

## Strategies To Enhance Transdermal Drug delivery

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### ABSTRACT

**Background:** Transdermal drug delivery system (TDDS) is a promising delivery system that provides controlled drug release at a predetermined time. It has many advantages such as bypassing first-pass effect, increase patient convenience by providing single application rather than multiple dosing frequencies, and extends the action of short half-life drugs. There are three ways for drug penetration into the skin either via appendageal (shunt routes), intracellular route, and intercellular route. Permeation of drug substances through the stratum corneum remains a great challenge because it is the rate-limiting step for permeation for most molecules.

**Aim:** This review article highlights the advances and limitations of the strategies to enhance transdermal delivery of the drugs into the skin, including both physical and chemical methods.

**Conclusion:** The transdermal drug delivery system represents a good alternative for oral and parenteral therapy. Various penetration enhancing strategies have been successfully employed to enhance the permeation of low molecular weight molecules. For high molecular weight molecules, physical strategies such as microneedles can be used.

**Keywords:** transdermal drug delivery, permeation enhancement, nanocarriers, microneedles.

### المخلص

**الخلفية:** نظام اعطاء وتوصيل الادوية عبر الجلد ( TDDS ) من الانظمة الواعدة لا يصلح الادوية في وقت محدد مسبقا ، تمتلك هذه الطريقة العديد من المزايا مثل تجاوز تأثير الجرعة الاولى ، وزيادة راحة المريض من خلال تطبيق واحد بدلا من تكرار اعطاء الجرعات واطالة فترة تأثير الادوية قصيرة نصف العمر. توجد ثلاث طرق لاختراق الادوية الجلد اما عن طرق التحوييلية والطرق داخل الخلايا والطرق بين الخلايا. لاتزال نفاذية الادوية عن طريق الطبقة القرنية تحديا كبيرا لأنه يمثل خطوة تحد من معدل التخلل لمعظم الجزئيات.

**الغاية:** هذا المقال يسلط الضوء على استراتيجيات توصيل الادوية عن طريق الجلد بما في ذلك الطرق الكيميائية والفيزيائية والتحديات التي تحد من استخدامها.

**المخلص:** يمثل نظام توصيل الأدوية عبر الجلد بديلا جيدا للعلاج عن طريق الفم وبالحقن. تم استخدام استراتيجيات تحسين الاختراق المختلفة بنجاح لتحسين تغلغل الجزئيات ذات الوزن الجزيئي المنخفض. بالنسبة للجزئيات ذات الوزن الجزيئي المرتفع، يمكن استخدام استراتيجيات فيزيائية مثل الابر الميكروية.

**الكلمات المفتاحية:** توصيل الدواء عن طريق الجلد، تحسين النفاذية، الناقلات النانوية، الابر الميكروية.

### 1. Introduction

**T**ransdermal drug delivery is the process of drug penetration via skin directly into the systemic circulation. Various dosage forms including patches or other transdermal forms applied to the skin

such as cream, ointment, and gel (1). The skin is the organ that protects the whole body from external factors and is characterized by easy accessibility and large surface area (2). Dermal patches are the most common form of transdermal drug delivery (3). Patch application offers a

painless way to deliver the drug and also bypassing the first-pass metabolism offering drug release in a controlled manner over an extended period of time. Transdermal patches vary in their design. In general, the patch consists of a backing layer that supports the patch, a drug layer which is in form of either a reservoir or a matrix, pressure –sensitive adhesive (PSA), and a release liner which is intended to be removed prior to patch application on the skin (4). Transdermal delivery systems have been studied for 50 years, and the first patch was approved by FDA in 1979 for the treatment of motion sickness that has contained scopolamine for three days of drug delivery. In addition to scopolamine, there are many other examples of drugs that are given as a transdermal patch such as nicotine to quit smoking, estrogen which is a hormone given in menopause and to prevent osteoporosis after menopause, nitroglycerin for angina, and lidocaine to relieve the pain of shingles (herpes zoster) (5). Nicotine patch was approved by the FDA in 1984 which after that helped over 1 million smokers gave up smoking (6). Unfortunately, not all drugs can be formulated as a transdermal patch; for a drug to penetrate the skin, should have molecular weight not exceeding a hundred Daltons and polar drugs cannot be delivered via the lipoid stratum corneum (7&8).

## **1.1 Advantages and Disadvantages of TDDS**

### **1.1.1 Advantages of TDDS**

TDDS have several advantages over the oral route of drug administration. By administration of drug via the skin,

gastrointestinal side effects of the drug such as bleeding, ulceration can be avoided. In addition, it provides a way to bypass the gastrointestinal first-pass effect, leading to enhanced drug bioavailability. Administration of drug via skin will also offer a way to extend the action of drugs that have a short half-life, wherein the patch provides a reservoir of the drug covered by a porous membrane to control the release of drug. Consequently, this will reduce dosing frequency and improve patient compliance. In the case of the patch application, drug action can be terminated easily by the removal of patch simply by the patient if side effects or toxicity occur (9).

### **1.1.2 Disadvantages of TDDS**

Due to skin impermeability which is imposed by the stratum corneum, only potent drugs consider as suitable candidates for these systems. Application of TDDS may also cause different side effects such as contact dermatitis due to one or more components of the system and local irritation of the skin. Sometimes patch application may be uncomfortable and difficult to maintain its adherence for long periods (10)(5).

## **2. Skin Structure and Anatomy**

Human skin is considered as the largest organ of the body, comprising about 10% of the total body mass. It's a highly complex multilayered structure. For designing TDDS, the skin is considered a great challenge to formulations scientists. The properties of the skin limit the number of active ingredients that can be successfully delivered through the skin and achieve therapeutic

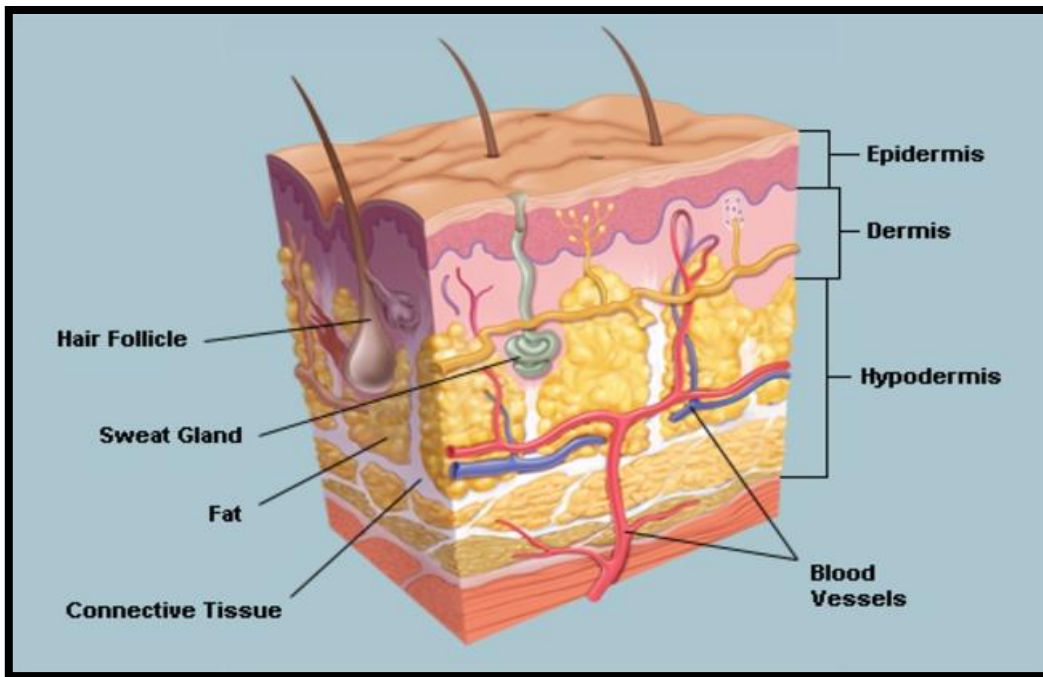


Figure 1: Human skin structure, this figure is adapted from Ref (72).

concentrations (11). Human skin as shown in figure (1) consists of three anatomically distinct tissues, epidermis, dermis, and hypodermis.

## 2.1 Epidermis

The epidermis is a stratified squamous epithelium layer. It consists of two types of cells: keratinocytes and dendritic cells. Keratinocytes are the main type of cells that synthesize the protein keratin. Desmosomes are protein bridges that connect the keratinocytes. The epidermis varies in thickness; ranging from 0.8 mm on the soles of the feet and palms of the hand down to 0.05 mm on the eyelids. Different stages of keratin maturation, as well as keratinocyte morphology and position give rise to four layers of the epidermis which are the stratum corneum (horny layer) and the remainder so-called viable epidermis that lies beneath the stratum corneum (12)(13).

**Stratum corneum (SC)** is the outermost layer of the skin; it is also called the horny

layer which constitutes the main barrier for drug transfer as well as being a protective layer against invasion by foreign materials and prevents water loss. It is made up of layers of dead, hexagonal-shaped cornified cells called corneocytes. This layer varies in thickness according to its location in the skin, being the thickest on the palms and the soles. The barrier nature of this layer depends mainly on its constituents; the corneocytes are composed from proteins mainly, and are low in lipid content, surrounded by stacked layers of lipid bilayers. The epidermal transit time is about 28 days and it's known as the time that the epidermal cells take to move to this layer (12-14).

**Viable epidermis** it lies beneath the stratum corneum. It consists of various layers from

the lower layers moving upwards include stratum basale (basal or germinativum cell layer), stratum spinosum (spinous or prickle cell layer), stratum granulosum (granular cell layer), stratum lucidum. The basal cell layer contains dividing and non-dividing keratinocytes, as these cells divide they move from this deep layer toward the surface, upon their movement they change both by morphology and histochemically, lose their nuclei and cytoplasm in the stratum granulosum layer and undergo keratinization to form the outermost layer of the stratum corneum (15&16).

### 2.2 Dermis

Dermis varies in thickness; ranging from 3 to 5 mm thick layer. It contains a matrix of connective tissue which includes blood vessels, lymph vessels, and nerves. Body temperature is regulated by continuous blood supply which also provides a continuous supply of oxygen and nutrients to the skin while removing toxins and waste products. Sink conditions for most penetrating molecules are maintained due to capillaries reach to within 0.2 mm of the skin surface. In turn, this keeps the dermal concentration of permeate low, and the resulting difference in concentration gradient across the epidermis is what provides the essential driving force for transdermal permeation (1).

### 2.3 Hypodermis

Hypodermis or alternatively subcutaneous fat layer. It represents a fat storage area that supports both the dermis and epidermis. This layer plays an important role in temperature regulation as well as nutritional and mechanical support. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. In the case of topical drug delivery, only penetration through the stratum corneum is essential and then retention of drug in skin layers is

desired whereas, for transdermal drug delivery, the drug has to penetrate through all these three layers and reach into the systemic circulation (17-19).

## 3. Drug Permeation Through the Skin

There are three main ways by which drug molecules can cross the skin; via the appendageal (shunt routes), intracellular or transcellular route and intercellular route.

Skin appendages include sweat glands, and hair follicles with their associated sebaceous glands. They are of little importance since they compromise only 0.1% of the total skin area (20). Transcellular drug transport involves partitioning of drug molecules into keratin-filled corneocyte and then diffusing of the drug through the corneocyte before partitioning into the intercellular lipid region and then diffusing through it (11). In regard to the 'brick and mortar' structure of the stratum corneum, the intercellular route represents a great challenge for drug permeation. The drug molecule needs to pass through a tortuous pathway in contrast to the direct path that observed with the transcellular route. Another reason is that intercellular route represents a region of alternating bilayers, as a result the drug molecule must partition into and diffuse through repeated aqueous and lipid domains. Most small unionized molecules can pass through this path (14).

## 4. Strategies to Enhance Transdermal Delivery

Although transdermal delivery of the drugs seems to be a great alternative to other routes of drug delivery, permeation via the stratum corneum remains a big challenge. Stratum corneum is a formidable skin barrier and efforts have been made to overcome it. There are many ways to improve the transdermal permeation of drugs; they can be classified into active or physical and passive or chemical strategies.

### 4.1 Physical Methods

They involve the application of external stimuli for the active enhancement of transdermal permeation (21).

#### 4.1.1 Sonophoresis

It refers to the application of ultrasound to enhance transdermal drug delivery. The exact mechanism of how ultrasound works to increase transdermal permeability is poorly understood. However, acoustic cavitation which structurally modifies stratum corneum lipids to create diffusional channels could be the possible mechanism of ultra-sound induced permeation(22). Increased skin permeation by thermal effects has been also hypothesized which increased skin permeability coefficient and drug diffusion coefficient (23). An enhancement of skin permeation by ultrasound widens the advantages and application of transdermal delivery. It can be classified into low, intermediate, and high-frequency sonophoresis according to the applied frequency. Sonophoresis can be used as pre-treat for the skin before drug application as a means to increase its effect or as a formulation that can be applied at the same time. Although that there are many compounds are marketed as ultrasound-enhanced transdermal delivery such as Lidocaine which was approved in 2004, there are still some challenges regarding this

technology which include the development of inexpensive ultrasound devices that can assure efficient transdermal delivery as well as safety of this technology remains an issue since high-frequency ultrasound may induce second-degree burns (21).

#### 4.1.2 Microneedles (MNs)

Recently, MNs have been introduced as an effective way to enhance drug penetration into the skin. They are painless, micronized projections arranged in arrays, when applied to the skin it can increase percutaneous permeation dramatically. The first report on this system was in late 1990. Since stratum corneum thickness is only 10-20 $\mu$ m, MNs with few hundreds of microns are capable of delivering the drug and bypass this barrier successfully (24). MNs are painless since they avoid the sensory nerve fibers (25). Structurally, MNs can be classified into four types namely, solid MNs, dissolving MNs, coated MNs, hollow MNs. Solid MNs can be used as skin pre-treatment to enhance percutaneous drug permeation. In this type, the MNs penetrated the skin, and then the drug is delivered by the channels that are generated, hence this type use the 'poke and patch' approach of delivery. Various materials such as silicon, polymers including both biodegradable and non-degradable polymers such as polylactic-coglycolic acid (PLGA), maltose, and metals including stainless steel and nickel has been used to form solid MNs (26). Dissolving MNs are driving attention due to their advantages over the other types including high drug loading, convenience, and easy method of fabrication. This type uses the 'poke and release' approach of delivery which relies on the penetration of the skin by the microneedle patch and then drug release from the loaded dissolving tips. Polymers such as polyvinyl alcohol were utilized and dissolved four minutes after their insertion into the skin (27). Hollow MNs use the 'poke and flow' approach of delivery via

micronized holes within the needles. Materials such as glass, silicone, and stainless steel can be used to fabricate this type of MNs. Flow rate via the holes has to be controlled since a high flow rate may cause pain. Besides drug delivery, hollow MNs can be exploited in blood extraction analysis as they utilize the poke and flow approaches. Coated MNs utilizes the 'coat and poke' approach of delivery, which includes insertion of the microneedle patch firstly into the skin followed by the release of the drug-coated on the microneedle tips. Coated MNs are solid MNs with superior advantage and patient compliance; they are considered as single-step administration systems comparing to solid MNs which are complex two-step administration systems(28). Stainless steel and titanium have been employed as materials to fabricate this system. In summary, MNs are advanced drug delivery systems that can be fabricated from a wide range of materials including polymers, inorganic materials, and metals with a variety of applications but safety concerns have to be considered such as pain associated with their administration and the potential of the materials used in fabrication to cause irritation and erythema and post-application infection (29-31).

#### 4.1.3 Iontophoresis

It involves the use of low current intensities ( $0.5\text{mA}/\text{cm}^2$ ) to enhance the transdermal permeation of ionized molecules. Phoresor™ system was pioneered by IOMED inc. has been approved by the FDA as a physical medicine delivery device (32). Iontophoresis depends on the fact that like repels like; when ionized drug molecules are to be delivered, the positive molecules will be attracted to the electrode with the same polarity; anode, and when electromotive gradient passes it will go through or into the stratum corneum (33). In the case of neutral or uncharged solutes, they can be candidates for iontophoresis as well after some

modifications in their physicochemical characteristics such as synthesis of water-soluble prodrugs with ionizable moieties (34). There are three ways for drug permeation into the stratum corneum; transcellular and intercellular and trans appendageal route with the latter thought to be the least electromotive resistance (35). Many factors affecting iontophoresis drug delivery include the concentration of the drug molecule, pH of the system, current intensity, and permeant type (36). Drawbacks of iontophoresis include current limitations which is  $0.5\text{mA}/\text{cm}^2$  or less and minor skin irritation and erythema at the site of application of iontophoretic patch (37).

#### 4.1.4 Thermal ablation

It's a technique that involves the application of heat to increase drug permeation via the skin causing depletion of the SC without damaging the deeper underlying tissues with an exposure period ranging from 1 microsecond to 100 millisecond. The underlying mechanism involves stratum corneum vaporization followed by its removal without damaging the deeper tissues. This can be done in two ways: 1) moderate temperature (less than  $100^\circ\text{C}$ ) for a long period or 2) high temperature (more than  $100^\circ\text{C}$ ) for short period with the latter being more favorable to avoid skin damage. Different ways can be used to perform thermal ablation include chemical heating, radiofrequency, and laser. Thermal ablation has been widely used to deliver macromolecules and vaccines but care should be taken since excessive heat may damage the deeper layers and cause thermohaemolysis(38&39).

#### 4.1.5 Velocity based devices

They include the application of velocity within the range of 100-200 m/s to punctuate the skin making use of compressed gas or coiled spring as a power source. This technique was used mainly to deliver vaccines as well as macromolecules

including monoclonal antibodies and hormones besides nucleic acids providing a needle-free approach based on jet injection for drug delivery. Although this technology offers a good alternative for the usage of conventional needles, it had some limitations reported during their usage including pain and bruising at the site of administration (40).

## 4.2 Chemical Methods

Chemical or passive methods to enhance transdermal permeation include: chemical penetration enhancers, eutectic systems, prodrug (41).

### 4.2.1 Chemical enhancers

Chemical enhancers are one of the most commonly used methods to enhance skin penetration. Drug partitioning into the skin can be increased by several mechanisms; either by extraction of intercellular lipids or proteins of the stratum corneum or by hydration of the stratum corneum which temporarily and reversibly change the barrier nature of the skin and increases drug penetration. Ideally, the chemical enhancer should be non-toxic and non-irritant, compatible with other ingredients, biodegradable, cheap, and available, and change the morphological nature of the skin reversibly. There are many classes of penetration enhancers depending on their chemical structure includes fatty alcohols like (propylene glycol, ethanol), fatty acids like (oleic acid), sulfoxides like (dimethylsulfoxide DMSO and dimethylformamide DMF), terpenes like camphor, surfactants (cationic, anionic, zwitterion, non-ionic) and urea (42). The safety of penetration enhancers should be concerned since they have the ability to cause skin irritation including swelling, local inflammation, erythema, and dermatitis (43).

### 4.2.2 Eutectic systems

Eutectic systems are drug formulation that combines two compounds in an adequate ratio and the resultant mixture substance have a melting point lower than this of each compound alone. This lowering of melting point leads to an increment insolubility in the stratum corneum lipids and hence better skin penetration. EMLA® cream a topical local anesthetic is an example of a eutectic mixture that composed of lignocaine and prilocaine (1:1), when compared to a placebo, it dramatically reduced the pain associated with venous cannulation in children. However, the formulation of this system is challenging originated from the use of two functional components in one topical formulation (44&45).

### 4.2.3 Prodrug

It's a compound that is inactive in its parent form and after entering the body it will convert back to its active form. This approach has been investigated for transdermal delivery; the resultant prodrug has different physicochemical properties including lipophilicity, partition coefficient and solubility, and as a result better skin penetration. Prodrug is formed upon modification of the chemical structure of the drug most commonly covalent linkage of the active drug with inactive moiety by an ester bond. Upon contact with skin, non-specific esterases of the skin will cleave the bond, liberating the active drug to exert its action (46&47). Many drugs showed improved permeation making use of this approach for example diclofenac acid prodrugs formation to enhance transdermal delivery (47).

## 4.3 Nanocarriers

Various nanocarriers systems have been used to enhance transdermal delivery. These carriers can be divided into lipid-based formulations and polymeric nanoparticles.

### 4.3.1 Lipid-based formulations

These include liposomes and their analogues and lipid nanoparticles.

#### 4.3.1.1 Liposomes

They are spherical vesicular systems consist of one or more lipid bilayers that contain a hydrophobic head and a hydrophilic tail. They consist of phospholipids with or without cholesterol. Phosphatidylcholine is the main phospholipid from egg yolk or soybean. Their unique structure allows them to incorporate both hydrophilic and hydrophobic drugs besides being non-toxic and biodegradable systems(48). However, it has been reported that these systems are able only to stay at the skin surface without penetration into the deeper layers of the epidermis which eventually leading to minimal amounts of the loaded drug reaching the systemic circulation. As a result, these systems are mainly used for topical preparations to treat skin diseases providing prolonged retention of the drug with sustained-release(49).

Manca *et al.* incorporated allantoin that is used for skin scars treatment into conventional liposomes and an argan oil containing liposomes to increase skin hydration and improve local accumulation. For comparison, allantoin in water dispersion and commercial gel formulation (sameplast®gel) were used. In the case of conventional liposomes, allantoin accumulation in the dermis was double ( $\sim 3.4 \mu\text{g}/\text{cm}^2$ ,  $p < 0.05$ ) with respect to that provided with the commercial gel. In argan oil liposomes, important drug accumulation improvement was observed in the epidermis ( $\sim 2.2 \mu\text{g} / \text{cm}^2$   $p < 0.05$  versus all) and mostly in the dermis ( $\sim 8.7 \mu\text{g} / \text{cm}^2$   $p < 0.01$  versus all). Besides, both of conventional liposomes and argan oil liposomes showed a significant increase in the amount permeated via the skin which was  $33 \mu\text{g} / \text{cm}^2$  ( $p < 0.05$  versus water dispersion and sameplast®gel

values) and only  $17 \mu\text{g}/\text{cm}^2$  in case of water dispersion and sameplast® gel(50).

#### 4.3.1.2 Niosomes

Niosomes are liposome-like structures, they are vesicular systems made of non-ionic surfactants associated mainly with cholesterol. They lack phospholipids in their structure, therefore prevent oxidative degradation and provide higher chemical stability in comparison to liposomes (48). They have been widely investigated to enhance drug permeation in TDDS, for example A.S. Zidan *et al.* prepared simvastatin niosomal gels as a possible transdermal application system for pediatric. *In-vivo* pharmacokinetic data showed a significant reduction in cholesterol and triglycerides level with an increment in high-density lipoprotein level after transdermal niosomal administration to rats and an augmentation in simvastatin bioavailability by three folds approximately when compared to an oral drug suspension. This finding suggests that niosomes do not only have the ability to improve bioavailability and enhance hypolipidemic activity but also can be a promising dosage form to treat pediatric hyperlipidemia (51). Ethosomes are soft, flexible vesicular systems that contain ethanol in relatively high concentrations 20-45%. They are composed of phospholipids bilayers enclosing the hydroalcoholic core. Hydrophilic and lipophilic molecules can be incorporated into ethosomes. The presence of ethanol in this system provides many advantages over other vesicular systems includes high permeation ability into the skin by acting as an effective penetration enhancer as well as the production of smaller particles when prepared under the same procedure besides, increases the flexibility and system fluidity(52). Ethosomes have a wide variety of applications includes microbial and viral



skin infection treatment, testosterone ethosomes for hormonal deficiency and minoxidil ethosomes for hair loss, and other miscellaneous applications (52).

#### **4.3.1.3 Transfersomes**

Transfersomes have been identified in the 1990s by Cevc *et al.*(53). They are composed of phospholipid bilayers along with edge activator, water, and small percentage of alcohol. The presence of edge activator confers the deformability and ultra-flexibility behavior of the transfersomes, providing an extraordinary ability for them to squeeze themselves into the barriers and pores of the skin and giving rise to excellent skin permeation(54). They are capable to squeeze themselves to about ten times smaller than vesicle diameter without deformation or fragmentation. Compared to liposomes, they can penetrate deeper into skin layers and reach the systemic circulation more efficiently. The most common edge activators used are surfactants such as span 80, tween 80, and sodium cholate. Besides vesicle flexibility, these surfactants can play a great role in skin permeation by fluidizing, and solubilizing skin lipids. Transfersomes have wide applications in transdermal delivery such as the delivery of antioxidants, anticancer drugs, corticosteroids, and anti-inflammatory drugs (55).

#### **4.3.1.4 Invasomes**

They are vesicular nanocarriers that have been developed after the encouraging results of transfersomes. They consist of phospholipid bilayers, ethanol, and terpenes. The presence of terpenes act as penetration enhancers; they create elastic vesicles and fluidize stratum corneum lipids which make invasomes have a superior advantage over liposomes(56). Ethanol addition aids to create deformable vesicles as well by fluidizing the lipids in the vesicle structure and hence increasing their permeation. Invasomes are used to enhance the

permeation of a wide variety of drugs examples including Avanafil, Isradipine, and phenyl ethyl resorcinol(57).

#### **Lipid nanoparticles**

They include solid-lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions.

#### **4.3.1.5 Solid-lipid nanoparticles**

Solid-lipid nanoparticles are colloidal dispersions consist of solid, biodegradable lipid matrices, ranging in diameter (10-1000 nm) and remain solid at room temperature (58). They can incorporate both lipophilic and hydrophilic drugs providing controlled release and excellent stability and protection of sensitive drugs from the surrounding environment. Besides, they can be used in targeted drug delivery (59). Major drawbacks of solid-lipid nanoparticles include limited drug loading and drug expulsion that follows the polymorphic transition of the solid lipids. Examples of drugs prepared as solid-lipid nanoparticles for cutaneous use include methotrexate and etanercept as combination therapy for topical psoriasis treatment and solid-lipid nanoparticles of aconitine which were prepared to improve drugs safety and permeation (60).

#### **4.3.1.6 Nanostructured lipid carriers**

The updated form of the solid-lipid nanoparticles. They were developed to overcome the limitations of solid-lipid nanoparticles. The internal core consists of solid lipid and liquid lipid which differs from solid-lipid nanoparticles wherein only solid lipids are present. They form a unique structure with high drug encapsulation efficiency and lesser drug discharge upon storage which makes them a suitable dosage form for long- term skin administration. When nanostructured lipid carriers have been used in topical delivery, they showed better skin targeting and permeation and minor skin irritation for many therapeutic agents such as flurbiprofen and

indomethacin as anti-inflammatory agents and podophyllotoxin for warts treatment (61).

#### 4.3.1.7 Nanoemulsion

Nanoemulsion is an emulsion with a very fine droplet size (20-200 nm) which is thermodynamically and kinetically stable (they do not show flocculation or coalescence upon storage). It consists of droplet (oil) phase dispersed in an aqueous phase and stabilized by surfactants or co-surfactants. Nanoemulsion is a lipid-based formulation and therefore it is suitable for the incorporation of lipophilic compounds, improving their solubility and bioavailability (62). Drawbacks of this system may include a costly manufacturing process, the availability of surfactants and Ostwald ripening which includes the growth of larger droplets when the smaller droplets dissolve, and deposit on the larger ones (63). Examples of compounds delivered transdermally using NEs include clobetasol propionate and calcipotriol as nanoemulsion loaded gel for psoriasis treatment (64), and nanoemulsion of caffeine for transdermal delivery (65).

#### 4.3.2 Polymeric nanoparticles

Polymeric nanoparticles are colloidal nanocarriers with a size range from 10 to 1000 nm. A polymeric nanoparticle is composed of a polymer that contains a drug either encapsulated, adsorbed, or chemically linked to the surface of the particle. Their structure has been identified in 2002 by Discher and Eisenberg (66). Polymeric nanocarrier-enhanced topical delivery of drugs has obtained an interest since it offers several advantages compared to other nanocarriers such as protecting the encapsulated drug from degradation, providing sustained and controlled release, and hence reduces side effects especially of toxic drugs and increases skin permeation of the drugs as well as improving the bioavailability of poorly water soluble drugs

(67). Polymeric nanoparticles can be classified into two types, including nanospheres and nanocapsules according to their structure. Nanospheres or matrix systems consist of a matrix in which both the drug and the polymer are uniformly dispersed, whereas nanocapsules have a core-shell structure with the active compound being encapsulated in an aqueous or oily core and surrounded by the polymer around (66). Their relatively small size, and surface modifications of polymeric nanoparticles can greatly enhance the interaction of the active substance with their targeted site (68).

P. Dong *et al.* investigated the cutaneous penetration of model drugs using pH-sensitive Eudragit L100 polymeric nanoparticles. In the case of dexamethasone-loaded Eudragit L100 PNPs, results showed an improvement in cutaneous penetration in comparison to a commercial cream. Besides, *in-vitro* rapid release of the drug was triggered by pH above than 5.9, and that faster drug release and higher penetration into skin layer obtained in barrier-disrupted skin. For the other drug, which is lipophilic, Nile red loaded with Eudragit L100 PNPs showed high transfollicular penetration of the drug and improved cutaneous penetration and controlled drug release of this lipophilic drug and most favorably on barrier-disrupted skin (69). In a different study, dexamethasone-loaded PNPs were formulated using various polymers, including Eudragit L100. The results showed that Eudragit polymers including the Eudragit L100 were dissolved at pH 7.5 and released 65-70% of the drug within 7 hours whereas they remained intact at pH 6 buffers and released the drug slowly and this ensures the pH-dependant action of Eudragit L100 and that it releases the drug in a different manner at the skin surface whereas it dissolves and gives fast release at the deeper hair follicles as it has higher pH levels (70).

Another study reported by Rajesh *et al.* included the preparation of Curcumin-encapsulated Chitosan Nanoparticles for transdermal delivery. *In-vitro* release studies for the nanoparticles were performed at two different pH; acetate buffer pH 5 and PBS pH 7.4 to simulate skin pH and physiological pH, respectively. Drug release results showed that no initial burst release was seen at either pH with the controlled release over time. At pH 5,  $41.5 \pm 1.1\%$  of the drug released by the end of 24 hours whereas only 19% of the drug was released in PBS 7.4 at the same period due to pH-dependant swelling behavior of the polymer, Chitosan. *In-vitro* permeation results using the Strat-M® membrane showed that a significant amount of Curcumin permeated from both formulations (3:1 and 5:1) in comparison to control (curcumin solution) ( $p < 0.05$ ) (71).

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## 5. Conclusion

The transdermal drug delivery system represents a good alternative for oral and parenteral therapy. Various penetration enhancing strategies have been successfully employed to enhance the permeation of low molecular weight molecules. For high molecular weight molecules, active strategies such as microneedles and iontophoresis can be used. Nanotechnology has derived great attention lately; by fabricating any kind of drugs into compounds within the nanometer range, permeation into skin could be enhanced greatly but challenges remain in the number of manufacturing steps as well as the cost of characterization methods.

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