbourhood Campus Rampura Phul,

Punjabi University, Patiala

Email: sumankaurpreet@yahoo.com

ABSTRACT:

An AI-assisted electrical device for transdermal drug delivery can improve drug absorption by using electricity to enhance delivery across the skin. This technology can be used to deliver various drugs, including those that are poorly absorbed through the skin, with greater efficiency and in a more targeted manner. Transdermal delivery represents an attractive alternative to oral delivery of drugs and is poised to provide an alternative to hypodermic injection too. For thousands of years, people have placed substances on the skin for therapeutic effects and, in the modern era, a variety of topical formulations have been developed to treat local indications. The first trans-dermal system for systemic delivery a three-day patch that delivers scopolamine to treat motion sickness was approved for use in the United States. Iontophoretic delivery generally improves penetration deep into the stratum corneum, the outer skin layer. The electric current increases the drug permeability of the skin, which is required for effective drug delivery.

Keywords: Artificial Intelligence, Iontophoretic, Transdermal, Medical Device.

INTRODUCTORY NOTES:

Drug delivery system (DDS) is a generic term for a series of physicochemical technologies that can control delivery and release of pharmacologically active substances into cells, tissues and organs, such that these active substances could exert optimal effects **[1].** DDS covers the routes of administration and drug formulations that efficiently deliver the drug to maximize therapeutic efficacy while minimizing any side effect. Depending on the delivery route, there are many types of administration modalities, such as oral administration, trans-dermal administration, lung inhalation, mucosal administration, and intravenous injection. Among them, the transdermal drug delivery system (TDDS) represents an attractive approach. [**2]** Transdermal drug delivery system (TDDS) is a widely accepted means of drug delivery and transdermal patches are devised to treat various diseases. TDDS are extended release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption. These therapeutic advantages reflect the higher marketing potential of TDDS. Most of the drug molecules penetrate through the skin through intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vital as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Chemical penetration enhancers act as

accelerators or sorption promoters and can enhance drug flux. Sulfoxides- dimethyl sulfoxide, azone, pyrrolidines- N-methyl-2-pyrrolidone, fatty acids lauric acid, capric acid, myristic acid, oleic acid, terpenes and essential oils- menthol, eugenol, oxazolidinones-4-decyloxazolidin-2-one, surfactants - tween 80, span 20 are the various classes of penetration enhancers used in TDDS.[**3**] The transdermal drug delivery system is a technique that provides drug absorption via the skin. The system has many advantages over conventional administration routes such as intravenous or oral administration for systemic and local drug delivery with simple administration. It is available outside medical institutions, which decreases the burden on patients caused by intravenous administration and decreases loss from the first pass effect of the liver, delivering therapeutic drugs at a controlled ratio. Overcoming the skin barrier, including the stratum corneum and epidermal layer, is necessary to develop transdermal drug formulations. Although chemical and physical enhancers have been developed, they need high doses or high potency to exert efficiency, which induces irritation, causes damage, and reduces the skin barrier function. Consequently, a nanoparticle delivery system is gaining increased attention as a transdermal drug delivery carrier. [**4**]

Fig no1: Electrical Device assisted drug delivery system [5]

The most common methods of Transdermal drug delivery systems are as follows.

- **Iontophoresis:**

This method uses a small electric current to push charged drug molecules through the skin.

- **Electroosmosis:**

This method uses an electric field to create a flow of water, which can carry drug molecules across the skin.

- **Electroporation:**

This method uses short, high-voltage pulses to create temporary pores in the skin, allowing larger drug molecules to pass through.

- **AI integration:**

AI can be used to optimize the device's settings (e.g., current, voltage, pulse duration) based on individual patient needs, drug characteristics, and real-time monitoring of skin response.

Advantages of AI-assisted electrical devices are now-a-days very common in use.

- **Enhanced drug absorption:**

These devices can overcome the natural barriers of the skin, improving drug penetration and bioavailability.

- **Targeted drug delivery:**

AI can help to optimize drug delivery to specific areas of the body or within the skin.

- **Personalized therapy:**

AI can be used to tailor drug delivery to individual patient needs, maximizing therapeutic effectiveness and minimizing side effects.

- **Controlled and on-demand drug release:**

AI-powered systems can enable precise control over drug release timing and dosage, leading to more effective therapy.

Examples of AI-assisted electrical devices:

- **Wearable transdermal devices:**

These devices can be attached to the skin and deliver drugs on demand, controlled by AI algorithms.

- **Microchip-based drug delivery systems:**

These systems can be implanted or placed on the skin and release drugs in a controlled manner, with AI monitoring and adjusting drug release based on patient needs.

- **Smart patches:**

These patches can monitor skin parameters, such as temperature and moisture content, and adjust drug release accordingly.

Research and development:

- Ongoing research focuses on improving the design and functionality of these devices, as well as exploring new applications for AI-assisted transdermal drug delivery.
- Researchers are also investigating the use of AI to predict drug release profiles, optimize drug formulations, and develop new methods for delivering drugs through the skin.

Potential applications:

- **Pain management:**

AI-assisted transdermal drug delivery can be used to deliver pain-relieving medications directly to the affected area.

- **Diabetes management:**

These devices can be used to deliver insulin and other medications to help control blood sugar levels.

- **Wound healing:**

AI-powered systems can be used to deliver medications that promote healing and reduce infection.

- **Vaccine delivery:**

Transdermal drug delivery systems can be used to deliver vaccines, providing a convenient and painless alternative to traditional injections.

- **Treatment of skin conditions:**

AI-assisted devices can be used to deliver medications that target specific skin conditions, such as acne or eczema.

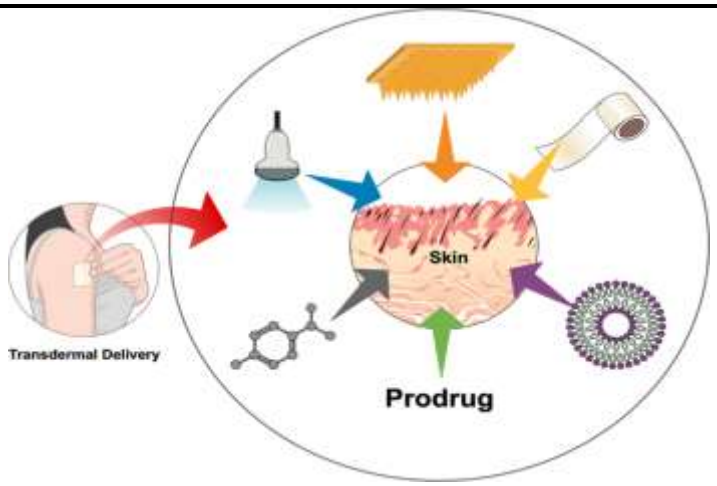

Fig no. 1: AI assisted Transdermal drug delivery systems [7]

Transdermal drug delivery system is the desirable drug delivery system to control and sustain the drug release via, skin. Control release drug system limits the release of drug and improve the efficiency of the drug, which is relatively fast release system containing the same drug. Now a days many drugs are administrated orally, but due to the first pass metabolism in increases the dose and decreases the effects of drug. So, transdermal drug delivery system is design to improve the efficiency and bioavailability of the drug and deceases the number of doses. Transdermal drug delivery system is administrated by skin and drug is delivered directly into systemic circulation maintaining continuous efficacy. These systems provide drug systemically at a predictable rate and maintain the rate for extended period of time thus eliminating numerous problems associated with oral products such as reduced bioavailability, enhanced first pass hepatic metabolism, relatively short residence time, dose dumping and dosing inflexibility.3 Physicochemical point of view, an ideal transdermal drug candidate has to meet a number of requirements such as drug is highly lipophilic in nature, melting point of the drug is above 150, molecular weight is above 500 Dalton, log p values 1-5, no local toxicity and irritation to skin.**[6]**Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action1. Tablets and injections have been the traditional way to take medications; new options are becoming increasingly popular. One highly successful alternative delivery method is the transdermal. Skin of an average adult body covers a surface of approximately 2 m2 and receives about one-third of the blood circulating through the body. The deliver a drug into the body through transdermal layer of skin, it is necessary to understand about the skin.**[7]**

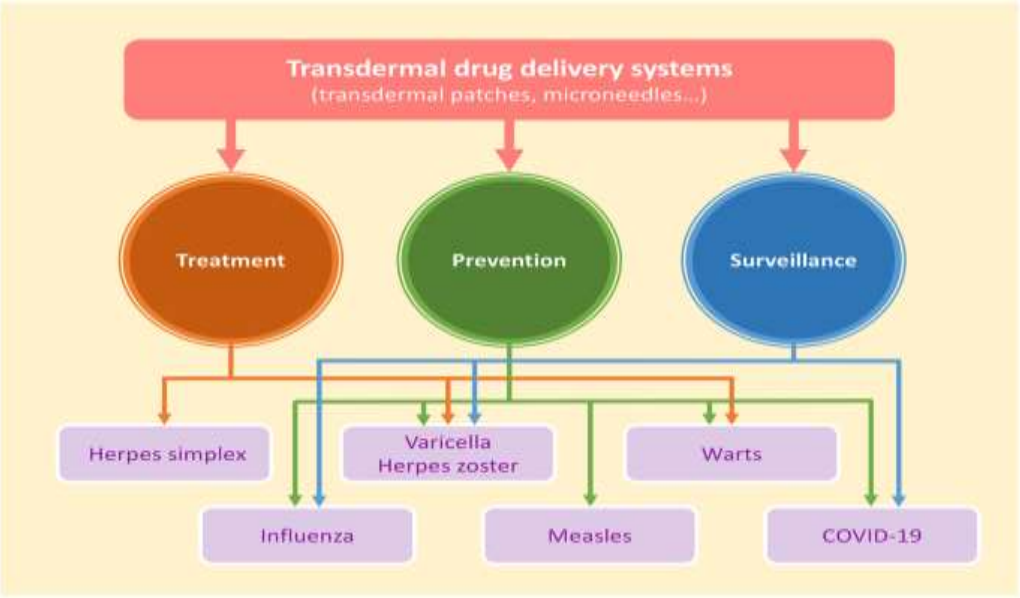

Fig no 3: Transdermal drug delivery system for fighting common viral infectious diseases[8]

The market price of TDDS products is rapidly expanding. More than 35 items have now been authorized for sale in the United States, and roughly 16 active substances have been approved for usage as a TDDS globally. It is a drug delivery system that has a bright future. It helps in reducing use of syringes for administering a wide range of drugs, but the price is an essential aspect to consider because developing countries like India have the world's second-largest population, but TDDS is a secret part of treatment used for the general population due to rising costs. This review article on transdermal drug delivery systems (TDDS) contains information on the transdermal drug delivery system, Advanced development and the evaluation procedure. **[9]** Transdermal drug delivery systems are topically administered medicaments in the form of patches or semisolids that deliver drug for systemic effects at a predetermined and controlled rate. Drugs which undergoes extensive first pass metabolism can be formulate as Transdermal drug delivery system. Drugs which are unstable in gastro intestinal environment can be formulate as Transdermal drug delivery system. If drug is having serious adverse effects, if action is required locally. **[10]**

Table no1: Marketed Products of Transdermal Patches. [12], [13]

Brand name	Drug	Manufacturing name	Uses
Nicotinell^{R}	Nicotine	Novartis	Pharmacological smoking cessesion.
NuPach 100	Diclofenacdiet hylamine	ZydusCadila	Anti-inflammatory
Androderm	Testesterone	TheraTech/ Protocol and Gambie	Hypogonadism in male
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Catapres TTS	Clonidine	Alza/BoehingerIngelheim	Hypertension
Oxytrol^{R}	Oxybutynin	DuchefaFarma B.V.	Over reactive bladder
Xylocaine	Lidocaine	Cerner Multum,Inc	Post herpatic neuralgia pain
maldemar^{R}	Scopolamine	Alza/Norvatis	Motion sickness
Delestrogen	Estradeol	3M Pharmaceutical/Bariex Lab	Menopausal symptoms
Exelon^{R}	Rivasgmine	Manus AkttevaBiopharma LLP	Dementia
Neupro^{R}	Rotigotine	UCB and Schwarz Pharma	Pakinson’s disease
Imitrex	Sumastriptane	Mylan Laboratories Inc	Migraine

Saphris	Asenapine	Schering –Plough	Antipsychotic
Jasmiel	Ethinyl estradiol	Hangzhou Longshine Bio Tech	Contaceptive
Ritalin	Methylphenidate	Mallinckrodt and Kudco	ADHD
Eldepryl	Selegiline	Flavine from Germany	Depression
Kytril	Granisetron	Niksan Pharmaceutical	Chemo induced emesis
Capzasin	Capsaicin	SAE Manufacturing Specialties Corp	Neuropathy pain
Buprenex^{R}	Buprenorphine	Titan Pharmaceuticals	Chronic pain
Actiq^{R}	Fentanyl	Nycomed	Chronic pain

Diseases targeted transdermal drug delivery system.

Alzheimer's disease is a neuropathological disease with symptoms such as language problems, confusion as to place or time, loss of interest in activities, which were previously enjoyed, behavioral changes, and memory loss. Alzheimer's disease and other types of dementia affect almost 46.8 million people globally and are estimated to strike about 131.5 million people in 2050. It has been reported that Alzheimer's is the sixth main cause of mortality. The most used drugs, which are currently approved by the Food, and Drug Administration for Alzheimer's disease are donepezil, rivastigmine, galantamine, memantine, and the combination of donepezil and memantine. However, most of the drugs present various adverse effects. Recently, the transdermal drug delivery route has gained increasing attention as an emerging tool for Alzheimer's disease management. Besides, transdermal drug delivery systems seem to provide hope for the management of various diseases, due to the advantages that they offer in comparison with oral dosage forms. Herein, the current advancements in transdermal studies with potent features to achieve better Alzheimer's disease management are presented. Many researchers have shown that the transdermal systems provide higher efficiency since the first-pass hepatic metabolism effect can be avoided and a prolonged drug release rate can be achieved. In summary, the transdermal administration of Alzheimer's drugs is an interesting and promising topic, which should be further elaborated and studied. **[14]** The study of nanoparticles (NP) as an efficient drug delivery medium has been in the spotlight for the past few decades. Compared to other modes of transdermal drug delivery systems (TDDS), nanoparticles often show superior drug release, deeper drug penetration, and allow for the encapsulation of both hydrophilic and hydrophobic drug molecules. Due to this, there has been significant research into nanoparticles ranging between 50 and 500 nm as an option for TDDS. Having drug delivered across the skin has multiple advantages such as increased patient compliance compared to other painful invasive routes of drug delivery, avoiding the first-pass effect in the liver caused by orally administered drugs, and decreased demand for multiple doses due to long-term controlled release of drugs. Substantial effort and investigation have led to the commercialization of NP and consequent FDA approval (for example: Abraxane for breast cancer treatment). However, the delivery of nanoparticles in effective concentrations to the desired target is limited by multiple biological barriers that prevent foreign materials from entering the body (Wang et al., 2015, Peng et al., 2015). In this chapter will examine the various pathways of NP penetration across the skin barrier, the types of NPs and nanoemulsions being currently investigated, their desired characteristics, and finally present some recent studies with NP in TDDS. Enhanced drug delivery using a combination of iontophoresis and nanoparticle system will also be reviewed. **[15]** From a fundamental perspective, transdermal drug delivery (TDD) has been limited by the skin's tough and lipid rich outer layer known as the stratum corneum (SC) thus rendering the skin

impermeable to most biopharmaceuticals and small molecules, the hydrophobic nature of the skin's outer layer limits the formulations for percutaneous delivery to be creams, gels, ointments and non-invasive transdermal patches. Due to the skin being a versatile and effective biological barrier possessing a heterogeneous anatomy and complex physiology, there is a high variability in the pharmacokinetic properties of substances applied topically. The SC lends itself as the rate-limiting step in the course of cutaneous penetration or transdermal absorption, and several systemic physiologically based models exist for assessing cutaneous absorption and transdermal delivery of xenobiotics from the pharmacokinetic and toxicokinetic aspects. TDD systems are considered to be patient-friendly as they are non-invasive, do not need to be administered by professionals, decrease gastrointestinal (GI) adverse effects and increase patient adherence. Further, since they bypass the metabolic processes that are exhibited by oral administration, bioavailability, efficacy and translocation are improved. This also eliminates the use of invasive, irritating needles that generate medical waste, pose the risk of infection and need to be administered by medically trained professionals. Some of the disadvantages associated with transdermal drug delivery include potential skin sensitization or irritation, discomfort from adhesives, imperfect skin adhesion, cost and selectivity for specific physicochemical drug properties. In order to achieve the desired systemicity with a drug, it is imperative to not only consider SC and drug properties, but also the body site of application and blood flow in the skin by additives and body temperature, in addition to the transdermal patch itself. It is important to note that the dosage is controlled by the active surface of the patch that comes in contact with the skin, which is controlled via the patch surface area; the dose size and frequency should always be determined by a trained medical professional.

Site of application.

The site of application has been demonstrated to affect human skin penetration fluxes. Many parts of the body (trunk and upper arm) appear to have similar fluxes allowing for interchangeable placement of patches to achieve similar plasma concentrations over recommended wear time. Testosterone, nicotine, norelgestromin, oestradiol and clonidine all have evidenced similar drug plasma concentrations, with similar uptake at different skin sites. However, studies have shown that Rivastigmine had demonstrated higher plasma exposure after application to the upper back, chest or upper arm versus the thigh or abdomen, but it is important to follow the advice of trained medical professionals for application to ensure that efficacy is attained by correct dosage and wear.

Effect of drug characteristics.

The properties of a drug that enable good penetration through the SC can be deduced from the equation for steady-state flux. When the cumulative mass of a diffusant, m, passing per unit area through a membrane is plotted, versus time *t*, the graph approaches linearity and the slope yields the steady flux d_m/d_t'

where *D* is the diffusion coefficient, C_0 the constant concentration of drug in donor solution, *K* the partition coefficient of solute between membrane and bathing solution, and *h* the thickness of the membrane. Therefore, for a drug to penetrate well, it should have low molecular mass (high *D*), adequate solubility in oil (high C_o) and a moderately high partition coefficient. This explains why all the drugs formulated into passive patches on the market have the narrow physicochemical and pharmacokinetic properties that they do. The commercial need for any new drug product is fulfilling an unmet medical need at a reasonable cost,that is achieving the required plasma concentration and transdermal delivery rate to be deemed efficacious, with advantages not yet achieved through current drug delivery techniques. There are many drugs that are not suitable to formulate into TDP. If a very

affordable, inexpensive, efficacious orodispersible already exists, or there is no commercial viability (patch is too large, drug cannot penetrate the skin, unacceptable activity, etc.) Predicting individual skin flux of candidate drugs to be used in patches is often defined by physicochemical boundaries as discussed before (moderately lipophilic, log P range from 1 to 5, MW < 500Da and MP < 250°C). Overall, the drugs in a patch have a necessity to be potent enough to be considered active in that form, that is have a therapeutically attainable plasma concentration defined by the rate of delivery from the patch through the skin. This can ultimately be controlled by the patch size, application at the appropriate skin site and incorporation of adjuvant or skin penetration enhancer. The controlled release that avoids fluctuating blood levels (seen with oral dosing) and convenience offered by patches, makes TDP an ideal candidate for drugs with short elimination half-lives. Systemic delivery can be stopped at any time by simply removing the patch**. [16]**

Mitigation Disease Through Transdermal Drug Delivery System.

Transdermal drug delivery system (TDDS) is an appealing alternative to minimize and avoid the limitations allied with oral and parenteral administration of drugs. Later delivery systems, suffer from certain restrictions like Peak and Valley phenomenon i.e. they exhibit fluctuations in plasma drug levels and do not render sustained effect while the TDDS meets the requisitions and provides a proper and prolonged delivery of drug, in a steady-state profile and reduces the prospects of peak-associated side effects, and ensures that the level of the drug is above the minimal therapeutic concentration. Overall, as a form of controlled drug delivery, transdermal patches are extremely commodious, user-friendly and provides the ease of termination, if need arises (e.g. systemic toxicity) with less pain sensation while administrating drug candidates. Transdermal delivery allows the permeation of drugs across the skin and into the systemic circulation thus avoiding the hepatic first-pass effect observed during oral administration and the inconvenience of frequent parenteral administration. However, the penetration of drugs across the skin and their percutaneous delivery are limited by the barrier function of the enormously organized structure of Stratum corneum (SC). As we know that, the skin occupies about 15% of the total body weight of an adult and has a surface area of about 2 m^2. The skin is a multilayered organ composed of many histological layers generally described in terms of tissue layers i.e. the epidermis and the dermis. Epidermis, composed of keratinocyte (95% of cells) which is the principal cell forms a ‘brick and mortar’ structure that has been used to conceptualize the barrier property of skin inclusion melanocytes, langerhans cells and merkel cells (minor components). These cells proliferate and commit daughter cells to terminal differentiation, which ends in the formation of the SC. The corneocytes of hydrated keratin comprise the ‘bricks’, embedded in a ‘mortar’ composed of multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semi crystalline gel and liquid crystal domains. The second layer beneath the epidermal layer is dermis which is much thicker than the epidermis (usually 1–4 mm). The main components of the dermis are collagen and elastic fibers. Compared to the epidermis, there are much fewer cells and much more fibers in the dermis. TDDS or skin patch is used for the delivery of a controlled dose of a drug through the skin over a period of time.The components of TDDS are liners, adherents, drug reservoirs, drug release membrane etc, that play an imperative role in the release of the drug through the skin. It is considered that a well-designed TDDS can supply the drug at a rate, to sustain the required therapeutic plasma concentration without much fluctuation that may cause basic manifestation or therapeutic inefficacy. Lag times to reach steady state fluxes are in hours as the transport of most drugs across the skin is very slow. Attainment of a therapeutically effective

drug level is, therefore, difficult without enhancing skin permeation. Consequently, there has been intensive study of strategies to undermine, in a controlled and reversible fashion, the permeability barrier of the SC. A number of techniques have been developed to enhance and control transport across the skin, and enlarge the range of drugs delivered. These involve chemical and physical methods, based on two strategies: increasing skin permeability and/or providing driving force acting on the drug. There have been many ingenious technologies developed to enhance TDDS for therapeutic and diagnostic purposes ranging from chemical enhancers to iontophoresis, electroporation, and pressure waves generated by ultrasound effects or the synergistic mixtures of both the mechanism. The transdermal route has become a most accepted and innovative spot light. Researchers in drug delivery which is proved in quantitative research with around 40% of the drug moiety being under clinical evaluation and also approved by FDA (Food and Drug Administration). The transdermal product has foreseeable future because of its noteworthy upward trend. The TDDS products have continued to provide bona fide therapeutic benefits to patients around the world. In the year 2005, the global market for drug delivery systems was $12.7 B and is projected to be $32 B by 2015. The fate of effectiveness of TDD system lies on the drug's ability to invade the skin barrier and how its reaches the targeted site. **[17]** Development of functional delivery systems for new active pharmaceutical ingredients is a challenging task. Drug can be administered through most common routes like the oral, parenteral, ophthalmic and transdermal route, as well as less explored routes such as nasal, pulmonary and buccal. Each of these routes have specific merits and disadvantages. Oral drug delivery systems offer advantages such as patient compliance, large surface area with rich blood supply for absorption, low cost, ease in engineering of drug release in stomach/ intestine, etc. However, limitations, like drug degradation in the gastrointestinal tract, first-pass metabolism, poor absorption, local irritation and variability in absorption (due to factors like pH, motility, food, mucus layer, etc.), are associated with these drug delivery systems. The parenteral route offers advantages like quick onset of action, accurate drug delivery and continuous drug delivery by infusion; its limitations include pain associated with the injections, expertise required to deliver the drug, risk of infection and difficulty in obtaining sustained drug delivery. Transdermal drug delivery involves the transport of drug across the skin. Optimal physiochemical properties are required in drug candidates for delivery via transdermal patches. Traditional transdermal patches can be divided into two categories – reservoir-based and matrix-based – according to their physical structure. Transdermal drug delivery offers advantages like patient compliance, avoidance of first pass metabolism, large surface area of skin over which to deliver the drug, quick termination of dosing, etc. However, only a few drug products with optimum characteristics have been successfully marketed to deliver a drug through the skin. This is due to the resistance to drug transport offered by the stratum corneum. The problem of poor drug transport can be addressed by development of micron-sized needles, which deliver the drug painlessly across the stratum corneum.

Microneedles

Microneedles can be defined as solid cannula with an approximate length of 50–900 mm and an external diameter of not more than 300 mm. Microneedles can be fabricated within a patch for transdermal drug delivery. Patches containing microneedles have been evaluated in the delivery of drugs, biopharmaceuticals, vaccines, etc. A quick response can be observed due to disruption of stratum corneum by microneedles. Although microneedles were first proposed in 1976, the technology needed to make needles of micron dimensions was not widely available until

2000s. Using the low-cost mass production tools of the microelectronics industry, needles have been fabricated out of silicon, metals and other materials. Microneedles have been designed to penetrate through the epidermis up to a depth of 70–200 mm. Microneedles are thin and short and do not penetrate the dermis layer with its nerves; hence painless application is possible. Microneedles are more capable of enhancing the transport of drug across the skin as compared with other transdermal delivery methods.

Advantages of microneedles

The advantages of microneedles are:-

- Large molecules can be administered
- Painless administration of the active pharmaceutical ingredient,
- First-pass metabolism is avoided,
- Faster healing at injection site than with a hypodermic needle,
- No fear of needle,
- Ease of administration,
- Decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures only the epidermis,
- Specific skin area can be targeted for desired drug delivery,
- Enhanced drug efficacy may result in dose reduction,
- Good tolerability without long-term oedema or erythema,
- Rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropump, and
- The rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.

Disadvantages of microneedles

The Disadvantages of microneedles are:

- Dosage accuracy may be less than with hypodermic needles,
- Careful use of the device may be needed to avoid particles'bouncing off' the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees,
- The thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too,
- The external environment, like hydration of the skin, could affect delivery,
- Repetitive injection may collapse the veins,
- The tip of the microneedle may break off and remain within the skin on removal of the patch,
- A small amount of drug (less than 1 mg) can be given by bolus, and
- Compressed dermal tissue can block hollow microneedles.

Materials Used to Constitute Microneedles

Microneedles can be broadly divided into three categories: -

- solid,
- degradable/dissolvable

- hollow**. [18]**

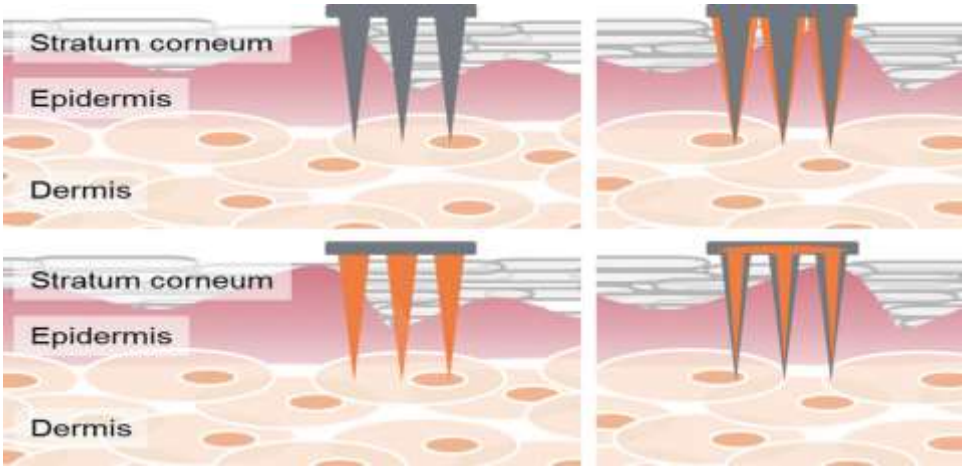

Fig no 4: Types of Electrical microneedles. [19]

Transdermal drug delivery systems (TDDS) have many advantages and represent an excellent alternative to oral delivery and hypodermic injections. TDDS are more convenient and less invasive tools for disease and viral infection treatment, prevention, detection, and surveillance. The emerging development of microneedles for TDDS has facilitated improved skin barrier penetration for the delivery of macromolecules or hydrophilic drugs. Microneedle TDDS patches can be fabricated to deliver virus vaccines and potentially provide a viable alternative vaccine modality that offers improved immunogenicity, thermostability, simplicity, safety, and compliance as well as sharp-waste reduction, increased cost-effectiveness, and the capacity for self-administration, which could improve vaccine distribution. These advantages make TDDS-based vaccine delivery an especially well-suited option for treatment of widespread viral infectious diseases including pandemics. Because microneedle-based bioassays employ transdermal extraction of interstitial fluid or blood, they can be used as a minimally invasive approach for surveying disease markers and providing point-of-care (POC) diagnostics. For cutaneous viral infections, TDDS can provide localized treatment with high specificity and less systemic toxicity. In summary, TDDS, especially those that employ microneedles, possess special attributes that can be leveraged to reduce morbidity and mortality from viral infectious diseases. In this regard, they may have considerable positive impact as a modality for improving global health. In this article, we introduce the possible role and summarize the current literature regarding TDDS applications for fighting common cutaneous or systemic viral infectious diseases, including herpes simplex, varicella orherpes zoster, warts, influenza, measles, and COVID-19. The three anatomical layers of skin are the epidermis, dermis, and subcutis. The outermost epidermal layer is composed of four or five layers from superficial to deep, including the stratum corneum, stratum lucidum (only in palms and soles), stratum granulosum, stratum spinosum, and the stratum basale. The stratum corneum, the outermost layer of the epidermis, is only 10 to 20 μm thick. Nevertheless, it is the most important barrier for protecting underlying tissue from water loss, infection, chemical or mechanical irritation, and drug absorption. The stratum corneum allows primarily passive diffusion by drugs with specific physicochemical properties (molecular weight < 500 Da, high lipophilicity, and low melting point). Transdermal drug delivery systems (TDDS) are an excellent alternative to oral delivery and hypodermic injections. Because of the delivery route, they naturally avoid potentially detrimental digestive/metabolic effects associated with oral drug delivery including the effluence of enzymatic digestion, gastric emptying time, gastrointestinal tract pH, and the first-pass effect, which occurs in the liver. They are also superior to oral delivery because they can be administered on unconscious or nauseated patients. Compared to injection

delivery, TDDS avoid pain, bruising, and bleeding, which improves patient acceptance and compliance. They also eliminate the risk of needle-associated disease transmission and accidental needle injury, and reduce the generation of dangerous medical waste sharps. The advantages of TDDS are not just safety-based; they have been shown to reduce overall healthcare treatment costs. Furthermore, TDDS can provide prolonged and controlled drug release, minimize the peak of drug concentration, and reduce associated systemic toxicity. They have unique administrative flexibility they are easy to apply and to remove, which not only means that drug delivery can be easily terminated if it causes localized or systemic side effects, but also means that they are well suited for self-administration. TDDS are especially well suited for treatment of dermatological diseases. Direct application of a drug to a target skin site can maximize drug efficacy and minimize side effects. **[20]**

NOVELITY OF ELECTRICAL DEVICE ASSISTED DRUG DELIVERY SYSTEMS.

The novelty of these drug delivery systems lies in their ability to provide a non-invasive, convenient, and controlled method of administering medications through the skin for systemic distribution. Unlike traditional routes such as oral ingestion or injections, transdermal delivery offers several unique advantages:

1. **Non-invasive**: Transdermal delivery avoids the need for needles or invasive procedures, reducing patient discomfort and risk of infection.
2. **Steady and controlled release**: Transdermal patches can provide a continuous and controlled release of medication over an extended period, ensuring consistent therapeutic levels in the bloodstream. This can improve efficacy and reduce side effects compared to peaks and troughs associated with oral medications.
3. **Improved patient compliance**: Transdermal patches are easy to apply and require less frequent dosing compared to oral medications, which can enhance patient adherence to treatment regimens.
4. **Avoidance of first-pass metabolism**: Drugs delivered transdermally bypass first-pass metabolism in the liver, which can enhance bioavailability and reduce the required dose of medication.
5. **Targeted delivery**: Transdermal patches can be designed to deliver drugs directly to the site of action, offering localized therapy while minimizing systemic side effects.
6. **Suitable for sensitive populations**: Transdermal delivery can be particularly beneficial for patients who have difficulty swallowing oral medications, such as pediatric or geriatric populations.
7. **Potential for improved safety**: Transdermal delivery can reduce gastrointestinal irritation and other systemic side effects associated with oral medications, potentially improving the safety profile of certain drugs. **[21-25]**

In recent years, there have been advancements in transdermal drug delivery technology, including the development of novel materials for patches, enhanced permeation enhancers, and innovative drug formulations. These advancements have expanded the range of drugs that can be delivered transdermally and have improved the efficiency and reliability of transdermal delivery systems. As a result, transdermal drug delivery continues to be an area of active research and development in the pharmaceutical industry.

DISCUSSION

Transdermal Drug Delivery Systems have been shown to be both safe and reliable. The promise of their role in supervised release is being explored all over the world. Scientists who have a high degree of success. Transdermal delivery is a remarkable successful route of administration if a drug has the perfect combination of physical chemistry and pharmacology. Delivery is a very efficient method of administration. Because of the TDDS's many

benefits, several new studies are currently being conducted to bring newer medications into the scheme. Chemical enhancers have a number of drawbacks, including their efficacy and protection. They have low permeation in the SC, and their presence is restricted to just the top few layers. Their focus, as well as their behaviors, declines as they progress further through the SC. Chemical enhancers with a higher concentration in the formulation improve drug transport through the skin, but this is equal to their tendency to irritate the skin. As a result, maintaining an ideal balance between the protection and efficacy of chemical enhancers in drug permeation is difficult. As healthy and appropriate permeation enhancers, essential oils and their constituents can be favoured to the traditionally used synthetic materials, encourage the percutaneous absorption of a variety of medications from topical formulations into the deeper layers of the skin Essential oils help hydrophilic and lipophilic drugs permeate more easily and with less cytotoxicity. Many organizations, such as the Research Institute for Fragrance Materials, the International Flavor and Fragrance Association, have well-documented their toxicity. The National Toxicology Program, the Fragrance Association, and the Flavor Essence Manufacturers Association Basic oils and their constituents have been shown to have a low toxicity as compared to the majority of synthetic penetration enhancers. As a result, essential oils and their components are significant, can be used to improve the prevention of drug permeation across the skin.

CONCLUDATORY COMMENTS:

Recently, the demand for innovative medical devices based on bioelectronics for enhanced performance and cost-effectiveness has increased. In particular, transdermal drug delivery systems have received considerable attention . To increase the driving force for drug delivery, several physical stimuli, such as chemical enhancers, microneedles, and electric currents, have been applied. For instance, the iontophoresis process induced by an electric current repels ions and induces an electric field. Since the introduction of the first TDP about forty years ago and the introduction of 3DP over thirty years ago, it is evident that the potential exists to revolutionize drug delivery systems in the pharmaceutical market. A TDD systems and an investigation into how 3DP can benefit drug delivery techniques are presented here. Specifically, tailored formulation approaches would be favoured as patients can move away from the ‘one size fits all approach’ to a more customized approach. Despite all the research being done, 3DP of API formulations and TDD systems remain in their infancy as many regulatory issues still need to be addressed before the techniques becomes mainstream, and many drugs are still not suitable for the techniques. Ink jet and photo polymerization-based technologies have dominated as techniques to produce MN or micromoulds for MN casts. Published literature highlights the benefits of 3DP, with improvements upon current orodispersible or hypodermic deliveries, alleviating the effects of metabolism and bioavailability in the former and the invasive and waste generating injections with the latter. The pharmaceutical industry is aware of the advantages and disadvantages associated with 3DP, and it is imperative that AM gets incorporated effectively into pharmaceutical manufacturing so that its benefits can be reaped in patient health care in the very near future.

ACKNOWLEDGEMENT:

The author is sincerely acknowledged and appreciate the academic guidance, support and the continuous intellectual patronage of all teaching staffs of Guru Kashi University, Bathinda. Without their profound skills and insight of subject, this work would not have been possible. The authors heartily acknowledge their continuous commitment to help to achieve this goal. The author hereby declare “**No Conflict of Interest**”

REFERENCES & BIBLIOGRAPHY:

1. Mark R. Prausnitz, Robert langer; Transdermal drug delivery; Nat Biotechnol; 26(11); 1261-1268; 2009.
2. Woo YeupJeong, Mina Kwon, HyeEun Choi, Ki Su Kim ; Recent advances in transdermal drug delivery systems; Biomaterials Research ; 25(24); 1-15; 2016.
3. Suneetha Cherukuri, Uma RajeswariBatchu, Kiranmai Mandava, Vidhyullatha Cherukuri, KoteswaraRaoGanapuram ; Formulation and evaluation of transdermal drug delivery of topiramateInt .J. Pharm Investig ; 7(1) ; 10–17;2017
4. KeishiroTomoda , Kimiko Makino ; Nanoparticles for Transdermal drug delivery system (TDDS); Colloid and Interface Science in Pharmaceutical Research and Development ; 1(1); 131-147; 2014.
5. Hyunjae Lee, Changyeong Song , SeungminBaik, Dokyoon Kim , TaeghwanHyeon , Dae-Hyeong Kim; Device-assisted transdermal drug delivery; Advanced Drug Delivery Reviews;127(1); 35-45;2018.
6. KajalSahu ; Transdermal Drug Delivery System ; pharmatutorjornal organization ;1(1) ; 2018 |
7. Nikhil sharma, Getaagarwal , A. c. Rana , Zulfiqaralibhat , Dinesh kumar ; Transdermal Drug Delivery System: A Tool For Novel Drug Delivery System ; . International Journal of Drug Development & Research; 3(3); 0975-9344;| 2010.
8. Fang-Ying Wang , Yunching Chen, Yi-You Huang ,Chao-Min Cheng ; Transdermal drug delivery systems for fighting common viral infectious diseases ; Drug Delivery and Translational Research; 11(1); 1498–1508 ; 2016.
9. AnkitaSoni, J.S. Dua, D.N. Prasad; Reviewing Transdermal Drug Delivery System; JDDT [Internet]; 12 (1); 176-80; 2018.
10. Sirisha V, Sailaja AK; Transdermal Drug Delivery System; Journal of Nursing and Patient Health Care; 1(1); 103; 2018.
11. DellyRamadon, Maeliosa T. C. McCrudden, Aaron J. Courtenay , Ryan F. Donnelly; Transdermal drug delivery systems; Drug Delivery and Translational Research; 12(1) 758- 791, (2012).
12. TandaleAdeshManmohan, Dr.L.D.Hingane; Formulation and evaluation of aspects of transdermal drug delivery system; International Journal of Creative Research Thoughts; 9 (12); 1-20; 2015.
13. H. Michael Wolff; Future transdermal drug delivery systems; American Pharmaceutical Review 1(1); 1-11; 2014.
14. Siafaka, Panoraia I., Bülbül, Ece Ö, Mutlu, Gökce, Okur, Mehmet E., Karantas, Ioannis D.,Okur, Neslihan Ü; Transdermal Drug Delivery Systems and their Potential in Alzheimer's Disease Management; CNS & Neurological Disorders;19(5);360-373;2012
15. Prerana Carter, BalajiNarasimhan, Qun Wang; Biocompatible nanoparticles and vesicular systems in transdermal drug delivery for various skin diseases; International Journal of pharmaceutics; 555(1); 49-62; 2017.
16. David bard, Nuggehalli M. Ravindra; Transdermal drug delivery and patches; National device &sensor; 1(1); 1-15; 2016.

17. Amit Alexander, ShubhangiDwivedi , Ajazuddin , Tapan K. Giri , SwarnlataSaraf , ShailendraSaraf , Dulal Krishna Tripathi ; Approaches for breaking the barriers of drug permeation through transdermal drug delivery ; Journal of Controlled Release ; 164(1) ; 1-16 ; 2012.
18. Shital H. Bariyaa , Mukesh C. Gohelb , Tejal A. Mehtaa , Om Prakash Sharma ; Microneedles: an emerging transdermal drug delivery system ; Journal of Pharmacy and Pharmacology ;1(1) ;1-19 ;2012.
19. Ki Mun Kwon, Su-Min Lim, Seulgi Choi, Da-Hee Kim, Hee-Eun Jin, Grace Jee, Kee-Jong Hong, Joo Young Kim ; Microneedles: quick and easy delivery methods of vaccines ; clinical experimental vaccine research ; 1(1) ; 1-4 ; 2017.
20. Fang Ying Wang , Yunching Chen , Yi You Huang , Chao Min Cheng ; Transdermal drug delivery systems for fighting common viral infectious diseases ; Drug Delivery and Translational Research ;11(1) ; 1-11 ;2015.
21. A.runachalam, M.Karthikeyan, D.Vinay Kumar, Prathap. M, S. Sethuraman, S.Ashutoshkumar, S.Manidipa; Transdermal Drug Delivery System: A Review; Current Pharma Research; 1(1); 1-12; 2010.
22. KharatRekhaSudam, Bathe Ritesh Suresh; A Comprehensive Review on: Transdermal drug delivery systems; International Journal of Biomedical and Advance Research; 7(4); 1-13; 2016.
23. R. PannerSelvam, Anoop Kumar Singh, T. Sivakumar; Transdermal drug delivery systems for antihypertensive drugs; International Journal of pharmaceutical and biomedical research; 1(1); 1-8; 2010.
24. SrilathaMalvey, J VenkateshwarRao and KottaiMuthuArumugam; Transdermal drug delivery system; The Pharma Innovation Journal; 8(1); 1-17; 2011.
25. PreetamBala, SonaliJathar, Sangeeta Kale, Kavita Pal; Transdermal Drug Delivery System - A Multifaceted Approach for Drug Delivery; Journal of Pharmacy Research; 8(12); 1-31;2014.