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Recent Advances in Transdermal Drug Delivery System

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ABSTRACT

Various non-invasive administrations have recently emerged as an alternative to conventional needle injections. A transdermal drug delivery system (TDDS) represents the most attractive method among these because of its low rejection rate, excellent ease of administration, and superb convenience and persistence among patients.

TDDS could be applicable in not only pharmaceuticals but also in the skin care industry, including cosmetics. Because this method mainly involves local administration, it can prevent local buildup in drug concentration and nonspecific delivery to tissues not targeted by the drug. However, the physicochemical properties of the skin translate to multiple obstacles and restrictions in transdermal delivery, with numerous investigations conducted to overcome these bottlenecks.

In this project, we describe the different types of available TDDS methods, along with a critical discussion of the specific advantages and disadvantages, characterization methods, and potential of each method. Progress in research on these alternative methods has established the high efficiency inherent to TDDS, which is expected to find applications in a wide range of fields

Introduction

Transdermal drug delivery has been used for decades to deliver drugs. The process is, however, limited by the outer layer of the skin, the stratum corneum, which protects the body by preventing the entry of foreign substances

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

Depending on the delivery route, there are many types of administration modalities, such as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. Among them, the transdermal drug delivery system (TDDS) represents an attractive approach.

DDS covers the routes of administration and drug formulations that efficiently deliver the drug to maximize therapeutic efficacy while minimizing any side effect

The drug is transported by blood streaming to the whole body without the first-pass effect, which is a metabolism on the digestive system that reduces the effect of drug. and drugs can be delivered without interference from pH, enzymes, and intestinal bacteria

Over the past few years, different methods have been proposed to increase the permeability of this barrier. Such methods include the use of chemical penetration enhancers , iontophoresis ,sonophoresis , and other

SKIN: -

Skin is the most accessible and largest organ of the body with a surface area of 1.7 m^2, compromising 16% of the total body mass of an average person . The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the permeation of ultraviolet (UV) radiation, chemicals, allergens and the loss of water . Skin can be divided into three main regions:

the outermost layer, the **epidermis,** which contains the stratum corneum;

the middle layer, the **dermis**

the inner most layer, the **hypodermis**

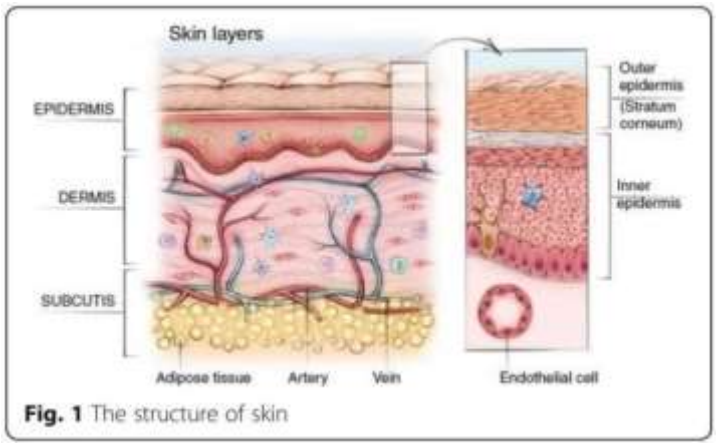


Fig. 1 The structure of skin

Epidermis:

The epidermis is the outermost layer of the skin and varies in thickness with approximately 0.8 mm on the palms of the hands and soles of the feet . It consists of multi-layered regions of epithelial cells and the viable epidermis is often referred to as the epidermal layers below the stratum corneum

It is in direct contact with the external environment and its barrier properties may be partly related to its very high density (1.4 g/cm^3 in the dry state) and its low hydration of 15%–20%.

The cells of the stratum corneum are composed mainly of insoluble keratins (70%) and lipid (20%) . Water in the stratum corneum is associated with keratin in the corneocytes.

Dermis

The dermis is approximately 2–3 mm thick and consists of collagenous (70%) and elastin fibres which give strength and elasticity to the skin. Blood vessels found in the dermis provide nutrients for both the dermis and epidermis. Nerves, macrophages and lymphatic vessels are also present in the dermis layer, as depicted in Figure 1

Hypodermis

The hypodermis or subcutaneous layer is the deepest layer of the skin and consists of a network of fat cells . It is the contact layer between the skin and the underlying tissues of the body, such as muscles and bone. Therefore, the major functions of the hypodermis are protection against physical shock, heat insulation and support and conductance of the vascular and neural signals of the skin . Hypodermis-resident fat cells account for approximately 50% of the body's fat with the other predominant cells of the hypodermis consisting of fibroblasts and macrophages**.**

The problem is that only a small amount of the drug can be delivered through the skin tissue [20, 21]. To solve this problem, various novel TDDS techniques have been intensively developedTransdermal drug delivery technologies:

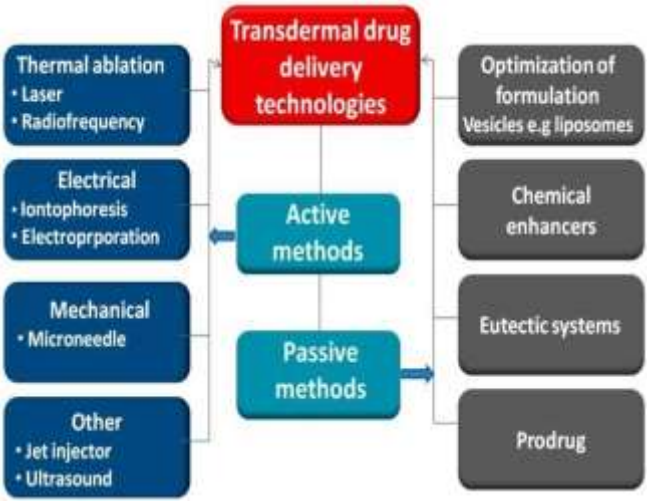


Fig no: 02 Transdermal drug delivery technologies

Thermal ablation

Thermal ablation, also known as thermophoresis, is a promising technique for selectively disrupting the stratum corneum structure by localized heat which provides enhanced drug delivery through microchannels created in the skin [55]. To ablate the stratum corneum by thermal ablation, a high temperature above 100 °C is required and this leads to heating and vaporization of keratin. Additionally, the degree of alteration of the stratum corneum structure is proportional to the locally elevated temperature, indicating that it is an ideal technique for precise control of drug delivery.

Thermal ablation can usually be induced by laser and radiofrequency methods depending on the different sources of thermal energy [56, 57]. Laser thermal ablation methodologies utilize a laser to induce micropore structure of skin as well as the increase of the skin temperature which increases skin diffusivity

Laser light energy is absorbed by water and pigments of the skin and transforms to thermal energy leading to water excitation and explosive evaporation from the epidermis. The degree of the ablated skin depth can be precisely controlled upon tuning many parameters such as wavelength, pulse length, energy, number and repetition rate, tissue thickness, absorption coefficient, and duration time of laser exposure

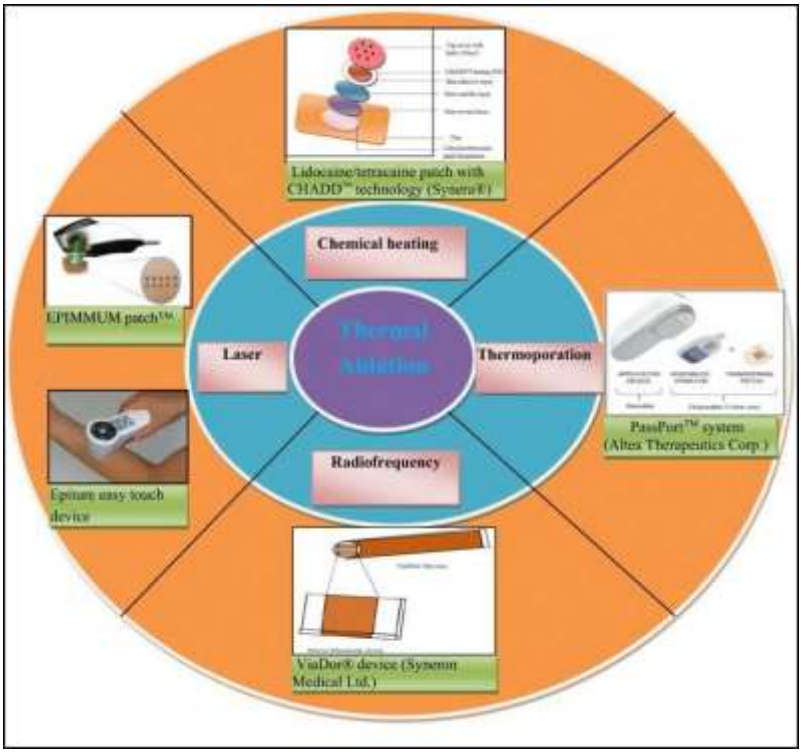


Fig no 03 thermal ablation

Laser thermal ablation, especially when using **Er:YAG** laser, makes it possible to increase the penetration of drugs by more than 100 times and enhance the delivery of both lipophilic and hydrophilic drugs including biomacromolecules such as peptides, proteins, vaccines, and DNAs [56–58].

Enhancement of transdermal delivery by equipment (active delivery)

External stimuli, such as electrical, mechanical, or phyical stimuli, are known to enhance skin permeability of drugs and biomolecules, as compared to the delivery of drugs by topical application on the skin [73]. TDDS supplemented by appropriate equipment is termed as active transdermal delivery, which is known to deliver drugs quickly and reliably into the skin. In addition, this mode of enhanced TDDS can accelerate the therapeutic efficacy of delivered drugs (Fig. 2) [75–77].

Iontophoresis

Iontophoresis promotes the movement of ions across the membrane under the influence of a small externally applied potential difference (less than 0.5 mA/cm2), which has been proven to enhance skin penetration and increase release rate of several drugs with poor absorption/permeation profiles. This technique has been utilized in the in vivo transport of ionic or nonionic drugs by the application of an electrochemical potential gradient. [25]

The efficacy of iontophoresis depends on the polarity, valency, and mobility of the drug molecule, the nature of the applied electrical cycle, and the formulation containing the drug. In particular, the dependence on current makes drug absorption through iontophoresis less dependent on biological

parameter,unlike most other drug delivery systems (Fig. 2A, B) [26]. This modality could additionally include electronic means of reminding patients to change dosages, if desired, to increase patient compliance [27, 28].

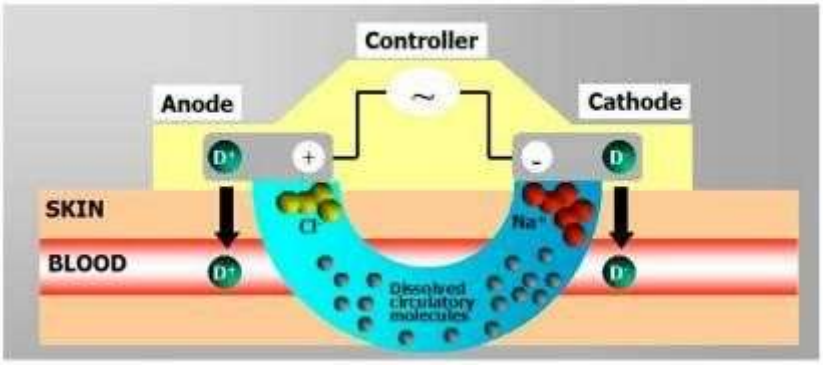


Fig no 04 Ionotophoresis

This method uses the application of high voltage electric pulses ranging from 5 to 500 V for short exposure times (~ms) to the skin, which leads to the formation of small pores in the SC that improve permeability and aid drug diffusion [34, 35]. For safe and painless drug administration, electric pulses are introduced using closely positioned electrodes.

This is a very safe and painless procedure involving permeabilization of the skin and has been used to demonstrate the successful delivery of not only low MW drugs, such as doxorubicin, mannitol, or calcein, but also high MW ones such as antiangiogenic peptides, oligonucleotides, and the negatively charged anticoagulant heparin. However, this method has the disadvantages of small delivery loads, massive cellular perturbation sometimes including cell death, heatinginduced drug damage, and denaturation of protein and other biomacromolecular therapeutics.

The desired range of ultrasound frequencies generated by an ultrasound device can improve transdermal drug delivery [30, 31]. Low-frequency ultrasound is more effective, because it facilitates drug movement by creating an aqueous path in the perturbed bilayer through cavita [32].

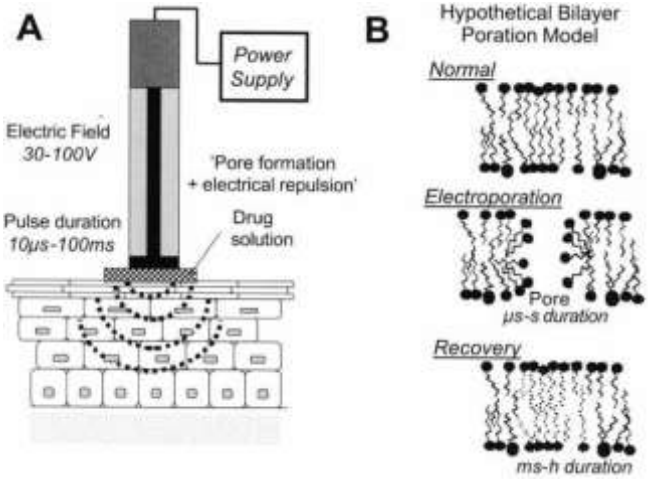
The drug under consideration is mixed with a specific coupler, such as a gel or a cream, which transmits ultrasonic waves to the skin and dis turbs the skin layers, thereby creating an aqueous path through which the drug can be injected. Drugs typically pass through passages created by the application of ultrasonic waves with energy values between 20 kHz and 16 MHz. Ultrasound also increases the local temperature of the skin area and creates a thermal effect, which further promotes drug penetration.

Several drugs of different classes have been delivered by this method regardless of their solubility, dissociation and ionization constants, and electrical properties (including hydrophilicity), such as mannitol and high molecular weight (MW) drugs such as insulin. However, the exact mechanism of drug penetration through this method is not yet completely understood, and problems with de vice availability, optimization of duration of exposure and treatment cycles for delivery, and undesirable side effects including burns persist.

Electroporation

This method uses the application of high voltage electric pulses ranging from 5 to 500 V for short exposure times (~ms) to the skin, which leads to the formation of small pores in the SC that improve permeability and aid drug diffusion [34, 35].

Fig no 05 Electroporation



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Photomechanical Waves

Photodynamic waves transmitted to the skin can penetrate the SC, allowing the drug to pass through the transiently created channel [37, 39]. The incident wave produces limited ablation, which is achieved by low radiation exposure of approximately 5–7 J/cm2 to increase the depth to 50–400 μm for successful transmission.

This limited ablation showed a longer increase and duration as compared to that in other direct ablation techniques, which made it necessary to control properties of the photodynamic waves to ensure delivery of the product to the intended depth in the skin. The wave generated by a single laser pulse also showed increased skin permeability within minutes, allowing macromolecules to diffuse into the skin. Dextran macromolecules of 40 kDa weight and 20 nm latex particles could be delivered by a single photodynamic laser pulse of a 23-ns duration

Microneedle

The microneedle drug delivery system is a novel drug delivery system, in which drugs are delivered to the circulatory system through a needle [41]. This represents one of the most popular methods for transdermal drug delivery and is an active area of current research. This involves a system in which micron-sized needles pierce the superficial layer of the skin, resulting in drug diffusion across the epidermal layer. Because these microneedles are short and thin, these deliver drugs directly to the blood capillary area for active absorption, which helps in avoiding pain [42].

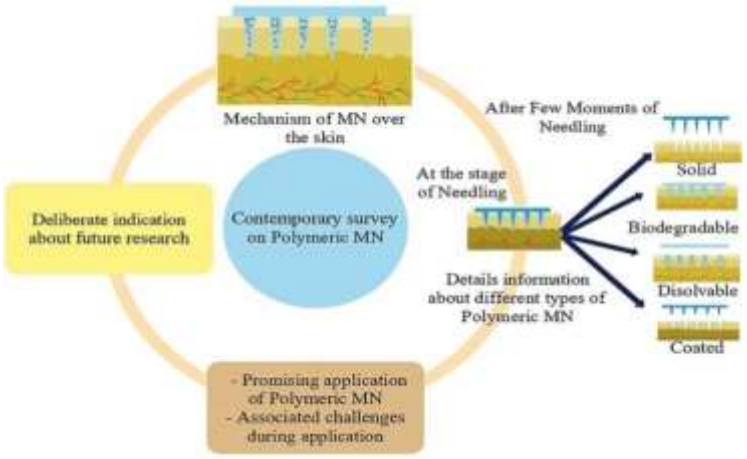

Fig no 06 microneedle drug delivery

Scientists have attempted to use multiple techniques for appropriate optimization and geometric measurements required for effective insertion of microneedles into human skin, which also represents the broad objective of research on microneedles.

MN are multiple microscopic projections typically assembled on one side of a supporting base or patch, generally ranging from 25 to 2000 μm in height, 50 to 250 μm in base width and 1 to 25 μm in tip diameter. The needles should be of suitable length, width and shape to avoid nerve contact when inserted into skin layers. They are usually designed in arrays in order to improve the surface contact with the skin and facilitate penetration of therapeutic molecules into the skin.

The first two commercially marketed MN-based products are Intanzia® and Micronjet® which are based on metal and silicon MN, respectively . Intanza® is the first influenza vaccine that targets the dermis, a highly immunogenic area. It was developed and licensed by Sanofi Pasteur MSD Limited and is being marketed in two strengths; Intanza® 9 μg for adults aged between 18 and 59 years and Intanza® 15 μg for adults of 60 years and above. The Intanza® influenza vaccine system has a needle length of 1.5 mm [132]. MicronJet is a single use, MN-based device for intradermal delivery of vaccines and drugs. It was developed and licensed by NanoPass.

L- JET injector

Liquid-jet injectors propel liquid from a nozzle with an orifice diameter ranging from 50 to 360 μm, which is much smaller than the outer diameter of a standard hypodermic needle (810 μm for a 21G needle) [20,93,94].

The jet can deliver drug into different layers of skin e.g., intradermal (i.d.), subcutaneous (s.c.) or intramuscular (i.m.), by changing the jet velocity and orifice diameter [20]. The major advantage of using needle free devices relates to concerns regarding safe needle disposal and avoidance of accidental

needle stick injuries [20]. However, the risk of cross contamination is not excluded, since splash back of interstitial liquid from the skin may contaminate the nozzle [95]. Therefore the use of multi-use nozzle jet injectors has been terminated and such devices are now only used for multi-dose drug delivery to the same individual, e.g., the Tjet®device which delivers somatropin (human growth hormone (hGH))

Fig no 07 T-jet

The basic design of solid jet injectors consists of compressed gas as the power source, drug loaded compartment containing solid drug formulation, and a nozzle to direct the flow of particles towards the skin [99]. By triggering the actuation mechanism, compressed gas expands and forces drug powder through a nozzle into the skin. Upon impacting on the skin, particles create micronsized holes and deposit in the stratum corneum or viable epidermis.

The most important parameters that govern particle delivery across the stratum corneum are particle properties (size, density) and impact velocity e.g., for DNA vaccination, the particle size range should be between 0.5 and 3 μm

Vesicles

Vesicles are colloidal particles filled with water and consist of amphiphilic molecules in a bilayer arrangement. Under conditions of excess water, these amphiphilic molecules form concentric bilayers with one or more shells (multilayer vesicles). Vesicles can carry water soluble and fat-soluble drugs to achieve transdermal ab sorption. When utilized for topical applications, vesicles can be used to achieve sustained release of stored drugs. It is also possible to employ vesicles in TDDS to control the absorption rate through a multilayered structure. Owing to the presence of different components, vesicle systems can be divided into several types, such as liposomes, transfersomes, and ethosomes, depending on the properties of the constituent substances [60].

Polymeric nanoparticles Nanoparticles (NPs) are nanocarriers with sizes ranging between 1 and 1000 nm and can be classified into several types according to their composition. Drug administration in the form of NPs leads to targeted and controlled release behavior, changes in in vivo dynamics of the drug, and extends the drug residence time in the blood, which further lead to improved drug bioavailability and reduced toxicity and side effects. NPs are conventionally generated by polymerization and crosslinking, and bio degradable polymeric materials such as gelatin and poly lactic acid (PLA) are often used [67, 69, 70].

In the field of TDDS, polymeric NPs are gaining increased attention because they can overcome the limitations of other lipid-based systems, such as by conferring protection to unstable drugs against degradation and denaturation and achieving continuous drug release to reduce side effects. Increase in the concentration gradient improves trans dermal penetration of the drug. Depending on the manufacturing method and structure, polymeric NPs can be classified as nanospheres, nanocapsules, and polymer micelles. Widely used polymers include polylactic acid, poly(D,L-lactide-co-glycolide) (PLGA), polycaprolactone, polyacrylic acid, and natural poly esters (including chitosan, gelatin, and alginate).

Nanoemulsion

Nanoemulsions are a mixture characterized by low viscosity and isotropic, thermodynamic, and dynamic stability [71]. The mixture consists of transparent or translucent oil globules dispersed in an aqueous phase stabilized by an interfacial membrane formed by surfactant or co-surfactant molecules of extremely small drop let size. The particle size of commonly used nanoemulsions ranges from 100 to 1000 nm, although an upper limit to the particle size has been proposed on account of its nanoscale dimensions.

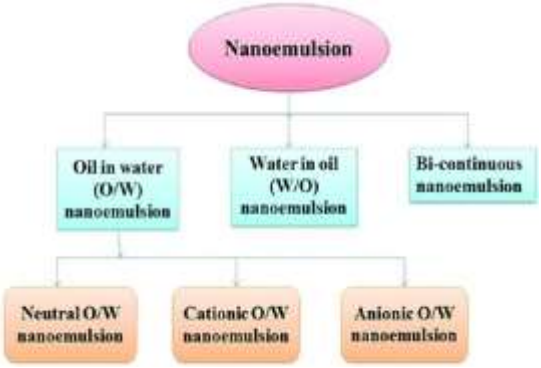

Fig no: 08 types of nanoemulsion

Nanoemulsions are different from microemulsions; although nanoemulsions have almost the same droplet size range, composition, and appearance as microemulsions, they differ greatly in terms of structural aspects and long-term thermodynamic stability. The small particle size, large specific surface area, and low surface tension of nanoemulsions provide excellent wettability that ensures close contact with the skin.

In addition, nanoemulsions offer many other benefits such as high solubilization capacity and physical stability, improved bioavailability, ease of preparation, production with less energy input, and long shelf life.

Methods for Characterizing TDDS Tape stripping

Tape stripping is a commonly used minimally invasive method to test the penetration of topically applied formulations through the SC, where a layer of the SC is removed with an adhesive tape followed by examination of the skin layer on the adhesive tape (Fig. 5) [74, 83, 86, 87]. The tape stripping process is performed after an ap propriate incubation time post topical application of the test composition. The composition may be removed or left on the skin to provide the original amount of components to be used during the measurement.

The adhesive tape is placed on the skin surface and is always removed from the same selection. It is important that the adhesive tape is always flattened with the same force as the roller to eliminate the effect of creases and re cesses on tape stripping. In addition, the removal rate is an important factor.

The slower the adhesive tape removal rate, the higher the adhesion of the SC to the patch, which increases the amount of skin removed from the patch. The removed adhesive tape contains both the SC layer and the active ingredients of the composition used. Several methods can be used to test samples harvested using adhesive tape. High-performance liquid chromatography (HPLC) analysis produces quantitative results, whereas spectroscopic methods produce semiquantitative insights.

During HPLC analysis, the test material on the adhesive tape is extracted and analyzed on chromatographic separation. It is also possible to detect active substances using atomic absorption spectroscopy. However, the most prevalent method used to characterize skin harvested by tape stripping is attenuated total reflectanceFourier transform infrared spectroscopy (ATR-FTIR).

Microscopic and Spectroscopic Methods

Microscopy-based techniques can also provide import ant information about the spatial distribution of the drug within different skin layers or shed light on the mechanism of penetration. The two most common modalities of microscopy are confocal laser scanning microscopy (CLSM) and two-photon fluorescence microscopy (2- PFM) [58, 68, 71, 72, 74,80–87, 90].

CLSM is a non-invasive method developed for fluorescence microscopy [88, 91, 92]. In the past few years, CLSM has been widely adopted as a technique to visualize fluorescent model compounds in the skin. CLSM can be used to examine skin structure without destroying tissue samples and is widely employed to evaluate the effect of physical and chemical enhancers on skin permeability. This method can be adapted for use in both in vivo and in vitro conditions.

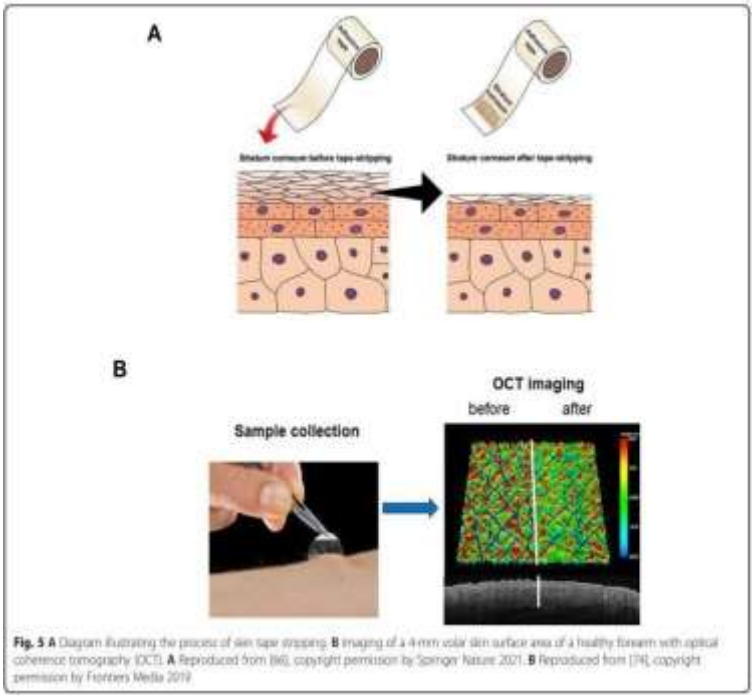

Fig. 5 **A** Diagram illustrating the process of skin tape stripping. **B** Imaging of a 4-mm volar skin surface area of a healthy forearm with optical coherence tomography (OCT). **A** Reproduced from [86], copyright permission by Springer Nature 2021. **B** Reproduced from [74], copyright permission by Frontiers Media 2019

Conclusion:

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive atches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. It promises to eliminate needles for administration of a wide variety of drugs in the future. TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS realistic practical application as the next generation of drug delivery system

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