Review

Naseem Akhtar, Varsha Singh, Mohammad Yusuf and Riaz A. Khan*

Non-invasive drug delivery technology: development and current status of transdermal drug delivery devices, techniques and biomedical applications

https://doi.org/10.1515/bmt-2019-0019
Received January 23, 2019; accepted August 30, 2019

Abstract: Pay-load deliveries across the skin barrier to the systemic circulation have been one of the most challenging delivery options. Necessitated requirements of the skin and facilitated skin layer cross-over delivery attempts have resulted in development of different non-invasive, non-oral methods, devices and systems which have been standardized, concurrently used and are in continuous upgrade and improvements. Iontophoresis, electroporation, sonophoresis, magnetophoresis, dermal patches, nanocarriers, needled and needle-less shots, and injectors are among some of the methods of transdermal delivery. The current review covers the current state of the art, merits and shortcomings of the systems, devices and transdermal delivery patches, including drugs' and other payloads' passage facilitation techniques, permeation and absorption feasibility studies, as well as physicochemical properties affecting the delivery through different transdermal modes along with examples of drugs, vaccines, genes and other payloads.

Keywords: biomedical applications; drug delivery devices; drug delivery systems; drug release; electroporation; enhanced bioavailability; iontophoresis; magnetophoresis; sonophoresis; transdermal drug delivery.

***Corresponding author: Prof. Riaz A. Khan,** Department of Medicinal Chemistry, College of Pharmacy, Qassim University, Qassim 51452, Saudi Arabia; and Manav Rachna International University (MRIU) and Manav Rachna International Institute of Research and Study (MRIIRS), Faridabad, HR 121 001, India, E-mail: kahnriaz@gmail.com. https://orcid.org/0000-0003-0185-0149
Naseem Akhtar: Department of Pharmaceutics, College of Pharmacy, Buraydah Colleges, PO Box 31717, Qassim 51418, Saudi Arabia
Varsha Singh: Manav Rachna International University (MRIU) and Manav Rachna International Institute of Research and Study (MRIIRS), Faridabad, HR 121 001, India
Mohammad Yusuf: College of Pharmacy, University of Taif, Taif Al-Haweiah, Taif, Saudi Arabia. https://orcid.org/0000-0003-1417-7774

Developmental perspective: an introduction to TDDS

The transdermal drug delivery system (TDDS) is a painless, non-invasive method of drug delivery and takes precedence over other conventional delivery routes in this matter. Here, the drug is delivered in a discrete dosage form from a skin-sticker patch or other transdermal methods/device by crossing through the skin layers to the systemic circulation. The TDDS has made a significant influence on a number and variety of therapeutic agents' delivery, especially in pain management, hormonal therapy, and cardiovascular and central nervous systems' diseases. The technique has proven to be a successful substitute for various routes of administration, e.g. oral, parenteral, intravenous, intramuscular, hypodermal shots, and other invasive delivery modes. However, it is still far from utilizing its complete potential, and the basic TDDS/devices still deliver small doses of drugs which are preferably lipophilic in nature. However, more advances in the TDDS techniques and discovery of delivery devices over time have resulted in delivering both lipophilic and hydrophilic, as well as amphiphilic drugs, sometimes with the help of delivery/permeation enhancers as well as newer physical techniques of delivery with minimal damage to the soft tissues of the skin. Nonetheless, the dose levels are still not competitive in comparison to the traditional delivery options. In this connection, the ability to use voltage-gradient iontophoresis with proper and steady regulation of drug distribution has afforded better delivery choices and performance. Microneedles, thermal ablation, microdermabrasion, electroporation, radiofrequency usage, microporation, use of thermal techniques, micro and radio waves, electro-mechanical devices, nano deliveries and cavitational ultrasound techniques have immensely contributed toward making the initial TDDS techniques more user-friendly, competitive in dose delivery levels, cost-effective, viable to opt and feasible to use. The advent of innovative new approaches and continuous technology development has made the TDDS today a top contender for drug delivery modes preferences.

Historically, after the successful launch of scopolamine patch as the first TDDS to treat motion sickness and nausea, nicotine patches have turned out to be a mega medicine after a decade of launch, which has increased the acceptance and importance of transdermal delivery in therapy and prophylactics with greater interest for people in them. The transdermal route for administering a drug also has great potential in the medical device markets for both over-the-counter and prescription drug segments. The current (*ca* 2019) market of transdermal patches in the US and globally is estimated to be very high at between 1500 million and 4500 million USD (US Dollars), respectively, and is expected to rise at ~7% annually over the period until 2024 [1]. Patches for nicotine replacement therapy and female contraceptives are very popular, while patches made for insulin and other vaccinations are in early marketing and clinical trial levels, respectively, which may be commercialized soon (Table 1).

The TDDS technique helps to decrease the dose, enhance the therapeutic efficacy and therapeutic value, and circumvent the problem associated with a drug's toxicity, drug formulation problems as well as related troublesome pharmacokinetics, if any. The technique also avoids therapeutic failures, losses of dose-frequency and chronological dosings for the patient. The technique works as a self-administered, non-invasive, painless tool and typically allows less frequent or one-time dosing application in comparison to oral and other routes of administration. It is also, by and large, inexpensive and convenient for patients who want to get rid of remembering to take tablets/pills, and is a relief for their caregivers [2–5]. The delivery mode is helpful in maintaining the drug plasma levels due to consistent infusion and bioavailability of the drug. The drug spreads in the systemic flow by escaping the first-pass metabolism in the liver, and no obliteration of the drug takes place [4]. Moreover, the technique provides an extended period of bioaction, which also results in dropping of the dosing frequency, and as a result, the associated side effects, if any, are minimized. The estradiol patches, popular in millions of patients worldwide, avoid causing liver damage as compared to its oral formulations. The first transdermal patch, scopolamine for treating motion sickness and nausea, is more comfortable than medications such as Zofran (ondansetron) and Phenergan (promethazine). People suffering from angina wear the nitroglycerine patch for 12–14 h a day to relax blood vessels, which considerably lowers the frequency of angina and the consumption of sublingual nitroglycerin [5]. A comparative study among oral formulations (in tablet form of 50 mg, 3 times daily for 3 days) and a transdermal patch of diclofenac (applied once a day for 3 days) was carried out on 20 young pre-orthodontic patients, and statistical records of pain relief and pain intensity were recorded. Though both had nearly the same outcomes, the subjects were happier with using patches (as it was a one-time per day application) with comparatively less of systemic adverse effects [6]. However, skin reactions, skin decoloration, allergies, disruption of the skin-barrier layers and blood level alterations are the pitfalls of this technique. Skin reactions, although many, including contact dermatitis, with the most common and foremost being allergy and/or topical irritation, are wide-spread for certain patches but also depend upon the individual using them. Nonetheless, the majority of drugs' adverse reactions (ADRs) are mild in nature and the cessation rate is low (1.7–6.8%) [7–10]. The permeability levels and barrier functions of the skin keep on conditionally changing with the change of patch, sticking-site on the skin and the age of the person. However, some of the drugs necessitate high blood levels and hence cannot be administered topically. Another important disadvantage of the TDDS, especially for patches, includes an inherent adhesive system which may become the cause of the failure or the reason for problematic delivery. However, modified adhesives are continuously improving the situation but the same adhesive may or may not work for all skin types and its properties may get disrupted due to sweating, showering or swimming [2, 7, 11] and at certain times, the drug permeation may not

Table 1: Some recently developed/to-be-launched TDDS products.

Serial	Product's usage	Product's description	Manufacturer
1.	Smoking therapy	Reduces smoking desire by administering nicotine	Chrono Therapeutics
2.	PAQ	Deliver insulin for type-II diabetics	CeQur
3.	Dermo-patch	Skin rejuvenation and spot correction treatment	Filigree Dermo-Innovation
4.	Energizing eye patch	Cosmetic patch for skin rejuvenation	Patchology
5.	Beauty patch (at R and D stages)	A printed bio-battery for innovative energy efficiency. The beauty patch is used for cosmetic improvement by releasing enzymes into the skin	VIT-Technology for Beginners

TDDS, transdermal drug delivery system.

be feasible due to compatibility reasons associated with the adhesive, and various problems may arise making the device uncomfortable to wear. Another major shortcoming of the TDDS patches is that they are late in performing the therapeutic action in comparison with other routes of administrations, especially intravenous delivery. Additionally, the drug infusion frequency may also fluctuate by the site of the TDDS application. Infusion rates are good at places like palms, face and genitalia, although some cases have been reported where an overdose of the drug was delivered by a broke-up, cut-open or chewed-upon TDDS patch/device, or too many non-compatible devices were worn, or multiple TDDS devices used by the patient. Over-dosing can also happen if a child wears the patch prescribed for an adult. At times, the TDDS can cause local edema, skin irritations and burns, which may be due to the drug's nature, reactivity, nature of the formulation, the patch's paste material, or other excipients, delivery enhancers and adhesives present or, used and retained in the TDDS preparations. Therefore, the transdermal patches have several limitations and they may act as hindrance to effective delivery of a variety of drugs.

Skin and drug permeation: routes and factors

For the TDDS to be effective, it is required that the drug loaded inside of the transdermal drug delivery device is absorbed into the systemic circulation after passing through skin layers at an effective level of consistent rate and continuous supply during the usage period. The percutaneous absorption facilitates the infusion of diverse but characteristically defined molecular entities across the skin barrier, and any further absorption of the substance gets it into the systemic circulation. The absorption ideally follows two ways, the trans-epidermal and the trans-follicular routes. The drug from the TDDS device comes to the blood tributary and enters the systematic circulation either from the stratum corneum (SC, a layer in skin), (trans-epidermal) or, from the appendage (trans-appendage) areas of the skin. In the case of the trans-epidermal route, the drug diffusion can further follow two likely paths: intracellular and intercellular. In the intracellular or transcellular route, the hydrophilic drug crosses through the cells with assistance from lipid lamellae, and the hydrophilic drugs cross the SC due to the hydrophilic nature of the keratinocytes, both ultimately reach to the systemic circulation. The intercellular route is considered the principal transdermal delivery route which lets molecules pass between the cells of the SC that facilitate the nonpolar, lipoid entities. Transfollicular penetration (shunt pathway) is also of great importance for delivering large polar products wherein the drug molecules sense their paths through hair cavities, the sebaceous gland of pilosebaceous units or the watery/fluid route. Although hair cavities and sweat glands merely encompass 0.1% of the entire skin layer zone, which comparatively is a very minor part, the shunt pathway entails minimum risk and is ranked the most feasible among all other skin routes [12, 13] (Figure 1).

The physiochemical and physiological factors are vital in the drug infusion phenomenon through the skin. Moisture contents, anatomical location and age of the skin have important roles to play in controlling the absorption rate. Due to lack of moisture, aged skin does lesser and slower absorption than younger skin [14, 15]. The local metabolism and decreased blood flow results in a negative impact on drug influx through the skin [15], which is a passive process, and an increase in the temperature changes the dynamics of the absorption due to increase in drugs' kinetic energy. As a consequence, some perturbations take place in SC and the tissues located below it which makes the drug material move faster [15, 16]. Nonetheless, there are issues affecting the drug absorption. For a molecule to get a clear path across the SC, it should have desirable physicochemical traits compatible with the skin barrier properties [17].

The SC, a selectively permeable and rate-determining layer, is a lipophilic coat [18]. The low levels of

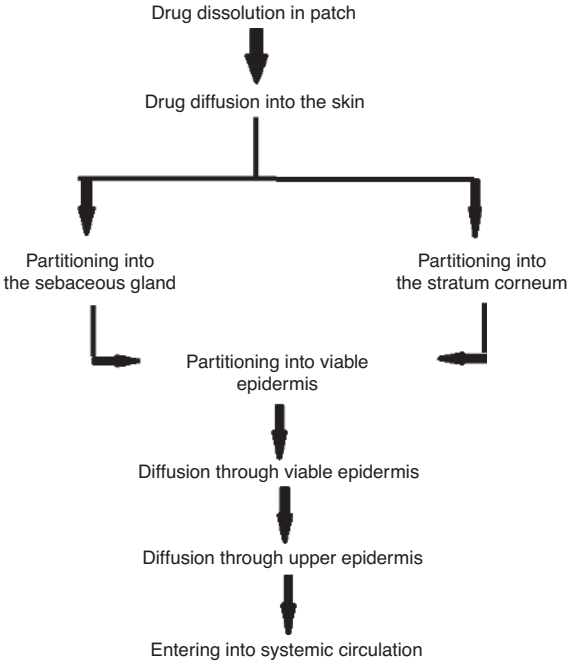

Figure 1: Drug absorption routing through the skin.

hydration in the living cells of the viable epidermis and other SC underneath layers of the skin together with the inherently present aqueous affinity therein allows the drugs having both hydrophilic and lipophilic properties to infuse through the skin layers [19, 20]. However, structural changes to adjust the required amphoteric solubility in a hydrophilic drug can be achieved by salt formation, esterification and methylation or capping of the hydrophilic moieties in the drug, as also approached for prodrug formation, and can help with the solubility issues and consequently enhances permeation. However, hydrogen bonding decreases drug permeation, and increased bonding tends to inhibit the drug permeation [15].

Diffusion through the skin needs drug partitioning in the skin layers [21], and based on this partitioning behavior, hydrophilic drugs pass easily *via* the intracellular paths while lipophilic drugs would normally use the intercellular pathway. Partitioning of the drug, represented by the partition coefficient, log P, is a crucial indicator of skin permeability of a drug [22, 23]. Again, the log D (distribution coefficient) value of a drug is also an important factor determining transdermal infusions. Under normal diffusion conditions, the skin easily allows drugs with an average molecular weight (MW) of <500 Da [15]. Molecular size and transdermal penetration follows an inverse relationship [24].

Among other physical factors influencing permeation are the drugs' melting points, ionization capabilities and the crystallinity of the drug molecule. Drugs with higher melting points, generally above 150°C, show lower aqueous solubility [25], and therefore, drugs with a low melting point possessing increased solubility show enhanced permeation. A relationship between the melting point and solubility has been devised [26].

The partition coefficient of a drug is an other important factor determining the choice of the pathway of permeation. The log P values of drugs lower than –1 pose difficulty in permeation through SC, and molecules above log P – 1 are good enough for delivery. However, products with a log P value above 2 are stuck in the SC [22]. However, another report states that drugs with a log P value in the range of 1–3 have crossed the SC barrier and were delivered to the intended site [15]. A linear relationship between the partition coefficient and transdermal delivery has been noticed. Moreover, higher loading/higher concentrations of the drug are favored for elevated levels of the concentration gradient across the skin which facilitates the delivery. However, any injury to the skin affecting the SC disrupts the delivery [27, 28].

The degree of drug passage, in case of ionized drugs, is comparatively lesser than the unionized drug, and the shunt pathway is followed [15]. The pH value of the epidermis layer of the skin ranges from 7.3 to 7.4, while the pH in the SC layer is 4.2–5.6. The level of the uncharged drug passage at the site of absorption depends on its hydrogen ion concentration [H^+] and the dissociation constant (D) [17, 29–31]. The SC favors hydrogen bonding, and the drug molecules' H-bonding with various skin components have lengthy/paused duration of drug absorption and drugs infusion effectively stops through the skin albeit a little over time [15]. Melting point and drug solubility are inversely proportional [25], and an increase in drug solubility decreases the SC infusion and passage through the skin [32]. Moreover, saturated solutions have maximum thermodynamic activity [33] and are helpful in permeation.

Other physiological factors that influence drug absorption are temperature, blood flow to the skin and enzymatic activity of the skin. The anatomical location of the skin plays its part in the delivery. The genital areas have greater absorption capacity as compared to the head, neck, trunk, arms and legs [15]. Racial differences in relation to lipid contents in skin permeation have been researched and been found to vary according to the lipid component ratio in the skin layers [14, 15, 30, 31, 34, 35]. An increase in temperature increases the kinetic energy of the drug molecule and the molecule passes the skin-barrier easily and fast [15, 16].

The metabolic enzymes present in the skin cause biotransformation and may help the prodrug if it is designed to pass the skin barrier through structural changes sought by the metabolic bioconversions, making it one of the rate-determining steps, and the metabolic phenomenon is the highest in the epidermis section of the skin [36].

In this context of permeability, the obviousness lies in the size of the drug molecule. Low molecular weight (LMW) under 500 Da and smaller size and molecular volume of drugs have preferentially been found suitable for passive diffusion through the skin, although with some exceptions [37] suggesting that the upper limit of the MW range of a drug could indeed exceed 500 Da, but they still efficiently permeate the skin through passive diffusion. However, the drug cannot attain a very high level of concentration in the plasma, and periodic or pulsating drug delivery is not possible in the TDDS yet.

Product development approach: quality by design (QbD)

Several approaches have emerged over time to develop the desired TDDS products and devices. The development has

centered on the physicochemical properties of the drug, formulating and device's constitutional components, and their characteristics in considerations with the skin sites. Fundamentally, the initial development was focused on the indirect methods to cross the skin barrier and enhance the drug influx and permeability by design considerations. The membrane permeation, diffusivity, maintaining drug gradient in transport through the skin, adhesive properties and its role in drug release, the micro-reservoir of the drug for constant, uniform and sustained release kinetics are some of the factors. Membrane-moderated delivery systems were developed wherein the solid drug is dissolved in a solid polymer matrix or kept suspended in a viscous media inside a shallow compartment from where the drug was modulated through a drug-impermeable metallic plastic laminate and a rate-controlling polymer-based diffusible membrane. The drug molecules are allowed to be released only through the rate-controlling polymeric membrane, which needs to be a microporous or a non-porous entity with known drug permeability properties. To achieve an intimate contact of TDDS with the skin surface, a thin layer of the drug-compatible hypoallergenic adhesive is applied [28, 36, 38–40]. The intrinsic rate of the drug release from this type of drug delivery system has the delivery relationship expressed as follows:

$$dQ/dT = CR/(1/Pm + 1/Pa)$$

where dQ/dT expresses release rate, and CR equals the drug concentration in the reservoir compartment, Pa denotes the permeability coefficient of the adhesive layer and Pm stands for the permeability coefficient of the rate-controlling membrane.

Thus, the TDDS drug release was maneuvered by polymer composition, the permeability coefficient, thickness of the rate-limiting membrane and the adhesive.

Another design approach, the adhesive diffusion control system, utilized a thin layer of the non-medicated, rate-controlled, adhesive polymer of constant thickness wherein the drug disperses into the adhesive polymer and then spreads across the medicated adhesive and onto the reservoir layer (Figure 2).

The rate of drug release for the adhesive diffusion control system is denoted as follows:

$$dQ/dT = (Ka/r) \times Da \times (CR/\delta a)$$

where Ka/r equals the partition coefficient for interfacial partitioning of the drug from the reservoir layer to the adhesive layer, Da is equal to the diffusion coefficient in the adhesive layer, δa is equal to the thickness of the adhesive layer, and CR represents the drug concentration in the reservoir compartment.

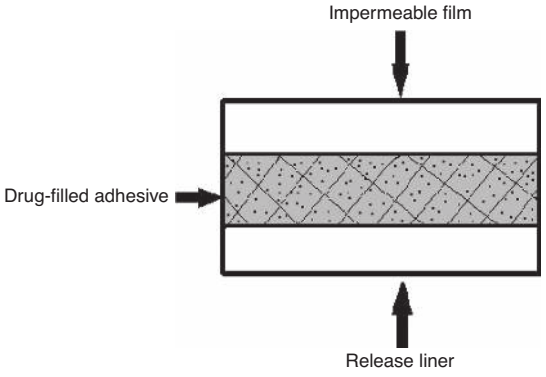

Figure 2: Adhesive dispersion system.

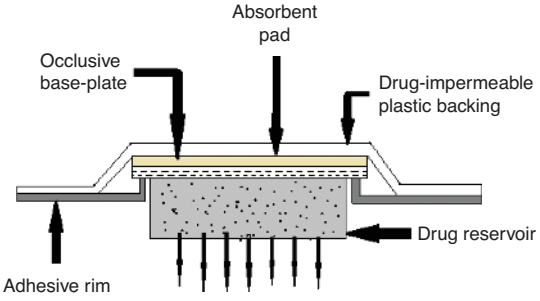

Figure 3: Matrix dispersion system.

The matrix dispersion type systems (Figure 3) were also developed where the reservoir was formed by homogeneously dispersing the drug in a hydrophilic or a lipophilic polymer matrix and then modulated into a medicated disc with a definite and predefined surface area and controlled thickness. For testing, this disc was then glued to an occlusive base-plate in a compartment fabricated from a drug-impermeable plastic backing. The adhesive polymer was spread in circumference to form an adhesive rim around the medicated disc.

The rate of drug release (dQ/dT) from this matrix dispersion system is defined as follows:

$$dQ/dT = \sqrt{A} \times Cp \times Dp/2T$$

where A is equal to the initial drug loading in the polymer matrix dispersal unit, and Cp and Dp are the solubility and diffusivity of the drug in the polymer, respectively, and T stands for the time.

The microreservoir system was formed by suspending the (solid form) drug in an aqueous solution of water-soluble polymer and homogeneously dispersing drug suspension in a lipophilic polymer through high shear mechanical force. The cross-linking of the polymer chain to the medicated polymer disc of constant surface area

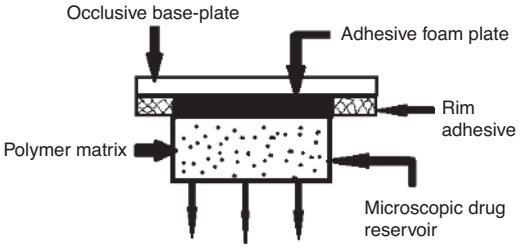

Figure 4: Micro-reservoir system.

and defined thickness stabilized the transdermal drug delivery device/system [41, 42] (Figure 4).

Drug selection: physical, pharmacokinetic and biological parameters

Permeation across skin layers and reach out to the systemic circulation is a gradual process involving penetration, partition and passing through the SC to the epidermis, diffusion into the upper dermis, permeation through downward layers to final absorption into the systemic circulation. The drug in the TDDS is either stored as solid dosage form in a reservoir or is present as a liquid/gel-dissolved material. The flux across the skin is expressed as μg/cm^2/h and the drug is released until the concentration gradient exists [43, 44]. An initial lag time, small or large, exists, and the drug typically follows steady-release kinetics.

The TDDS needs to provide the thermodynamic thrust toward passive diffusion across the skin. As the ability of drugs to penetrate the skin barrier varies, certain drugs have low fluxes and the delivery is constricted. Drug load in the TDDS first meets the challenge of being highly potent in pharmacological action, and secondly being compatible with the transdermal delivery by having a favorable set of physicochemical properties. Nonetheless, the low permeability of drugs owing to the skin barrier has been enhanced through a number of chemical-, physical-, physicomechanical-, radiative- and acoustics-based techniques to enhance the delivery output [44, 45].

Additionally, some of the pharmacokinetic parameters influencing the transdermal drug delivery include half-life of the drug, its volume of distribution, whole body clearance, therapeutic concentrations in plasma and its bioavailability. However, the physicochemical constraints to the TDDS applicability include favorable levels of the molecular properties, and available drug concentration including its solubility, crystallinity, molecular weight, polarity, melting point, partition coefficient (log P), dissociation constant, ionization capability, hydrogen bonding and distribution coefficient (log D) [46]. The biological factors restricting the transdermal drug delivery technique used in patients include skin irritation, site of application, skin toxicity, on-site metabolism, allergic reactions, permeability, and most importantly, the acceptability of the undesired effect(s) by the patient [17]. Nonetheless, an estimate of drug input from the TDDS is considered by accounting the volume of distribution (Vd), whole body clearance time (Cl_T) and the steady therapeutic concentration (CPss) of the drug in the plasma. The input rate is expressed as a function of dosing and the bioavailability factor, while the output rate of the drug is a function of whole body clearance time of the drug multiplied by steady-state plasma concentrations of the drug. The input and output rates are supposed to be equal and follow concentration gradient-based diffusion. For the majority of drugs, the whole body clearance equals to the volume of distribution and the drug's elimination rate, and accordingly, the required flux of a drug is equal to a factor of whole body clearance and steady-state therapeutic concentration in the plasma divided by the surface area of the applied TDDS [47].

The influx of the drug, denoted as J, permeating the skin is considered as follows:

$$J = D\ dC/dT \tag{1}$$

where D is the diffusivity, and dC/dT denotes the concentration gradient.

For a constant delivery situation, considering passing mass M of the drug in time T:

$$\frac{dM}{dT} = \frac{DCo}{h} \tag{2}$$

where M is the aggregate of the mass of drug per unit area per unit time passing through the skin layers, and Co is the concentration of the diffusing drug through the starting layer of skin, while h is equal to skin thickness.

Then:

$$Co = PC'o \tag{3}$$

where P is equal to the partition coefficient.

Now, from equations 2 and 3:

$$\frac{dM}{dT} = \frac{DPC'o}{h} \tag{4}$$

Therefore, the skin permeation is a function of diffusivity, skin thickness, partition coefficient of the drug and available effective concentration of the drug, C'o. Nonetheless, an ideal drug suitable to function as part of the

TDDS/device needs to have a smaller dose, preferably below 20 mg/day, a half-life of 10 or lesser hours, molecular weight under 400 Da, partition coefficient between –1 and 3, permeability coefficient in excess of 0.5×10^{-3} cm/h, and non-toxic, non-irritant, no adverse reaction, near zero or zero metabolism as well as low oral bioavailability and low therapeutic index to qualify as an ideal transdermal drug delivery candidate.

Pharmaceutical ingredients for TDDS: desirable properties

The role of active pharmaceutical ingredient (API) is an important factor in determining the feasibility, worthiness levels and workability of TDDS patches and devices. All the ingredients, including the drug, need to be well tolerated by the patient. The drug and formulating ingredients need to support the drug influx to the systemic circulation on a continuous basis for the intended period of time as per the quantity loaded and duration of release of the drug-load of the device. The ingredients should not block the drug transport pathways, and should actively or passively support the drug penetration and help to maintain the drug content gradient across the skin for feasible and continuous transport, follow designated drug depletion rate and should be well tolerated by the skin layers. The cold flow properties, attachment of the patch and adhesive properties, the desirable period of time of application, adhesive properties and adhesive strength of the patch are other important factors playing positive roles in TDDS delivery and its performance. A state-of-the-art TDDS formulation technique in preparation, development and obtaining designed delivery characteristics according to the drug and site of action is essential to achieve the recommended quality as per various quality assurance guidelines [48, 49].

The pharmaceutical ingredients considered crucial in quality observance of the TDDS products also include polymers, permeation-enhancer chemicals, solvents, surfactants, excipients and miscellaneous other chemicals. The polymer matrix is the primary ingredient controlling the drug release from the TDDS/device. The polymer needs to be stable enough for the application, and its time span of activity should be compatible with other ingredients, be unreactive to the active pharmaceutical ingredient, should facilitate effective release of the drug from throughout the surface of the drug in a uniform manner, and be biodegradable, non-toxic and non-antigenic to the host [41, 50–52]. Some of the natural polymers used in TTDS/devices are cellulose, zein, gelatin, shellac, waxes, proteins, gums, natural rubber, starch, etc., while the list of synthetic polymers includes elastomers, i.e. polybutadiene, hydrin rubber, polysiloxane, silicone rubber, nitrile polymer, acrylonitrile, butyl rubber, styrene-butadiene rubber, neoprene polymers, etc. Among other synthetic polymers are polyvinyl alcohol (PVA), polyvinyl chloride (PVC), polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, polymethyl methacrylate (PMMA), epoxy polymers, etc.

Finally, the impermeable backing membrane of the TTDS/device provides the required and essential support for the drug reservoir in the device and prevents it from leaving from the top of the device. These are part of the printable component and protect the product during its use. It is supported by a metallic, plastic laminate, plastic backing with an absorbent pad, occlusive base-plate made of aluminum and adhesive foam-pad made up of flexible polyurethane with an occlusive aluminum foil/disc base plate [38].

The successful development of a TTDS/device also requires certain desirable, inherent properties in the drug candidate. A potent, short-half-life, non-irritating, non-allergic drug is preferred for incorporation into the TDDS/device. Drugs with a low melting point and <500 Da molecular mass are most preferred, as their permeability through skin layers is feasible. Additionally, the drugs need to have an affinity for both the lipophilic and hydrophilic phases, and any extreme partitioning characteristics are not conducive for successful delivery through the skin. Moreover, the drug in the device should not change the zero-order kinetics of the flow, and should not have extensive first-order metabolism, narrow therapeutic index and large dose requirements [41, 53].

Drug delivery systems: transdermal patches and devices

Based on design considerations emanating from various formulation factors, inherent physicochemical and desired biological properties, including adhesives and excipient characteristics, several TDDS patches have been developed, which include single- and multiple-layered devices, vapor patches, drug and polymer matrix characteristic-based products, as well as reservoir-based delivery systems.

A transdermal patch consists of a liner which is in direct contact with the drug and inhibits losing the drug while under storage, and is required to be peeled off before use. The layer after peel-off of the liner consists of an adhesive which serves to adhere to the components of the patch along with working as the sticking platform of

the patch to the skin. It provides the needed support to the patch and the loaded drug, while the membrane regulates the drug release from the reservoir and multi-layered patches to the skin and across the blood circulation over a fixed period of time. The backing membrane separates the TDDS from the outer environment [39, 54]. An adhesive serves two functions: it acts as the glue that keeps the patch adhered to the skin, and it also acts as the suspension that holds the drug. The major problem associated with this technique is the concentration of the drug within the adhesive, which directly affects the stickiness of the adhesive; so if large quantities of the drug are to be administered, either the size of the patch has to be increased or the patch needs to be reapplied again and again by the patient to supply enough, and continuously maintained doses of the drug. To overcome this problem, several biocompatible, biodegradable, pharmaceutical-grade chemicals, also termed as enhancers, have been combined with the formulation matrix to improve the existing drug's penetration through the skin, from the TDDS device, in order to improve the drug absorption. A transdermal patch filled with the precise drug dose and stuck to the skin easily makes the drug enter into the blood circulation with help from enhancers [55, 56].

The sheathing system controlling diffusion-based transdermal drug delivery devices have a polymeric membrane to control the drug release rate, which depends on the polymer properties, permeability coefficient, membrane thickness and the adhesive. The drug compartment is completely embedded in the metallic plastic seal, with the polymeric membrane controlling the drug release according to the following expression:

$$\text{The drug release rate } \frac{dQ}{dt} \text{ equals} \frac{C_R}{1/Pm + 1/Pa}$$

where C_R represents the drug concentration, and Pm and Pa represent the permeability coefficients of the membrane and the adhesive, respectively. Thus, the membrane and adhesive permeability control the drug release, no matter how strong the drug concentration might be present in the reservoir.

Adhesive-dispersion type TTDS/devices use polymer, e.g. polyisobutylene or polyacrylate, as the adhesive which is applied on the upper side of the reservoir to a uniform piece of drug-resistant metallic support to make a thin drug reservoir layer beneath it. The polymer has specific permeability and controls the drug diffusion rate. In the micro-reservoir device, the drug material is uniformly suspended in the biocompatible polymer which regulates its release rate [38].

Single and multi-layered drug loads in adhesives are the fundamental concept. In the single-layered drug load, a drug is loaded onto the adhesive which is surrounded by the temporary liner and backing membrane. In the multiple-layered drug load, an instant drug release layer is available while the next layers are loaded onto the adhesives. This adhesive layer is responsible for the long-term release of the drug. The adhesive layer of the device is also surrounded by a temporary liner and a backing membrane.

The vapor patch releases the drug as a vapor, and the adhesive layer serves to contain all layers and constituents together. The device is used for releasing essential oils, usually for decongestion. Various other vapor patches are also available for improving the quality of sleep and to reduce the cigarette smoking status.

The reservoir system-based transdermal drug delivery device holds the drug reservoir embedded in between an impervious backing layer and a rate-controlling polymer-based permeable membrane. The drug releases are only through the rate-controlling membrane, which can also be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or be dispersed in a solid polymer matrix. The hypoallergenic adhesive polymer can be also be applied as an outer surface polymeric membrane, which needs to be compatible with the drug.

Matrix-based systems control drug diffusion more efficiently where the reservoir holds the dispersed drug in an adhesive polymer, and this medicated adhesive polymer is spread by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose. This system is classified as a drug-in-adhesive system [56]. In the other prototype, called matrix-dispersion system, the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. The drug-containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer, and instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a rim of adhesive. The drug storage compartment is supported by an impermeable membrane from one side and a drug release rate regulator from the other side.

The microreservoir system is a combination of the reservoir and matrix-dispersion systems. The drug reservoir is formed by suspending the drug in an aqueous solution of water-soluble polymer and then this solution is homogeneously dispersed in a lipophilic polymer to form microscopic spheres of the drug. The thermodynamically unstable dispersion is immediately stabilized by *in*

situ cross-linking of the polymer by use of a cross-linking agent [57].

Micro-fabricated microneedle devices have the features of both the hypodermic needle and the transdermal patch. The device has very minute, needle-like outcrops. The device consists of a drug reservoir and projections (microneedles) extending from the reservoir to help in penetrating the SC and epidermis layers of the skin to deliver the drug [58]. The device pierces into the skin followed by the application of the drug patch at the site of treatment and is called as poke-with-patch. When the microneedles are loaded with the drug and inserted into the skin to release the drug, the approach is called a coat-and-poke approach. Other approaches utilize biodegradable polymeric microneedles for insertion into the skin, or hollow microneedles are used to inject the drug load [59]. The microneedle technique utilizes an array of several microscopic projections protruding from a support base or patch with 25–2000 μm height [60, 61], 50–250 μm of width on the support base and with 1–25 μm tip diameter [62–66]. The needle dimension avoids nerve contact upon insertion into the skin [63, 64, 67]. Several techniques are used to fabricate the microneedles, which include lithography, etching, injection molding, light amplification by stimulated emission of radiation (LASER) drilling, LASER cutting and electro-polishing [68].

Macro-flux devices or coated microneedle systems have an area of around 8 cm as well as 300 micro-projections per square centimeter with the length of individual micro-projections less than 200 μm. Three types of macro-flux devices have been made, and they include a dry-coated macro-flux system which is used for a short period of delivery and consists of micro-projection arrays coated with the drug that is adhered to the elastic polymer adhesive onto the backing strip. The other two types include D-Trans and E-Trans macro-flux systems, which are also used for administering the drugs through painless micro-projections and are used to deliver a variety of therapeutic agents including larger proteins, biodegradable macromolecular materials, insulin, hormones, vitamin B, calcein, bovine serum albumin (BSA), plasmid DNA, vaccine and other therapeutic agents [69]. These minimally invasive devices are microfabricated in mainly five types of configurations namely, solid, hollow, coated, dissolved and hydrogel-based [70]. Titanium-made micro-projections with a density about 300/cm^2 and less than 200 μm in length have been successfully used to deliver a variety of LMW and high-molecular-weight (HMW) larger drugs and biomacromolecules. These needles can be made of metal, carbohydrates and polymers [71]. The microneedles can also be made up of non-metals, such as silicon [72], mesoporous silicon [73], as well as metals such as stainless steel [74], titanium [75], and from synthetic and natural polymers. Among synthetic polymers, polylactic acid [76], polyglycolic acid, polylactide-co-glycolic acid [67], polycarbonate [77], polyvinylpyrrolidone (PVP) and polyvinyl acetate are used. Alginic acid, Gantrez AN-B9, carbopol 971 P-NF [78] and polyetherimide [79] are also employed. Starch [80], carboxymethylcellulose, amylopectins [81] and maltose [82] are other materials utilized for this purpose. The microneedles can also be made of natural and thermoplastic polymers. Polymer microneedles are considered better because of their controlled drug release property. Microneedles are feasible in fabrication, can be mass produced and are cost-effective [83]. Furthermore, microneedles in combination with techniques such as sonophoresis [84], electroporation [85, 86] and iontophoresis [74] are used to improve and further control the drug release rate to provide improved and exact delivery.

The metered-dose transdermal spray is a liquid preparation used topically and is made up of drug dissolved in a volatile liquid vehicle. The device achieves better permeation and desired dose levels of the drug are absorbed through the skin. The device improves delivery potential without skin irritation because of its non-occlusive nature. It also has dose flexibility, a simple manufacturing process and increased acceptability.

Evaluation of TDDS: system stability and parameters

Physicochemical, *in vivo* and *in vitro* evaluation tests are considered essential to establish the stability and viability of the TDDS/devices. Following evaluations are important in deciding the TDDS stability, especially of patches and other non-mechanical devices.

Physicochemical evaluation

The evaluation tests considered essential are the average thickness of the TDDS patch including the standard deviation of the thickness of the patch for the skin to ensure overall thickness of the prepared device, which is scaled by a micrometer screw. The weight uniformity is tested after 4-h drying of the patch at 60°C, for which several portions of the patch are cut, dried and weighed, and the standard deviation is calculated for the individual cut-pieces. The folding endurance, measure of tack, the peel-tackiness

test, polariscopic evaluation, shear adhesion, the quick stick test, flatness, elongation break, rolling back, moisture contents, moisture uptake, drug contents, water vapor permeability (WVP) evaluation, uniformity of the loaded dose and stability studies of the drug formulation of the TDDS patch are some of the physicochemical evaluations for quality control of the products [87–93].

In vitro evaluation of the TDDS load and drug permeation

Drug content determination as to the *in vitro* release of the drug incorporated in the TDDS device, i.e. the patch, is estimated by the paddle-blade-over-disc method (USP apparatus V), wherein the patch of known thickness is cut into defined shape, weighed and adhesive fixated over glass plate. The fixated patch is placed preferably in 500 ml phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32± 0.5°C and the paddle of the instrument is set at a 2.5-cm distance from the glass plate. The paddle is moved at 1 relative centrifugal force (RCF) from which samples of 5-ml aliquots are withdrawn at fixed times for 24 h and analyzed through ultraviolet (UV) spectrophotometer or high-performance liquid chromatography (HPLC) for content release, which is confirmed in triplicate. The mean value provides the released drug contents weight from the patch under optimized conditions, and the viability of the TDDS/device is confirmed. The released drug's permeation through the skin is also tested. The *in vitro* release is simulated on a full-thickness, isolated rat abdominal skin or diffusion cell maintained at 32±0.5°C under physiological pH 7.4. The skin is mounted between diffusion cell compartments and the sample volume from the donor compartment is analyzed intermittently at a fixed time through HPLC or UV-spectrophotometer. The flux is determined through the calibration curve obtained for the spectrophotometric determinations as the steady-state amount of the permeated drug ($mg \cdot cm^2$) over time (hour). The permeability coefficients are obtained by dividing the steady flux value by the initial drug load [28, 89].

In vivo evaluation of TDDS and skin sensitivity

The *in vivo* evaluations are of critical nature and determine the functional worthiness of the TDDS products. Skin sensitivity, allergic reactions and topical irritation evaluations are conducted on rabbit skin models. The TDDS patch is applied onto hair-removed, cleaned, 50 cm^2 dorsal surface of the skin, which is removed after 24 h application, and the skin condition is observed and classified according to the study plan for skin irritation and skin damage severity [89, 91].

In situ investigations

In situ tests are carried out using diffusion cell and the paddle-blade-over-disc method at 32±0.5°C and at pH 7.4, while among visceral prototypes the rhesus monkey is used for *in-vivo* evaluation and they have been observed as the best predictors of TDDS characteristics. Other visceral prototypes, i.e. rat, pig, cat, goat, rabbit, dog, monkey and chimpanzee are also employed. Nonetheless, the engagement of human volunteers for detailed TDDS behavior has also been used. Moreover, the pharmacokinetics and pharmacodynamics studies on the TDDS contents have been used through the radio-labeled drug, and the ratio of the drug absorbed and permeated is accounted for by the sensitive radio-counting of the drug contents at the sites of interest in relation to the drug load in the patch [28, 89]. Thus, the quality-by-design (QbD) parametric considerations lead to stable and viable TDDS products.

Skin permeability enhancers: increased drug absorption

Drug permeability enhancers lead to increased absorption by increasing the membrane permeation. An ideal permeation enhancer needs to be biocompatible with the applied biosystems, and preferably odorless, colorless and tasteless, with enough levels of chemical and physical stability. It also needs to be sterile, non-toxic and non-reactive to the drug without any adverse pharmacological activity including non-affecting the zero order skin permeation rate as well as rapid, sustainable and reproducible. The enhancers need to be tested *in vitro* before being applied in the TDDS. The enhancer is also required to not initiate body fluid leak. These permeation enhancer agents are functional excipients included in the TDDS formulation cocktail. The enhancement is achieved by SC hydration. The chemical enhancers act on lipid to alter the drug partition through changes in polarity of the environment and thereby changing the drug permeability, and the permeation in itself is the rate-limiting step for transdermal drug absorption. However, use of several enhancers at different concentrations at the same time is not recommended. Moreover, the same amount of single enhancer cannot be formulated with different drugs as part of a single TDDS [94].

Chemical permeation enhancers

The chemical permeation enhancer class of products help in containing the skin-barrier resistance by improving the penetration for the loaded drug through changes in the organized lipids, cell membrane and its components. These enhancers are also required to be non-reactive, non-bioactive, biodegradable, bio-compatible, non-allergic, non-toxic, and one-way delivered. These enhancers work by increasing the partition coefficient of the drug by increment in the diffusion coefficient, and by facilitating the skin permeability of the region of the interest (ROI) of the skin. The enhancers bring conformational changes in the proteins of the skin, and their swelling by hydrant molecules and solvents. The enhancers make the drug pass through the SC and help them diffuse through subsequent skin layers. Fatty acid-based enhancers alter the SC to behave as a more lipophilic layer [3, 81].

Natural and synthetic polymers as permeation enhancers

The drug storage compartment in TDDS/device is rooted in one or more types of polymers, and controlled discharge of the drug is allowed for the required time duration [95]. An ideal polymer should be inert, biocompatible and non-toxic to host tissues. Along with these requirements, the polymer needs to be freely available, inexpensive, and easy to formulate-fabricate. The polymer also needs to have an extensive variety of mechanical, physical and chemical properties [93], and needs to be constituted of a variety of structural variations. Natural polymers are easily available and make a suitable class of support for TDDS. Chitosan, a polysaccharide, is used as a rate-controlling material. Similarly, hyaluronic acid found in connective tissues is popular for the treatment of skin problems [96]. Microneedle arrays of hyaluronic acid are used to improve dermal permeation for drugs having HMW. It is a safe and effective way of treating skin problems without causing much damage to the skin [97]. For constant release of drugs, hydrogels are the best option. They are highly sorbent, made of over 99% water and are primarily sourced from natural origins. They are used as drug reservoirs in topical drug delivery, especially for ionic drugs [96]. These biodegradable, non-toxic polymer materials provide a constant drug release rate and are the safest class of polymers for drug delivery systems.

Furthermore, synthetic polymer-based hydrogels are prepared from polyacrylics and polyacrylamide. Poly(2-hydroxyethyl methacrylate (p-HEMA) transdermally delivers drugs through electrotherapy [98] at a faster rate. Methyl methacrylate copolymers (Eudragit®) are among the best fit for use as part of an enhanced delivery device for transdermal patches. Eudragit®, when combined with plasticizers, is good as a pressure-sensitive adhesive for use in transdermal drug delivery devices. Similarly, poly-N-vinylamide is also an important polymer which is widely used in transdermal drug delivery. A matrix made of poly-N-vinylamide along with drug permeation enhancer chemicals increases the transdermal flux with improved adhesive property [99]. Moreover, the blending of a water-soluble polymer, povidone, and ±lactic acid oligomers (DLLO) provides a stable transdermal drug delivery device. DLLO, a pressure-sensitive adhesive, when mixed with glycerol and water exhibits elasticizing/increased plasticity in nature due to strong hydrogen bond interactions between PVP and DLLO, and PVP's good miscibility enhances the delivery. The mix is non-irritant to skin [100].

Polyurethanes (PUs) are also recommended for use as drug reservoir material for transdermal drug delivery devices [101]. PU is capable of holding a variety of drugs for transdermal delivery at enhanced delivery rates [102]. Hydrophilic polyurethane elastomer hydrogels are also used for other drug delivery modes and as wound-dressing patch for transdermal delivery of androgenic agents with enhanced drug release kinetics [103].

Silicones exhibit adhesive properties and provide an improved drug delivery rate over a period of time [104]. It is used in several other types of medical devices and has been found to be risk-free [105]. Acrylates, silicones and polyisobutylenes are commonly used as drug-in-adhesive for transdermal drug delivery devices. Domperidone patches are more common than tablets and suspension for suppressing nausea, vomiting and motion sickness. The patch has more patient acceptability because of improved efficiency, reduced side effects and reduced dosing frequency [106].

PMMA membranes have good mechanical strength and also provide good drug permeability across the skin as in the case of nitroglycerine delivery [107]. Polyvinyl alcohol (PVA) patches have prolonged the drug release, and PVA and hydroxypropyl methylcellulose (HPMC) are mixed to prepare a drug matrix for the anti-diabetic patch, glyburide®, [108]. An addition of varying fractions of polyvidone and Eudragit RL-100 (ERL)/Eudragit RS-100 (ERS) has improved patch performance. These patches effectively prevent the intense insulin shock that results from abnormal lowering of blood sugar upon initial use of the patch at the beginning of its application [109]. These polymer entities are biocompatible and biodegradable and are processed and safely eliminated

from the body. Moreover, the byproducts of degradations have no antagonistic effects [110].

Solvents as permeation enhancers

Solvent enhancers increase the penetration by swelling the drug pathways and fluidizing the lipids on the way of permeation through skin layers. Polar pathways are swelled by water, alcohols (CH_3OH, C_2H_5OH), alkyl methyl sulfoxides [e.g. dimethyl sulfoxide (DMSO)], dimethylacetamide, dimethylformamide, pyrrolidones (2-pyrrolidone, N-methyl, 2-pyrrolidone), laurocapram (azone) and miscellaneous other solvents including propylene glycol, glycerol, silicone fluids and isopropyl palmitate, to name some of them [42, 87].

Surfactants as permeation enhancers

Surfactants or surface active agents also play an important role in breaking the resistibility of the skin barrier. The surfactant's effectiveness depends on its composition and nature. The drug infusion is dependent upon the surfactant's polar head and the length of the hydrophobic chain. Cationic surfactants which cause greater permeation, such as cetyltrimethylammonium bromide, disrupt cell-lipid bilayers more [111], while sodium lauryl sulfate (SLS) and diacetyl sulfosuccinate, and dodecyl methyl sulfoxide, the anionic surfactant, interact with the lipids and keratins to alter the skin permeability through cell membrane expansions [112–115]. The nonionic surfactants, pluronic F127 and pluronic F68, help to soften the SC lipid layers when soaked with these surfactants. The amphoteric surfactant, N-dodecyl-N,N-dimethyl betaine, also plays its role in membrane and lipidic constituent softening. However, the penetrability of surfactants is dependent upon their solubility, partitioning behavior and their effectiveness to cross the SC. The nature of the polar head group and the chain part of the surfactants play an important role in solubilizing and enhancing the pathways for transport of drug contents [116].

Excipients and adhesives as permeation enhancers

Among other permeation enhancers, excipients have major and multiple roles to play. In addition to skin attachment, adhesives support sorption and can accelerate permeation by weakening the skin through increased poration by working as pressure-sensitive adhesives (PSA), i.e. polyacrylics, polyisobutylene and silicone polymers [117]. An ideal PSA has better, consistent and durable stickiness as well as it supports the workability of transdermal drug delivery devices under varying temperatures, moisture and applied energy frequency conditions. These parameters are tested from 24 h to a week's time in accordance with the product's requirements. Some of the outcome quality include that the adhesive should stick aggressively, should be easily removed, should not leave an unwashable residue, and should not irritate or sensitize the skin. Moreover, it should also have physical and chemical compatibility with the drug and other components in the formulation [118, 119].

Miscellaneous permeation enhancers

Among natural constituents capable of behaving as permeation enhancers are bile acid salts. They are steroid in structure type, and are charged with surfactant-like properties. Trihydroxy bile salts, monosodium glycolate, taurocholate sodium, dihydroxy salts, deoxycholate sodium, sodium glyco-deoxycholate and sodium taurodeoxycholate are also used as permeation enhancers. Binary system-based fatty acids, i.e. propylene glycol-oleic acid and 1,4-butane diol-linoleic acid, also soften the multilaminate and continuous pathways for drug transport, while the fatty acid components, i.e. oleic and lauric acids, increase the absorption of drugs multifolds [120, 121]. Among a set of other chemicals employed as permeation enhancers are urea, a keratolytic agent [122], and oxazolidinones, i.e. 4-decyloxazolidin-2-one [123]. Oxazolidinones also restrict the administration of two or more drugs of opposite nature and have been demonstrated to enhance the permeation of vitamin-A and analgesics in dermal layers [124]. N, N-dimethyl-*m*-toluamide, calcium thioglycolate, eucalyptol, di-o-methyl-β-cyclodextrin, soybean casein and some of the anticholinergic agents have been reported as permeation enhancers though with little data on them [88]. Among other enhancers, a suspension of sodium caprylate mixed with glyceryl triglyceride, short chain glyceryl monocaprylate, imidic cyclic urea, cyclopentadecalactone, cyclodextrins, terpenes like L-menthol, and eucalyptus, peppermint and ylang-ylang essential oils are worth mentioning. Also, an interference in the skin barrier homeostasis through disturbing the lamellar membrane by temporarily blocking the synthesis of ceramide and other fatty materials, and cholesterol in the skin site enhances drug permeation across the skin. In a more recent approach, administration of inhibitors for skin-based metabolic activities as part of the TDDS formulation load have also been undertaken [94].

Payload delivery enhancements

Various passive and active techniques have been developed to provide control over the drug release rate and transdermal permeation of drugs. The need for expedited delivery has led to various approaches in polymer-based drug delivery modulations constituting complete chemical/structural changes, chemical/structural modifications, as well as formulation modifications as an approach to increase the rate of drug release. These techniques constitute passive methods of enhancements and these enhancers work through an increase in the fluidity of the SC lipid bilayers and SC hydrations, interaction with skin proteins, disruptions of intercellular lipids, and an increase in the thermodynamic activity of the drug. Some of the important passive and active approaches for increased but under-control release of the drug include structure-based, electrical and velocity-based enhancements including some other methodologies to achieve targeted higher levels of drug delivery [125].

Payload delivery enhancement techniques

Structure-based delivery enhancements

Structure-based or chemical-based drug delivery enhancement techniques utilize the structural diversity, modifications and introduction of new structural scaffolds/entity into the fabricating-formulating phase of the TDDS. Polymers of natural and synthetic origins have been plentifully utilized to achieve targeted delivery levels, as has been the introduction of chemical enhancers for the purpose to give the net enhanced delivery [126].

Transformations to prodrug approaches

The prodrug approach works through chemical modification involving the structural changes in the parent drug molecule. It transforms the drug, the majority of times into a lipophilic entity, which is a bioreversible molecule and is biotransformed into the desired parent drug or it's active structural format, in the biological system. The approach facilitates the new derivative of the drug to permeate through the skin barrier easily, and fast. The approach endows suitable physicochemical, pharmaceutical and pharmacokinetic characters to the parent drug molecule which enhances the permeability, therapeutic value and efficacy of the drug in the transdermal drug delivery device/system. The prodrug transformation carried out in a semi-synthetic manner alters the bioactivity of the drug, and can change an active drug into an inactive form which is to be converted to the parent drug within the body when it reaches the site of action or is converted by the skin enzymes, as the requirements might be. The transformation is simple for drug candidates possessing hydroxyl, carboxyl, amine and thiol groups, respectively, and the transformation to ester, amide and methoxyl derivatives are most common which convert the hydrophilic drugs into skin-permeable, biocompatible lipophilic entities. The levels of lipophilicity introduction into the parent drug molecule can also be controlled by transforming the number of hydrophilic groups, mainly hydroxyl and carboxyl, to their ester and amide or ether derivatives. Alkyl chain lengthening, PEGylation and complete chemical transformation to a newer entity are some of the other strategies employed for preparing prodrugs. The transformation changes the physicochemical properties of the drug candidate to be fit for enhanced transdermal delivery. The enzymes present in skin revert the prodrug into its parent drug. However, permeability-controlling factors maneuvered by the pharmacokinetics, physiological/biological and physicochemical properties of the resultant prodrug need to be taken into consideration while transforming the usually hydrophilic drugs into comparatively more lipophilic drugs [20, 127]. Captopril, atenolol, nalbuphine, propranolol palmitate and propranolol stearate, naltrexone ester, polyoxyethylene esters of ketoprofen, acyloxyalkyl esters of ketoprofen and naproxen, polyoxyethylene esters of diclofenac, 6-mercaptopurine, esters of prednisolone, testosterone derivative, and indomethacin esters are some of the examples of prodrug-based transdermal drug delivery devices/system drug components employed for facile and higher influx of the drug delivery [128].

Payload delivery enhancement devices

Electromechanical, physical and acoustics-based delivery enhancements

Poor efficacy, safety issues, skin irritation, undesired levels of skin disruptions to facilitate delivery, inability to increase drug transport, rate variation and low amount of delivery prompted to find alternative ways to passive enhancers, including various chemical enhancers to deliver drugs in comparatively larger quantities with ease

and deeper in-reach across the skin in rapid and confirmed ways. The use of external energy as the driving force for drug transport across the skin or physical disruption of SC constitutes the active approach of permeability enhancement, which enables the delivery of comparatively large quantities of drugs and biomacromolecules. The method offers more control over the delivery and helps to reduce the time lag between the TDDS application and onset time of therapeutic action at the site. Electromechanical, physical and acoustics-based enhancement techniques have revolutionized the performance of transdermal drug delivery devices [16, 33].

Iontophoresis

A limited value, short-timed and localized milli-ampere (0.1–1.0 mA/cm^2) current is applied to the skin through minor electrodes which remain in contact with the drug, and the drug can be delivered to both the entire and confined area beneath the skin layers (Figure 5). Pilocarpine delivery can be taken as an example to induce sweat in the diagnosis of cystic fibrosis. Iontophoretic delivery of lidocaine (LidoSite®) is a good example of this type of delivery for rapid onset of anesthesia [129–131]. Acne, cystic fibrosis and inflammation are some of the conditions where iontophoretic delivery has been successfully applied. Lidocaine [132], retinoids and steroids [133], anticholinergics [134], pilocarpine [135], and ketoprofen [136] are some of the therapeutic agents which have been delivered through this approach to give enhanced and long-term dosage at increased levels of drug release. However, iontophoresis was not found to be transporting drug substances of HMW, over 7 kDa [137], but the use of chemical class of permeation enhancers and liposomal formulation of insulin and BSA through micro-needle delivery made it possible [138, 139]. The technique also delivered enhanced levels of the drug to hair follicles and nails [139]. A single-use transdermal patch approved by the Food and Drug Administration (FDA) utilized electrical current of 4 mA and released sumatriptan over the hour with a fast onset of therapeutic action in the treatment of migraine, where sustained delivery was achieved for 3 h using a 2-mA current [140, 141]. There is no mechanical penetration in iontophoresis, but very minor effects are on the skin structure for a short period of time [142, 143]. Multiple factors such as pH of the drug solution, molecular size of the drug, hydrophilicity of the drug, type of electrode (preferred Ag/AgCl), current strength (physiological threshold 0.5 mA/cm^2), application time (maximum 3 min to avoid burns), pulsation of the current, intermittent application, type of current, etc. are responsible for controlling the delivery through this technique [65, 144–146]. Iontophoresis is also used in the diagnosis of cystic fibrosis [87], delivery of insulin and monitoring of blood glucose levels [147]. Recently, cytochrome c, ribonuclease A and human basic fibroblast growth factor (hbFGF), and a range of HMW biomacromolecular products over 12 kDa have been successfully delivered [148–152].

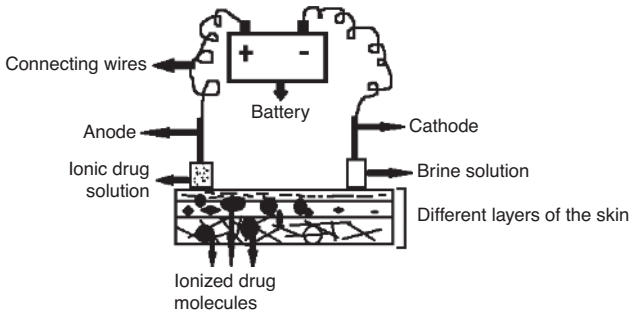

Figure 5: Iontophoresis apparatus.

Tape stripping

This technique utilizes repeated applications of an adhesive tape to remove the skin layer, SC [113]. The thickness of the skin layer, patient's age, skin site, lipid component composition and quantity at the skin site, pH of the skin area and moisture contents, force of tape removal, duration of the tape's presence, and effective adhesion of the tape govern the effectiveness of skin layer removal followed by drug delivery by the tape are factors to consider [153, 154].

Electroporation

This method utilizes short, millisecond and high-voltage, 5–500 V, electrical pulses which are applied to the skin to help diffuse the drug by enhancing permeability as a result of the formation of small pores in the SC. For safe and painless administration, electrical pulses are introduced by closely spaced electrodes [155]. This is a highly safe and painless procedure [156] which has demonstrated the successful delivery of LMW drugs, i.e. doxorubicin [157], mannitol [158], timolol [159], orcalcein [160] and HMW molecules, i.e. antiangiogenic metaargidin peptide (AMEP), oligonucleotide [161] and negatively charged anticoagulant heparin [162]. The technique is also useful in gene transfer through a two-step process of first

making the skin permeable followed by electrophoresis [163]. The use of electroporation with microneedles has enhanced the delivery of macromolecular drugs further [85]. However, the shortcomings include a small amount of delivery, enormous cell disturbance including sometimes cell death, damage to the heat-labile drugs and denaturation of the protein therapeutics, and other biomacromolecular therapeutic entities [164, 165].

Microneedles

Microneedles combine the use of patterns, convenience and efficacy of conventional injection needles with the TDDS device, i.e. transdermal patch. Microneedles work through pain-free piercing of the SC and are considered among the least-invasive methods of TDDS. Microneedles facilitate several kinds and larger quantities of drug infusion by creating superficial, hydrophilic pathways through the skin layers [166]. The pores stay for 72 h upon occlusion with liquid or a film, extendable to 7 days [167–170]. Drugs are delivered through a hollow needle or can be made biodegradable for leaving behind in the body to self-degrade through advanced fabrication methods [171].

Microneedles have also been used in vaccination, and drug and vaccine self-administrations. They also been used to effectively deliver small molecules, nanoparticles, fluid extractions and macromolecular entities such as antigens and proteins [172], LMW heparins [4, 173], insulin [174] and some vaccines [175]. The technique provided a rapid onset of 1 min with sustained delivery for up to 90 min from lidocaine-coated microneedles [176]. Polyvinyl pyrrolidone microneedles obtained from photopolymerization of N-vinyl pyrrolidone solution mixed with lyophilized vaccines showed fast dissolution upon insertion into the skin. Microneedle vaccine patches were more efficient than intramuscular vaccinations [177, 178]. The low mechanical strength, poor control in delivery, limited dose size, unavailability of appropriate biomaterials, specific biomaterial requirements for microneedle fabrication for specific deliveries, sterility and immunological issues in fabrication and use, and accidental reuse of non-biodegradable microneedles are some of the constraints of the technique [179, 180]. However, the method is a useful alternative to conventional needle-based vaccination and can be a replacement to the outbreak of pandemics to prevent risks arising out of reuse of hypodermic needles [181–183].

Hollow microneedles passively deliver the drug through the “poke and flow” act which involves drug solution passing through the bore of the needle much like the hypodermic syringe and needle [184–186]; however, an active delivery requires a driving force generated by a miniaturized pump or gas pressure [187, 188] for drug formulation delivery at the site as a patch or gel [60, 189]. The “coat and poke” technique pierces the skin with drug-loaded microneedles [185, 190]. The “poke and release” technique is used for dissolving the porous hydrogel-forming microneedles, wherein the drug diffuses into the systemic circulation through this technique. Dissolvable microneedle patches have successfully delivered LMW and HMW molecules *in vitro* and *in vivo* by the “poke and release” method [191–202].

Electroosmosis

The porous and charged membrane of the drug reservoir of the transdermal drug delivery device/system holding the drug comes under the osmotic gradient with the voltage gradient, and the bulk of fluid volume flows to the other end of the device to the skin area. The process is known as electroosmosis. The electroosmotic flow is more pronounced with the iontophoresis mechanism. Iontophoresis works by generating a force as a result of ions and electric field interaction to drive the generated ion, produced as a consequence of electric field application, through the skin. The presence of an electrical field increases permeability, and the electroosmosis carries the bulk of the solvent ions and neutral species as part of the solvent stream passing through the combined influence of iontophoresis and electro-osmosis. Bulk flow of fluid occurs from the anode to cathode upon voltage difference across a charged membrane [203]. However, skin damage is one of the concerns. Nonetheless, the electroosmotic flow facilitates the delivery of negatively charged entities including proteins from the anodic compartment [204].

Sonophoresis

The desired range of ultrasonic frequencies are generated by an ultrasonic device for improved transdermal drug delivery (Figure 6). A low-frequency ultrasound is more effective and enhances transportation of drugs multifold which creates water paths in the perturbed bilayers through cavitation [205]. The drug substance is mixed with certain couplers as gel or cream which transfers the sonophoretic waves at the skin, which in turn perturb the skin layers to create water paths to infuse the drug [206]. The drug penetrates through the passage created by the

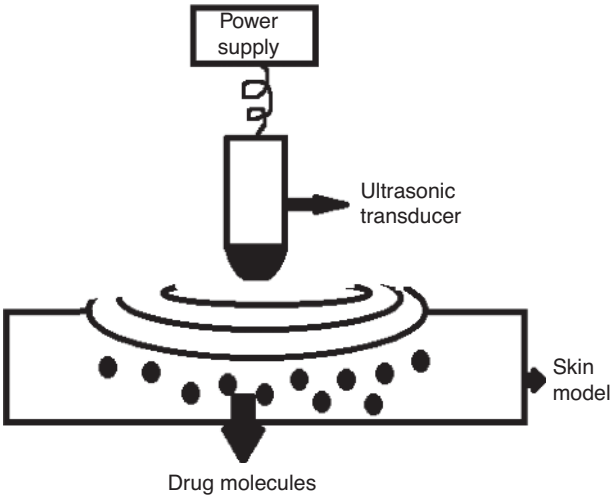

Figure 6: Sonophoretic apparatus.

ultra-sound energy perturbations, with the energy being usually between 20 KHz and 16 MHz [60]. The ultrasound also increases the temperature at the skin site, and thermal effects take place to facilitate the permeation [207–209]. The first US-FDA-approved device in 2004, SonoPrep®, delivered local dermal anesthesia. A number of drugs belonging to various classes, irrespective of their solubility, dissociation and ionization constants, electrical properties including hydrophilic nature, such as mannitol, and HMW drugs such as insulin, have been delivered [210, 211]. However, the exact mechanism of drug penetration through this method is still not fully clear [212] and challenges include availability of the device, duration of exposure and treatment cycles for delivery, and undesirable side-effects including burns [213].

Photomechanical waves

Photomechanical waves relayed on the skin make the SC significantly permeable for the drug to pass through the created transient channels. Photomechanical waves generate confined ablation which is achieved by lower radiant exposure of approximately 5–7 J/cm^2 for an increased depth from 50 to 400 μm for successful delivery. The confined ablation of the target showed a longer rise and time than other direct ablation techniques, and it required control over the photomechanical wave's characteristics to deliver the product at the intended depth into the skin [214]. The wave generated by a single LASER pulse also increases the permeability within minutes, which allows macromolecules to diffuse across the skin. Dextran macromolecules of 40 kDa and 20-nm latex particles were delivered by a single photomechanical 23 ns (nanoseconds) LASER pulse [215].

Electromagnetic microwaves

Electromagnetic microwaves with frequencies between 300 MHz and 300 GHz have worked as skin permeation enhancers. However, the technique is in developmental stages [216].

Miscellaneous methods for thermal ablations

These methods help to increase the permeability of SC but with the risk of damaging another skin layer following the SC. A number of support entities including gel patches, nanoentities and near-infrared (NIR) light have been used to provide thermal ablation. NIR irradiation coupled with nanoentities (gold nano-rods) helped to achieve ablation and transport materials through the skin [217]. Micro-scale skin pore generation by thermal ablation using a wireless induction heating system has also been developed. Micro-heating element arrays using nickel electrodeposition on SU8 patterned structure have been generated, and wireless AC magnetic excitation through a coil has been applied to an *in vitro* skin experiment to produce the sufficient heat to create micropores in human skin [76]. An enhanced permeation, at 1000× increase of sulforhodamine B and BSA, has been achieved [218]. The human growth hormone interferon α-2B [219, 220] and vaccines have been successfully delivered [221]. The process of thermal ablation and micromanipulation are under further development for facilitating the delivery of biopolymers, e.g. nucleic acids, proteins, antibodies and large non-bio polymeric lipid structures.

Velocity-based payload delivery devices

Delivery enhancements by micro-mechanical devices have entered the TDDS delivery enhancement scenario late. The need for mass delivery at a faster speed and in larger quantities seemed to be pertinent for the development of techniques. The fast-paced delivery, enough quantity, and need to cover a large population within a short period of time with a short span of therapeutic action and therapeutic control of the drug provided the impetus for velocity-based delivery devices.

Jet injectors

The drug is injected under high pressure through compressed air inbuilt in the needle-less micro-device. The jet syringe can be of single dose or multiple doses. It is also referred to as air gun, jet gun or pneumatic injection. It is fast and easy to use for delivering vaccines to masses and is also capable of delivering insulin on a personal basis to individuals. Among commercially available injectors, the Biojector 2000 is a spring-powered device which delivers formulated drug subcutaneously and intramuscularly in 1 mm area. It is ergonomically-designed, generally safe, and needle-free syringe system designed to deliver single doses and disposable, or also available for multiple injecting applications. The technique has disadvantages of contamination of nozzle, and the next dose may be a backsplash of the jet-stream from the previous delivery for multiple use device. Therefore, careful use is advised [222], although for certain applications the device has been abandoned. Another injector device Intraject® utilizes electroporation, and hydrophilic drugs are delivered by applying low-intensity current. It is a needle-free, drug pre-filled, single use, and disposable device. The process creates microchannels in the skin to deliver hydrophilic drugs, peptides and proteins. The Implaject® technique is easy to use, reliable, fast and with no pain. Drugs for pain relief, vaccines, insulin and other proteins have been delivered through this technique by needle-free injection device. Crossjet® (also needle-free device) consists of a gas generator to harness chemical energy, a formulation part as a syringe, and a polycarbonate-based control-valve with vents. It has been used to deliver insulin, Imitrex® for treating migraine and cluster headaches, and human growth hormones. The device produces a foul odor due to the burning of chemicals [40, 222].

Powderject devices

The device is a high-speed injection operating at a speed of 600–900 m/s delivering powdered drugs with the help of high-speed helium gas push. The drug, contained in cassettes between two membranes, is pushed and the membranes are ruptured creating pressure along with the gas push to deliver the drug through the skin. The penetration depth is adjusted by varying momentum of (solid) drug particles within the gas. This method causes the least damage to the skin in comparison to other mechanical and acoustics-based devices and uses no needles and does not produce bleeding. The method is site-specific with a fast and sustained release capability [40, 222, 223].

Needle-less shots

These are reusable devices which transfer highly viscous drug formulations across the skin with the help of forces like Lorentz, shock waves, high-pressure gas flow or electrophoresis. The technique has overcome the disadvantages of direct shot needle/syringe applications and avoids needle-based injuries [223].

Thermally assisted and controlled-heat-based devices

Miscellaneous approaches from magnetically driven devices, LASER and radiofrequency uses, and medicated tattoos including thermally-assisted devices have been reported for the purpose of delivery enhancement of several drugs.

Magnetophoresis

The effect of magnetic field on the diffusion flux of the drug substance was found to be enhanced with increasing applied strength [224]. The penetration of the drug in the systemic circulation is improved by applying a magnetic field of fixed intensity. The delivery of lidocaine with the help of a magnetophoretic TDDS patch was achieved at different magnetic field strengths of 30, 150 and 300 mT. The transfer of drug molecules takes place with the help of the magnetokinesis phenomenon. Magnetophoresis also improved the octanol/water partition coefficient of drugs to 25.94 from 13.80 at 300 mT. *In vivo* studies showed improved and better dermal bioavailability than normal nonmagnetic patches [225, 226].

Thermally-assisted drug delivery (TADD) systems/devices work on a heat-controlled mechanism which improves drug distribution by enhancing the blood circulation and absorptivity at the blood vessel levels in the skin. The prescribed quantity and relay time fixed heat are provided through chemoreactive oxidative responses generated by a micro-unit constituted in the device. Drug delivery from a nicotine-patch mounted on the upper arm on 10 healthy nonsmokers increased up to 13-folds at a 43°C controlled heat application [227]. Similar results were observed in the case of nitroglycerine patches during exposure to high but ambient temperature [228].

The controlled-heat aided drug delivery (CHADD) system/device facilitates the transfer of the drug to the blood circulation by applying heat to the skin. The

CHADD systems consist of a small heating unit working on a chemoreactive basis utilizing oxidation reactions to produce the heat of limited intensity and duration.

LASER ablation

A LASER beam is exposed to the ROI of skin to produce ablation without damaging consequent skin layers. Removal of the SC improves the delivery of both lipophilic and hydrophilic drugs. The selective removal of SC without damaging tissues underneath helps in enhancing the delivery, and LASER ablation results in water evaporation and generation of micro-channels [229, 230]. The use of controlled wavelength, pulse length and penetrating power, the thickness of tissue at the site, energy of the pulse, tissue absorption coefficient, duration of exposure, the repetition rate of the pulse, and number of pulses are the deciding factors in the effectiveness of the method [231]. Monochromatic LASER beams can also be used. The method is also helpful in delivering HMW drugs [160, 232]. A LASER pretreatment demonstrated the effectiveness of the technique in quick delivery and fast onset of therapeutic action of lidocaine in human volunteers [230].

Radiofrequency thermal ablation

The technique involves putting a thin, needle-shaped microelectrode into the skin, and a high-frequency AC (alternating current, ~100 kHz) is applied to generate permeation channels in the SC through energetic vibrations to ablate the ROI of the skin. High frequency, 100–500 kHz, can be used to deliver hydrophilic drugs and macromolecular entities across the skin [233–235].

Skin abrasion and scratching

This method involves direct removal or disruption of the upper layer of the skin to provide better permeation of the topically applied drug. In general, the approach creates micro-channels in the skin by eroding the impermeable outer layer with sharp microscopic metal granules, generally known as micro-scissuining. Skin scratching can also be done by metallic, sharp micro-particles to create miniature passages for penetration of the drug [236]. However, there are few reservations with the safety, and studies about skin abrasion safety during immunotherapy have been carried out [237].

Medicated tattoos (Med-Tats®)

This technique utilizes simple and ordinary tattoos loaded with required drug formulations. It is easy to erase and is painless in nature, other than the tattooing process itself. The method provides an easy way of drug administration. The validity period of the tattoo is decided by its hue to monitor the drug delivery as part of the visible method of qualitative monitoring of delivery. The colorants in the hue help to decide the delivery levels. Antimicrobials [160], acetaminophen and vitamin C [74] med-tats® are some of the examples. Med-tats® are produced by lithographic and silkscreen printing techniques to build various layers of the tattoo. The drugs are enclosed as micro-emulsion, liposome and hydrogel, and are released in a precisely controlled manner. Digital tattoos are also available [238–240].

Transdermal nanocarriers: a new approach

Nanoscale devices of solid, liquid and liquid crystalline phases have been used as a tool for transdermal delivery [241]. Solid polymeric lipid nanoparticles and colloidal nanogels, micelles, nanoemulsion and nanodispersions are some of the most used carriers for transdermal delivery purposes [242]. Tacrolimus, an immunosuppressive calcineurin inhibitor, was loaded into 10- to 50-nm-sized polymeric micelles to increase the penetration of the drug [243]. Lipid nanoparticles of tacrolimus measuring 20–100 nm showed increased skin targeting [244]. Fluticasone propionate was encapsulated into nano-lipid carriers [245, 246]. Positively charged polymeric chitosan nanoparticles of about 230 nm size were used to deliver hydrocortisone and hydroxyl-tyrosol through the skin, and an increased skin targeting and decreased systemic uptake were observed for the skin-specific delivery [247]. Nano-delivery illustrated lesser demand of the drug. Among other products reported utilizing the nanoscale device for transdermal drug delivery are retinoids, tazarotene and tretinoin encapsulated in polymeric nanocarriers [248, 249]. Methotrexate-coated 4-nm-sized nanoparticles have been used to enhance skin penetration and uptake of drug by keratinocytes [250]. Also, for lipid-based, drug-loaded nanocarriers, the *in vitro* penetration was greater [251–253], while sodium carbonate-mediated nanogels, 100 nm, also exhibited increased drug permeation than non-nano deliveries [254]. Cyclosporine-A polymeric nanoparticles [255] and 73-nm solid lipid nanocarriers

[256] have also been utilized for dermatitis delivery. Antimicrobial loaded, 200-nm nano lipid-complexed and electrostatically bound silver ions have been delivered for atopic dermatitis [257]. Zinc oxide nanoparticles [258], nC60 fullerenes [259], 200-nm lipid-core capsules loaded with clobetasol propionate [260], 200-nm-sized ketoprofen-loaded chitosan nanoparticles [261] and interleukin (IL)-6 siRNA-loaded 200–270-nm liquid crystalline nanodispersions [262] are some of the examples of nano-based delivery to the skin. Transdermal vaccinations [263], antiparkinsonian and anti-hypertensive drugs [10, 264], several chemotherapeutic agents, and siRNA delivery to the skin for targeted gene knockout which has potential to be developed as personalized medicine, are among successful nano-delivery applications [265].

Tracking and sensing: diagnostic imaging for TDDS

Stimulated Raman scattering (SRS) microscopy is a label-free, nondestructive, chemical imaging tool which provides high-resolution three-dimensional (3D) images from the mammalian skin. Drug penetration through hair follicles and drug crystal precipitation on skin-surface are visualized along with kinetic information on the delivery [266]. This technique is very sensitive and shows highly resolved spatiotemporal images of chemical distribution in the skin without any fluorescent label employed as an imaging aid [267–271], while the older technique utilized adhesive tape-stripping wherein the SC was removed and analyzed to estimate drug concentrations across the skin [272].

Another technique called Terahertz (THz) imaging is also a nondestructive, label-free and rapid way to provide real-time tracking of the drug within the skin. Imaging results from the technique were compared with the standard *in vitro* skin absorption test, Franz cell diffusion test, and were found to be working better. The feasibility of the technique was studied to obtain dynamic images to visualize serial changes in penetration and distribution of the DMSO-ketoprofen formulation on excised mouse skins which reflected the component [273].

Safety concerns: sterility, burns and immunity issues

TDDS development and commercialization have been going on since its inception, and several safety issues have cropped up during the period. The issues in immunological safety of the devices, sterility of products, burns related to electromechanical devices, in-process preparation issues of TDDS, devices and products, Current Good Manufacturing Practice (cGMP) adherence, longer and continued use-related health-issues of patches and devices, as well as the use of patches during magnetic resonance imaging (MRI) procedure causing burns are prominent. Serious burns from metallic components of devices, and electrical burns are some of the concerns, although not all devices and patches contain metal components; nonetheless, the removal of the metallic component from MRI patches and finding replacements for devices causing troubles and burns are suggested [274]. Lately, the nanoparticle and other nanocarriers' skin toxicity are recent concerns along with the safety of TDDS delivery [275].

Recent trends: concurrent developments in TDDS

The recent advances in TDDS span from the development of new techniques and improved procedures, upgradation in/of devices, and TDDS, along with a foray into new fields of delivery for a new segment of diseases including stem cell therapy in conjunction with the TDDS techniques are still taking shape. The report informing the initiation of microneedle patch-mediated delivery of hair follicle stem cell (HFSC) activator systems toward hair regrowth, and pigmentation for the delivery of molecular drug (UK 5099), and mesenchymal stem cell (MSC)-derived exosomes in a reduced dose in a mouse model demonstrated the versatility of the TDDS by achieving the therapy in the shortest possible time of 6 days by two consecutive dosings [276]. The use of microneedles, Derma-Roller®, with doxorubicin hydrochloride and celecoxib co-loaded liposomes provided a two-fold increased delivery which enhanced the antitumor effect and improved the tumor inhibition rate. The improved technique provided successful site targeting and increased inhibition efficiency with negligible side effects [277]. In another use of biocompatible, biodegradable and dissolvable quadrangular pyramid-shaped microneedles [278], the needles dissolved in 10 min with cumulative penetration at >95% and out-reach depth at 70 μm for the drug. There were no adverse effects as observed for 15 days. In another report, the microneedle array technology [279] was used for diagnostic and drug delivery purposes with continuous monitoring of the skin compartment through a closed-loop control method.

Among new vesicular drug delivery approaches through the transdermal route, transethosomes were employed for the delivery of low oral bioavailable, extensive first-pass metabolizing drug olmesartan medoxomil, which showed superiority in the dermatokinetic study as compared with the free drug suspension delivery [279]. Sadarani et al. [280] studied entrapped methotrexate in hydroxyethyl cellulose gel which showed high *ex vivo* transdermal flux (17.37 ± 1.5 μg/cm^2/h) without any irritation or toxicity and had sustained delivery for 48 h with low accumulation in the liver, kidneys and gut. The formulation was biocompatible and safe with high therapeutic effects.

An alternative cavitation seed method for sonophoresis improved drug delivery through the sonication method [281]. The perfluorohexane core concentrated on the skin by gravity adaption and opened the channel for possible delivery of very HMW products. The incorporation of transdermal patches loaded with contraceptive hormone, levonorgestrel, into an earring, ring, necklace and wristwatch tested the viability of pharmaceutical jewelry as a novel method of drug delivery. The transdermal patch constituting nonwoven-electro-spun polycaprolactone microfibers for delivery of levonorgestrel as a long-acting contraceptive agent for *in vitro* steady delivery across the skin were developed [282]. Another procedure towards electromechanical advancements [283] demonstrated the sustained anesthetic effect of ropivacaine® as part of reverse electrodialysis in combination with the transdermal patch, and showed high thermal threshold, lowered cool sensation and lesser depth of pain.

On penetration enhancers development front, terpene, d-limonene was discovered as a potential enhancer for TDDS components and was demonstrated to provide enhanced penetration with increased mechanical stability in various formulations for transdermal delivery at higher delivery rates [284]. In another development, Svenskaya et al., [285] reported the use of sub-micron-sized calcium carbonate-based microparticles as biodegradable carriers loaded with the drug. The topical application for transdermal delivery followed the therapeutic levels of ultrasound waves' treatment resulting in deep penetration of the drug and filling of the hair follicles down to the bulb region, which may serve as an intrafollicular storage for *in situ* drug release also.

The non-woven, nanofibrous TDDS patch for treating local muscular pain was fabricated using the electrospinning technique. The diclofenac-loaded TDD patch was fabricated from cellulose acetate nanofibers that showed sustained release of the drug for a 12-h period with minimum direct skin-drug contact, no over-dosing, and without any burst release [286].

Curcumin-loaded, biodegradable, biocompatible and biocomposite films of carrageenan were prepared from locust-bean gum and montmorillonite by the solvent casting method upon addition of propylene glycol (2.5% v/v). The films were well characterized and evaluated for their physicochemical properties, moisture contents, drug-material uptake, film thickness and its folding capacity, as well as swelling and water vapor transmission rates. The *in vitro* drug release profiles showed that the compositional ratio of locust-bean gum and montmorillonite modulated the sustained release of the curcumin from the films [287].

In another development, piroxicam transdermal patch was developed to treat dysmenorrhea [287] with benefits to avoid oral/tablet delivery produced nausea, vomiting, gastric disturbances and ulcer. The patch was made using sustained-release polymers, hydroxypropyl methylcellulose E15, PVP K30, ethyl cellulose, PEG 400 and SLS as the permeation enhancer. The patch showed 12-h sustained release of the drug [288].

Transdermal delivery of the anti-Alzheimer's drug, Donepezil®, was achieved through the transdermal route as a nanogel formulation [289] to avoid many drawbacks in oral administration, and restrain highly prevalent nonadherence of regular dosing among patients. The nanostructured lipid carrier-based gels improved the skin delivery of the donepezil-free base, a hydrophilic entity in a lipid medium using stearic and oleic acids, surfactant lecithin, and a co-surfactant, sodium tauro-deoxy cholate in the formulation. *In vitro* testing showed increased drug penetration of the nanostructured material and also the lipoid gel being the penetration enhancer.

TDDS technology commercialization: marketed products

Major technologies and devices invented and developed for transdermal delivery of drug have been commercialized and are available in the market world-over. However, the North American and European markets take precedence in development, marketing and utilization of these products. The market size, latest trends, sales drivers, competition, threats and opportunities including the product segments of TTDS/devices have affected and are driving the technical advancements and commercialization of the products. Major players in the TDDS market include Novartis

AG, Johnson & Johnson, GlaxoSmithKline, Boehringer Ingelheim GmbH, Biogel Technology Inc., Mylan Pharmaceuticals Inc., ProSolus Inc., Sanofi SA, Sandoz, The 3M Company, Watson Pharmaceuticals Inc. and Noven Pharmaceuticals Inc. contributing in the cardiovascular, central nervous system, pain management, hormone replacement therapy and smoking cessation segments. A representative list of products, brand-names, bio-applications and product progenitor pharmaceutical companies are listed (Table 2).

Conclusion: achievements and future prospects

Developments in TDDS technologies have made them widely accepted and more so with developments in bulk delivery methodologies which have made them the preferred medium of drug infusion across the skin for transdermal delivery to avoid first-pass metabolism and other sensitivities related to various routes of drug administrations. The transdermal infusion devices and transdermal drug delivery systems have inbuilt capabilities to deliver the drug and its pay-load through the skin layers to the systemic circulation. The drug is generally stable and safe from chemical reactivities in the transdermal drug delivery devices/systems, and normally safe and stable from biochemical transformations before reaching the intended site. Transdermal drug delivery devices/systems are non-invasive, non-allergenic, and have a fixed-time and dose delivery method with even distribution of drug at prescribed and controlled rates. Because of the easy administration route with feasibility for large doses over an extended period of time, formulation of many new and old drugs are in process to achieve improved bioavailability of poorly absorbed drugs. The TDDS technology is fast growing in the pharmaceutical sector and is successful in capturing major value in the market owing to their increasing biomedical applications as a topical formulation

Table 2: Commercialized TDDS products: a representative list.[a]

Active drug	Brand name	Company	Condition
Nitroglycerine	Nitro-Dur®	Key Pharmaceuticals	Angina pectoris
	Deponit®	Schwarz Pharma	
	Minitran®	3M Pharmaceuticals	
	Nitrodisc®	Roberts Pharmaceuticals	
	Transderm-Nitro®	Alza, Norvatis	
Estradiol	Alora®	TheraTech, Proctor & Gamble	Postmenstrual syndrome
	Estraderm®	Alza, Norvatis	
	Climaderm®	Ethical Holdings, Wyeth-Ayerest	
	FemPatch®	Parke-Davis	
Nicotine	Habitraol®	Novartis	Smoking cessation
	Nicoderm®	Alza, GlaxoSmithKline	
	Prostep®	Elan Corp, Lederle Lab	
Testosterone	Testoderm®TTS Patch	Alza Corporation	Hormone replacement therapy
	Androderm®	TheraTech, GlaxoSmithKline	Male hypogonadism
Lidocaine	Lidoderm®	Endo Pharmaceuticals Inc.	Anesthetic
Scopolamine	Transderm-scop®	Alza, Norvatis	Motion sickness
Fentanyl	Duragesic®	Alza, Janssen Pharmaceutical	Pain relief
Estrogen	Fematrix®	Ethical Holdings, Solvay Healthcare Ltd.	Postmenstrual syndrome
Progesterone	Nuvelle®TS	Ethical Holdings, Schering	Hormone replacement therapy
Clonidine	Catapres®TTS	Alza, Boehringer Ingelheim	Hypertension
Buprenorphine	BuTrans®	Purdue Pharma LP	Analgesic
Granisetron	Sancuso®	Kyowa Kirin International Plc	Nausea, vomiting
Rivastigmine	Rivastigmine TS	Sandoz®	Dementia
Rotigotine	Neupro®	Veronique UCB	Parkinson's disease
Methylphenidate	Daytrana®	Noven	Attention-deficit hyperactivity disorder (ADHD)
Selegeline	Emsam®	Somerset Pharmaceuticals, Inc.	Major depressive disorder
Oxybutynin	Oxytrol®	Actavis Pharma, Inc.	Anti-muscarinic agent

[a]www.usfda.gov and https://marketresearch.biz/purchase-report/?report_id=3981, accessed on June 10, 2019.
TDDS, transdermal drug delivery system.

system and device which is capable of improving drug delivery through the topical route. A number of developments have been recorded in a plethora of information such as reviews, monographs, books and technical notes from academia and industry [290–301].

A number of advanced transdermal drug delivery devices/systems and technologies have already been translated into marketed products which include improved-performance patches, fast and non-invasive infusion devices, and use of acoustics, LASER and thermal methods in drug delivery. The scenario is fast changing with a variety of new approaches in making and commercialization, advancements in delivery approach and drug formulation, and use of electro-mechanical, acoustics, LASER, sound, pressure and heating phenomenon in designing new devices and injectors including 3D printing of the transdermal drug delivery devices and other platforms including microneedle improvement which are being pursued. The advances in replacing the metallic components in transdermal drug delivery devices with biodegradable polymeric entities are under progress. The advancements in transdermal patches, skin-based immunomodulation, contact dermatitis allergy-control, and hydrogel fused TDDS patches as well as delivery-feasible conceptual devices, and transdermal drug delivery devices/systems are rapidly progressing toward commercialization [302, 303]. The prevalence of cardiovascular diseases, diabetes, central nervous system and neuromuscular disorders, genetic diseases including pandemics and localized epidemic control, vaccination advancements as well as preference for self-administration of drugs for long-term treatment are expected to be providing the necessary thrust for further development.

Acknowledgment: The authors thank their institutions for the infrastructure support.
Research funding: The authors state no funding involved.
Conflict of interest statement: The authors declare no conflict of interest.
Informed consent: Informed consent is not applicable.
Ethical approval: The conducted research is not related to either human or animals use.

References

[1] Global transdermal drug delivery market analysis: opportunity outlook 2024. Available from: https://www.researchnester.com/reports/global-transdermal-drug-delivery-market-analysis-opportunity-outlook-2024/111, accessed on June 10, 2019.
[2] Tanner T, Marks R. Delivering drugs by the transdermal route: review and comment. Skin Res Tech 2008;14:249–60.
[3] Subedi RK, Oh SY, Chun M-K, Choi H-K. Recent advances in transdermal drug delivery. Arch Pharm Res 2010;33:339–51.
[4] Prausnitz MR, Langer R. Transdermal drug delivery. Nature Biotech 2008;26:1261–8.
[5] Eldridge JE, Burdick DC, Jones RH, Hossack KF. Comparison of nitroglycerin patches and nifedipine. J Cardio Pharmacol 1987;10:315–9.
[6] Bhaskar H, Pranav Kapoor R. Comparison of transdermal diclofenac patch with oral diclofenac as an analgesic modality following multiple premolar extractions in orthodontic patients: a cross over efficacy trial. Contemp Clinic Dentist 2010;1:158–63.
[7] Ale I, Lachapelle J, Maibach H. Skin tolerability associated with transdermal drug delivery systems: an overview. Adv Ther 2009;26:920–35.
[8] Hulst KM, Amer EP, Jacobs C, Dewulf V, Baeck M, Vallverdu RMP, et al. Allergic contact dermatitis from transdermal buprenorphine. Contact Dermatitis 2008;59:366–9.
[9] Mishra MK, Ray D, Barik BB. Microcapsules and transdermal patch: a comparative approach for improved delivery of antidiabetic drug. AAPS Pharm Sci Tech 2009;10:928–34.
[10] Güngör S, Ozsoy Y. Systemic delivery of antihypertensive drugs via skin. Ther Del 2012;3:1101–16.
[11] Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eur J Pharm Biopharm 2006;64:1–8.
[12] Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol 2000;9:165–9.
[13] Heisig M, Lieckfeldt R, Wittum G, Mazurkevich G, Lee G. Non steady-state descriptions of drug permeation through stratum corneum. I. The biphasic brick-and-mortar model. Pharm Res 1996;13:421–6.
[14] Jackson EW. Toxicological aspects of percutaneous absorption. In: Zats JL, editor. Skin Permeation, Fundamentals and Application. Wheaton, IL, USA: Allured Publishing Corporation; 1993:177–92.
[15] Williams A. Transdermal and Topical Drug Delivery: From Theory to Clinical Practice. London: Pharmaceutical Press; 2003.
[16] Sun Y. Skin absorption enhancement by physical means: heat, ultrasound, and electricity. In: Gosh TK, Pfister WR, Yum SI, editors. Transdermal and Topical Drug Delivery Systems. Buffalo Grove, IL, USA: Interpharm Press; 1997:327–55.
[17] Naik A, Kalia YN, Guy RH. Transdermal drug delivery: overcoming the skin's barrier function. Pharm Sci Technol Today 2000;3:318–26.
[18] Flynn GL. Mechanism of percutaneous absorption from physicochemical evidence. In: Bronaugh RL, Maibach HI, editors. Percutaneous Absorption: Mechanism-Methodology-Drug Delivery, 2nd ed. NY, USA: Marcel Dekker; 1989:27–51.
[19] Chan S, Po ALW. Prodrugs for dermal delivery. Int J Pharm 1989;55:1–16.
[20] Sloan K, Koch SA, Siver KG. Mannich base derivatives of theophylline and 5-fluorouracil: syntheses, properties and topical delivery characteristics. Int J Pharm 1984;21:251–64.
[21] Hadgraft J, Wolff M. Physicochemical and pharmacokinetic parameters affecting percutaneous absorption. In: Dermal and transdermal drug delivery: new insights and perspectives. Proceedings of the 2nd Int Symp Int Ass Pharm Tech, Frankfurt, Germany, 11–13 Nov. 1991.

[22] Wester R, Maibach H. Structure-activity correlations in percutaneous absorption. Percutaneous absorption: mechanisms–methodology–drug delivery. New York: Marcel Dekker; 1985:107–23.
[23] Tenjarla SN, Puranajoti P, Kasina R, Mandal T. Terbutaline transdermal delivery: preformulation studies and limitations of in-vitro predictive parameters. J Pharm Pharmacol 1996;48:1138–42.
[24] Idson B. Percutaneous absorption. J Pharm Sci 1975;64:901–24.
[25] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997;23:3–25.
[26] Hadgraft J, Cordes G, Wolff M. Prediction of the Transdermal Delivery of β-Blockers. In: Rietbrock N, editor. Die Haut als Transportorgan Für Arzneistoffe. Darmstadt, Germany: Steinkopff Verslag; 1990:133–43.
[27] Donnelly RF, Singh TRR. Novel Delivery Systems for Transdermal and Intradermal Drug Delivery. NJ, USA: John Wiley & Sons Ltd.; 2015.
[28] Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal drug delivery system-design and evaluation. Int Adv Drug Deliv Rev 2010;1:201–11.
[29] Abdou HM. Dissolution, Bioavailability, and Bioequivalence. Easton, PA, USA: Mack Publishing Company; 1989:52–73.
[30] Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 2001;14:101–14.
[31] Bronaugh RL, Maibach HI. Percutaneous Absorption: Mechanisms–Methodology–Drug Delivery. NY, USA: Marcel Dekker Inc.; 1989.
[32] Stott PW, Williams AC, Barry BW. Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen. J Control Release 1998;50:297–308.
[33] Higuchi T. Physical-chemical analysis of percutaneous absorption process from creams and ointments. J Soc Cosmet Chem 1960;11:85–97.
[34] Weigand DA, Haygood C, Gaylor JR. Cell layers and density of Negro and Caucasian stratum corneum. J Inves Dermatol 1974;62:563–8.
[35] Reinertson RP, Wheatley VR. Studies on the chemical composition of human epidermal lipids. J Inves Dermatol 1959;32:49–59.
[36] Tojo K. The Prediction of Transdermal Permeation: Mathematical Models. Buffalo Grove, IL, USA: Interpharm Press; 1997.
[37] Billich A, Vyplel H, Grassberger M, Schmook FP, Steck A, Stuetz A. Novel cyclosporin derivatives featuring enhanced skin penetration despite increased molecular weight. Bioorg Med Chem 2005;13:3157–67.
[38] Mathiowitz E, Chickering DE, Lehr CM, editors. Bioadhesive Drug Delivery Systems Fundamentals: Novel Approaches and Development. New York, NY: Marcel Dekker; 1999:477–505.
[39] Hopp SM. Developing custom adhesive systems for transdermal drug delivery products. Pharma Tech 2002;26:30–6.
[40] Wolff HM. Future of Transdermal Drug Delivery Systems (TDDS). Available at: https://www.americanpharmaceuticalreview.com/Featured-Articles/163672-Future-of-Transdermal-Drug-Delivery-Systems-TDDS/, accessed on June 10, 2019.
[41] Keith AD. Polymer matrix consideration for transdermal devices. Drug Dev Ind Pharm 1983;9:605–25.
[42] Lec S, Yac S, Kim S, Berner B. One way membrane for Transdermal drug delivery systems/system optimization. Int J Pharm 1991;77:231–7.
[43] Subramony JA. Needle-free parenteral drug delivery: leveraging active transdermal technologies for pediatric use. Int J Pharm 2013;455:14–8.
[44] Ghosh TK, Jasti BR. Theory and Practice of Contemporary Pharmaceutics. Boca Raton, FL, USA: CRC Press; 2004.
[45] Choy YB, Prausnitz MR. The rule of five for non-oral routes of drug delivery: ophthalmic, inhalation and transdermal. Pharm Res 2011;28:943–8.
[46] Ramesh P. Transdermal delivery of drugs. Ind J Pharmacol 1997;29:140–56.
[47] Chandrashekar N, Rani RS. Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. Ind J Pharm Sci 2008;70:94–6.
[48] Otberg N, Patzelt A, Rasulev U, Hagemeister T, Linscheid M, Sinkgraven R, et al. The role of hair follicles in the percutaneous absorption of caffeine. Brit J Clin Pharmacol 2008;65:488–92.
[49] van der Maaden K, Jiskoot W, Bouwstra J. Microneedle technologies for (trans) dermal drug and vaccine delivery. J Control Release 2012;161:645–55.
[50] Minghetti P, Cilurzo F, Casiraghi A, Molla F, Montanari L. Dermal patches for the controlled release of miconazole: influence of the drug concentration on the technological characteristics. Drug Dev Ind Pharm 1999;25:679–84.
[51] Guyot M, Fawaz F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol. Int J Pharm 2000;204:171–82.
[52] Gabiga H, Cal K, Janicki S. Effect of penetration enhancers on isosorbide dinitrate penetration through rat skin from a transdermal therapeutic system. Int J Pharm 2000;199:1–6.
[53] Sachan R, Bajpai M. Transdermal drug delivery system: a review. Int J Res Dev Pharm Life Sci 2013;3:748–65.
[54] Heller J, Trescgny P. Controlled drug release by polymer dissolution II: enzyme-mediated delivery device. J Pharm Sci 1979;68:919–21.
[55] Heller J, Baker R, Gale R, Rodin J. Controlled drug release by polymer dissolution. I. Partial esters of maleic anhydride copolymers-properties and theory. J Appl Polym Sci 1978;22:1991–2009.
[56] Saroha K, Yadav B, Sharma B. Transdermal patch: a discrete dosage form. Int J Curr Pharm Res 2011;3:98–108.
[57] Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev 2012;64:128–37.
[58] Donnelly RF, Singh TRR, Woolfson AD. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Drug Del 2010;17:187–207.
[59] Yan-yu X, Yun-mei S, Zhi-peng C, Qi-Neng P. Preparation of silymarin proliposome: a new way to increase oral bioavailability of silymarin in beagle dogs. Int J Pharm 2006;319:162–8.
[60] Schoellhammer CM, Blankschtein D, Langer R. Skin permeabilization for transdermal drug delivery: recent advances and future prospects. Expert Opin Drug Deliv 2014;11:393–407.
[61] Tuan-Mahmood TM, McCrudden MT, Torrisi BM, McAlister E, Garland MJ, Singh TRR, et al. Microneedles for intradermal and transdermal drug delivery. Eur J Pharm Sci 2013;50:623–37.
[62] Indermun S, Luttge R, Choonara YE, Kumar P, Du Toit LC, Modi G, et al. Current advances in the fabrication of microneedles for transdermal delivery. J Control Release 2014;185:130–8.
[63] McAllister DV, Wang PM, Davis SP, Park J-H, Canatella PJ, Allen MG, et al. Microfabricated needles for transdermal delivery of

macromolecules and nanoparticles: fabrication methods and transport studies. Proc Natl Acad Sci USA 2003;100:13755–60.
[64] Yung K, Xu Y, Kang C, Liu H, Tam K, Ko S, et al. Sharp tipped plastic hollow microneedle array by microinjection moulding. J Micromech Microengg 2011;22:015016.
[65] Gratieri T, Alberti I, Lapteva M, Kalia YN. Next generation intra-and transdermal therapeutic systems: using non-and minimally-invasive technologies to increase drug delivery into and across the skin. Eur J Pharm Sci 2013;50:609–22.
[66] Pattani A, McKay PF, Garland MJ, Curran RM, Migalska K, Cassidy CM, et al. Microneedle mediated intradermal delivery of adjuvanted recombinant HIV-1 CN54gp140 effectively primes mucosal boost inoculations. J Control Release 2012;162:529–37.
[67] Park J-H, Allen MG, Prausnitz MR. Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. J Control Release 2005;104:51–66.
[68] Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. J Control Release 2007;117:227–37.
[69] Ye Y, Yu J, Wen D, Kahkoska AR, Gu Z. Polymeric microneedles for transdermal protein delivery. Adv Drug Deliv Rev 2018;127:106–18.
[70] Donnelly RF, Singh TRR, Morrow DI, Woolfson AD. Microneedle-Mediated Transdermal and Intradermal Drug Delivery. NJ, USA: John Wiley & Sons; 2012.
[71] Donnelly RF, Majithiya R, Singh TRR, Morrow DI, Garland MJ, Demir YK, et al. Design, optimization and characterisation of polymeric microneedle arrays prepared by a novel laser-based micro moulding technique. Pharm Res 2011;28:41–57.
[72] Ashraf M, Tayyaba S, Nisar A, Afzulpurkar N, Bodhale D, Lomas T, et al. Design, fabrication and analysis of silicon hollow microneedles for transdermal drug delivery system for treatment of hemodynamic dysfunctions. Cardiovasc Eng 2010;10:91–108.
[73] Ji J, Tay FEH, Miao J, Iliescu C. Microfabricated microneedle with porous tip for drug delivery. J Micromech Microengg 2006;16:958–64.
[74] Chen H, Zhu H, Zheng J, Mou D, Wan J, Zhang J, et al. Iontophoresis-driven penetration of nanovesicles through microneedle-induced skin microchannels for enhancing transdermal delivery of insulin. J Control Release 2009;139:63–72.
[75] Widera G, Johnson J, Kim L, Libiran L, Nyam K, Daddona PE, et al. Effect of delivery parameters on immunization to ovalbumin following intracutaneous administration by a coated microneedle array patch system. Vaccine 2006;24:1653–64.
[76] Park J-W, Park J-H, Yoon Y-K, Joung Y-H, Choi S-O, Prausnitz MR, et al. Wireless thermal micro-ablation of skin for transdermal drug delivery. The 13th International Conference on Solid-State Sensors, Actuators and Microsystems, 2005 Digest of Technical Papers TRANSDUCERS '05: IEEE; 2005:1238–41.
[77] Jin CY, Han MH, Lee SS, Choi YH. Mass producible and biocompatible microneedle patch and functional verification of its usefulness for transdermal drug delivery. Biomed Microdev 2009;11:1195–203.
[78] Sullivan SP, Koutsonanos DG, del Pilar MM, Lee JW, Zarnitsyn V, Choi SO, et al. Dissolving polymer microneedle patches for influenza vaccination. Nat Med 2010;16:915–20.
[79] You S-K, Noh Y-W, Park H-H, Han M, Lee SS, Shin S-C, et al. Effect of applying modes of the polymer microneedle-roller on the permeation of L-ascorbic acid in rats. J Drug Target 2010;18:15–20.
[80] Hirschberg HJ, van de Wijdeven GG, Kelder AB, van den Dobbelsteen GP, Kersten GF. Bioneedles™ as vaccine carriers. Vaccine 2008;26:2389–97.
[81] Lee JW, Park J-H, Prausnitz MR. Dissolving microneedles for transdermal drug delivery. Biomaterials 2008;29:2113–24.
[82] Li G, Badkar A, Nema S, Kolli CS, Banga AK. In vitro transdermal delivery of therapeutic antibodies using maltose microneedles. Int J Pharm 2009;368:109–15.
[83] Lee JW, Han M-R, Park J-H. Polymer microneedles for transdermal drug delivery. J Drug Target 2013;21:211–23.
[84] Chen B, Wei J, Iliescu C. Sonophoretic enhanced microneedles array (SEMA)-improving the efficiency of transdermal drug delivery. Sens Actuators B Chem 2010;145:54–60.
[85] Yan K, Todo H, Sugibayashi K. Transdermal drug delivery by in-skin electroporation using a microneedle array. Int J Pharm 2010;397:77–83.
[86] Wilke N, Hibert C, O'Brien J, Morrissey A. Silicon microneedle electrode array with temperature monitoring for electroporation. Sens Actuators A Phys 2005;123:319–25.
[87] Wade A, Weller PJ. Handbook of Pharmaceutical Excipients. Washington: American Pharmacists Association; 1994:362–6.
[88] Jain NK. Controlled and Novel Drug Delivery. New Delhi, India: CBS Publishers & Distributors; 2008:1–50.
[89] Singh J, Tripathi K, Sakya T. Effect of penetration enhancers on the in vitro transport of ephedrine through rat skin and human epidermis from matrix based transdermal formulations. Drug Dev Ind Pharm 1993;19:1623–8.
[90] Yuk SH, Lee SJ, Teruo O, Berner B, Kim SW. One-way membrane for transdermal drug delivery systems. II. System optimization. Int J Pharm 1991;77:231–7.
[91] Naik A, Pechtold LA, Potts RO, Guy RH. Mechanism of oleic acid-induced skin penetration enhancement in vivo in humans. J Control Release 1995;37:299–306.
[92] Nagarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system: a potential approach for ocular drug delivery. J Control Release 2009;136:2–13.
[93] Vyas SP, Khar RK. Targeted and Controlled Drug Delivery Novel Carrier Systems. 1st ed. New Delhi, India: CBS Publishers and Distributors; 2002:411–47.
[94] Roy N, Agrawal M, Chaudhary S, Tirkey V, Dhwaj A, Mishra N. Review article on permeation enhancers: a major breakthrough in drug delivery technology. Int J Pharm Sci Res 2017;8:1001–11.
[95] Heller J. Controlled drug release from poly (ortho esters) – a surface eroding polymer. J Control Release 1985;2:167–77.
[96] Sharma K, Singh V, Arora A. Natural biodegradable polymers as matrices in transdermal drug delivery. Int J Drug Dev Res 2011;3:85–103.
[97] Liu S, Jin M-N, Quan Y-S, Kamiyama F, Kusamori K, Katsumi H, et al. Transdermal delivery of relatively high molecular weight drugs using novel self-dissolving microneedle arrays fabricated from hyaluronic acid and their characteristics and safety after application to the skin. Eur J Pharm Biopharm 2014;86:267–76.
[98] Banga AK, Chien YW. Hydrogel-based Iontotherapeutic delivery devices for transdermal delivery of peptide/protein drugs. Pharm Res 1993;10:697–02.
[99] Landrau FA, Nedberge DE, Hearney LM. Alza Corporation. Incorporating poly-N-vinyl amide in a transdermal system. US Patent 1999.US5, 919,478.

[100] Zhang J, Deng L, Zhao H, Liu M, Jin H, Li J, et al. Pressure-sensitive adhesive properties of poly (N-vinyl pyrrolidone)/D, L-lactic acid oligomer/glycerol/water blends for TDDS. J Biomat Sci Polymer Ed 2010;21:1–15.
[101] Shelke NB, Sairam M, Halligudi SB, Aminabhavi TM. Development of transdermal drug delivery films with castor-oil-based polyurethanes. J Appl Polym Sci 2007;103:779–88.
[102] Venkatraman SS, Stein T, Snider J, Hamlin R. Transdermal drug delivery devices comprising a polyurethane drug reservoir. US Patent, 2005, US 20050048104A1.
[103] Chen TF, Chiang CM, Jona J, Joshi P, Ramdas A, Cygnus, Inc. Polyurethane hydrogel drug reservoirs for use in transdermal drug delivery systems, and associated methods of manufacture and use. US Patent 1999, US 5,902,603.
[104] Houze D, Hantman S. Noven Pharmaceuticals Inc. Transdermal drug delivery system for diclofenac. US Patent 2014. US 8,852,628.
[105] Pfister W. Customizing silicone adhesives for transdermal drug delivery systems. Pharm Technol 1989;13:126–38.
[106] Prabhu P, Shah S, Gundad S. Formulation development and investigation of domperidone transdermal patches. Int J Pharma Invest 2011;1:240–6.
[107] Tekin R, Kiremitçi M, Erbetçi AI, Pikin E. Swelling of PHEMA based membranes in ethanol and their nitroglycerin permeabilities. Biomat Artif Cells Artif Organs 1990;18:95–106.
[108] Caro JF. Effects of glyburide on carbohydrate metabolism and insulin action in the liver. Am J Med 1990;89:S17–25.
[109] Mutalik S, Udupa N. Glibenclamide transdermal patches: physicochemical, pharmacodynamic, and pharmacokinetic evaluations. J Pharm Sci 2004;93:1577–94.
[110] Berkland C, King M, Cox A, Kim KK, Pack DW. Precise control of PLG microsphere size provides enhanced control of drug release rate. J Control Release 2002;82:137–47.
[111] Kitagawa S, Kasamaki M, Ikarashi A. Effects of n-alkyltrimethylammonium on skin permeation of benzoic acid through excised guinea pig dorsal skin. Chem Pharm Bull 2000;48:1698–701.
[112] Froebe C, Simion F, Rhein L, Cagan R, Kligman A. Stratum corneum lipid removal by surfactants: relation to in vivo irritation. Dermatol 1990;181:277–83.
[113] Leveque J, De Rigal J, Saint-Leger D, Billy D. How does sodium lauryl sulfate alter the skin barrier function in man? A multiparametric approach. Skin Pharmacol Physiol 1993;6:111–5.
[114] Patil S, Singh P, Maibach H. Radial spread of sodium lauryl sulfate after topical application. Pharm Res 1995;12:2018–23.
[115] Scheuplein R, Ross L. Effects of surfactants and solvents on the permeability of epidermis. Int J Soc Cosmet Chem 1970;21:853–73.
[116] Som I, Bhatia K, Yasir M. Status of surfactants as penetration enhancers in transdermal drug delivery. J Pharm Bioallied Sci 2012;4:2–9.
[117] Farlow MR, Alva G, Meng X, Olin JT. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. Curr Med Res Opin 2010;26:263–9.
[118] Pathan IB, Setty CM. Chemical penetration enhancers for transdermal drug delivery systems. Tropical J Pharm Res 2009;8:173–9.
[119] Venkatraman S, Gale R. Skin adhesives and skin adhesion: 1. Transdermal drug delivery systems. Biomaterials 1998;19:1119–36.
[120] Funke AP, Schiller R, Motzkus HW, Günther C, Müller RH, Lipp R. Transdermal delivery of highly lipophilic drugs: in vitro fluxes of antiestrogens, permeation enhancers, and solvents from liquid formulations. Pharm Res 2002;19:661–8.
[121] Goodman M, Barry BW. Lipid-protein-partitioning (LPP) theory of skin enhancer activity: finite dose technique. Int J Pharm 1989;57:29–40.
[122] Singh PB, Choudhury P. Penetration enhancers for transdermal drug delivery of systemic agents. J Pharm Res 2007;6: 44–50.
[123] Saini S, Chauhan SB, Agrawal SS. Recent development in penetration enhancers and techniques in transdermal drug delivery system. J Adv Pharm Edu Res 2014;4:31–40.
[124] Asbill CS, Michniak BB. Percutaneous penetration enhancers: local versus transdermal activity. Pharm Sci Technol Today 2000;3:36–41.
[125] Hsieh D. Drug Permeation Enhancement-Theories and Application. New York: Marcel Dekker; 1987.
[126] Tanwar H, Sachdeva R. Transdermal drug delivery system: a review. Int J Pharm Sci Res 2016;7:2274–90.
[127] Ita KB. Prodrugs for transdermal drug delivery – trends and challenges. J Drug Target 2016;24:671–8.
[128] Nair A, Ghosh B. Prodrugs for transdermal delivery. Pharm Rev 2007;4:1–10.
[129] Tipre DN, Vavia PR. Formulation optimization and stability study of transdermal therapeutic system of nicorandil. Pharm Dev Technol 2002;7:325–32.
[130] Calhoun DA, Murthy SN, Bryant BG, Luedtke SA, Bhatt-Mehta V. Recent advances in neonatal pharmacotherapy. Ann Pharmacother 2006;40:710–9.
[131] Dhote V, Bhatnagar P, Mishra PK, Mahajan SC, Mishra DK. Iontophoresis: a potential emergence of a transdermal drug delivery system. Sci Pharm 2012;80:1–28.
[132] Maloney JM. Local anesthesia obtained via iontophoresis as an aid to shave biopsy. Arch Dermatol 1992;128:331–2.
[133] Schmidt J, Binder M, Macheiner W, Bieglmayer C. New treatment of atrophic acne scars by iontophoresis with estriol and tretinoin. Int J Dermatol 1995;34:53–7.
[134] Rai R, Srinivas CR. Iontophoresis in dermatology. Indian J Derm Venereol Leprol 2005;71:236–41.
[135] Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. Pediatrics 1959;23:545–59.
[136] Panus PC, Campbell J, Kulkarni SB, Herrick RT, Ravis WR, Banga AK. Transdermal iontophoretic delivery of ketoprofen through human cadaver skin and in humans. J Control Release 1997;44:113–21.
[137] Kanikkannan N. Iontophoresis-based transdermal delivery systems. BioDrugs 2002;16:339–47.
[138] Garland MJ, Caffarel-Salvador E, Migalska K, Woolfson AD, Donnelly RF. Dissolving polymeric microneedle arrays for electrically assisted transdermal drug delivery. J Control Release 2012;159:52–9.
[139] Kajimoto K, Yamamoto M, Watanabe M, Kigasawa K, Kanamura K, Harashima H, et al. Noninvasive and persistent transfollicular drug delivery system using a combination of liposomes and iontophoresis. Int J Pharm 2011;403:57–65.
[140] Dan WU. Improvement of transdermal delivery of Sumatriptan succinate using novel water emulsion patch or self-dissolving microneedle array, and their in vitro and in vivo characterizations. PhD Thesis, Kyoto Pharmaceutical University, Japan;

2014; Available at: https://pdfs.semanticscholar.org/5dc4/41e188e5b9d68e33b3bc77a37661d04bc718.pdf, accessed on June 10, 2019.
[141] Pierce MW, Marbury T, O'Neill C, Siegel S, Du W, Sebree T. Zelrix™: a novel transdermal formulation of sumatriptan. Headache 2009;49:817–25.
[142] Krueger E, Claudino Junior JL, Scheeren EM, Neves EB, Mulinari E, Nohama P. Iontophoresis: principles and applications. Fisioterapia em Movimento 2014;27:469–81.
[143] Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. Adv Drug Deliv Rev 2004;56:619–58.
[144] Kotzki S, Roustit M, Arnaud C, Godin-Ribuot D, Cracowski J-L. Effect of continuous vs pulsed iontophoresis of treprostinil on skin blood flow. Eur J Pharm Sci 2015;72:21–6.
[145] Dixit N, Bali V, Baboota S, Ahuja A, Ali J. Iontophoresis-an approach for controlled drug delivery: a review. Curr Drug Del 2007;4:1–10.
[146] Khan A, Yasir M, Asif M, Chauhan I, Singh AP, Sharma R, et al. Iontophoretic drug delivery: history and applications. J Appl Pharm Sci 2011;1:11–24.
[147] Sun T, Shieh H, Ching CT. Carbon nanotube composites for glucose biosensor incorporated with reverse iontophoresis function for noninvasive glucose monitoring. Int J Nanomed 2014;9:3069–76.
[148] Cázares-Delgadillo J, Naik A, Ganem-Rondero A, Quintanar-Guerrero D, Kalia Y. Transdermal delivery of cytochrome C-A 12.4 kDa protein-across intact skin by constant – current iontophoresis. Pharm Res 2007;24:1360–8.
[149] Gratieri T, Kalia YN. Targeted local simultaneous iontophoresis of chemotherapeutics for topical therapy of head and neck cancers. Int J Pharm 2014;460:24–7.
[150] Dubey S, Kalia Y. Non-invasive iontophoretic delivery of enzymatically active ribonuclease A (13.6 kDa) across intact porcine and human skins. J Control Release 2010;145:203–9.
[151] Dubey S, Perozzo R, Scapozza L, Kalia Y. Non-invasive electrically-assisted transdermal delivery of human basic fibroblast growth factor. Mol Pharm 2011;8:1322–31.
[152] Dubey S, Kalia Y. Understanding the poor iontophoretic transport of lysozyme across the skin: when high charge and high electrophoretic mobility are not enough. J Control Release 2014;183:35–42.
[153] Lademann J, Jacobi U, Surber C, Weigmann H-J, Fluhr J. The tape stripping procedure – evaluation of some critical parameters. Eur J Pharm Biopharm 2009;72:317–23.
[154] Escobar-Chavez JJ, Merino-Sanjuán V, López-Cervantes M, Urban-Morlan Z, Pinon-Segundo E, Quintanar-Guerrero D, et al. The tape-stripping technique as a method for drug quantification in skin. J Pharm Pharm Sci 2008;11:104–30.
[155] Sugar IP, Neumann E. Stochastic model for electric field-induced membrane pores electroporation. Biophys Chem 1984;19:211–25.
[156] Al-Saidan S, Krishnaiah Y, Chandrasekhar D, Lalla J, Rama B, Jayaram B, et al. Formulation of an HPMC gel drug reservoir system with ethanol-water as a solvent system and limonene as a penetration enhancer for enhancing in vitro transdermal delivery of nicorandil. Skin Pharmacol Physiol 2004;17:310–20.
[157] Blagus T, Markelc B, Cemazar M, Kosjek T, Preat V, Miklavcic D, et al. In vivo real-time monitoring system of electroporation-mediated control of transdermal and topical drug delivery. J Control Release 2013;172:862–71.
[158] Mori K, Watanabe T, Hasegawa T, Sato H, Sugibayashi K, Morimoto T. Electroporation on the in vitro skin permeation of mannitol. Drug Deliv Sys 1999;14:101–16.
[159] Denet A-R, Preat V. Transdermal delivery of timolol by electroporation through human skin. J Control Release 2003;88:253–62.
[160] Kumar R, Philip A. Modified transdermal technologies: breaking the barriers of drug permeation via the skin. Trop J Pharm Res 2007;6:633–44.
[161] Escobar-Chávez JJ, Bonilla-Martínez D, Villegas-González MA, Revilla-Vázquez AL. Electroporation as an efficient physical enhancer for skin drug delivery. J Clinic Pharmacol 2009;49:1262–83.
[162] Prausnitz MR, Edelman ER, Gimm JA, Langer R, Weaver JC. Transdermal delivery of heparin by skin electroporation. Nature Biotech 1995;13:1205–9.
[163] Calvet CY, Thalmensi J, Liard C, Pliquet E, Bestetti T, Huet T, et al. Optimization of a gene electrotransfer procedure for efficient intradermal immunization with an hTERT-based DNA vaccine in mice. Mol Ther Methods Clin Dev 2014;1:14045.
[164] Ainslie KM, Lowe RD, Beaudette TT, Petty L, Bachelder EM, Desai TA. Microfabricated devices for enhanced bioadhesive drug delivery: attachment to and small-molecule release through a cell monolayer under flow. Small 2009;5:2857–63.
[165] Hezaveh H, Muhamad II. Impact of metal oxide nanoparticles on oral release properties of pH-sensitive hydrogel nanocomposites. Int J Biol Macromol 2012;50:1334–40.
[166] Ita K. Transdermal drug delivery: progress and challenges. J Drug Deliv Sci Technol 2014;24:245–50.
[167] Prausnitz MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev 2004;56:581–7.
[168] Bal S, Kruithof A, Liebl H, Tomerius M, Bouwstra J, Lademann J, et al. In vivo visualization of microneedle conduits in human skin using laser scanning microscopy. Laser Phy Lett 2010;7:242–6.
[169] Liu S, Jin M-N, Quan Y-S, Kamiyama F, Katsumi H, Sakane T, et al. The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. J Control Release 2012;161:933–41.
[170] Banks SL, Pinninti RR, Gill HS, Paudel KS, Crooks PA, Brogden NK, et al. Transdermal delivery of naltrexol and skin permeability lifetime after microneedle treatment in hairless guinea pigs. J Pharm Sci 2010;99:3072–80.
[171] Dardano P, Battisti M, Rea B, Serpico L, Terracciano M, Cammarano A, et al. Polymeric microneedle arrays: versatile tools for an innovative approach to drug administration. Adv Ther 2019;2:1900036.
[172] Burton SA, Ng C-Y, Simmers R, Moeckly C, Brandwein D, Gilbert T, et al. Rapid intradermal delivery of liquid formulations using a hollow microstructured array. Pharm Res 2011;28:31–40.
[173] Maurice D. Practical issues in intravitreal drug delivery. J Ocul Pharmacol Ther 2001;17:393–401.
[174] Patton TF, Robinson JR. Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes. J Pharm Sci 1976;65:1295–301.
[175] Kumari A, Sharma PK, Garg VK, Garg G. Ocular inserts – advancement in therapy of eye diseases. J Adv Pharm Technol Res 2010;1:291–6.
[176] Zhang Y, Brown K, Siebenaler K, Determan A, Dohmeier D, Hansen K. Development of lidocaine-coated microneedle

product for rapid, safe, and prolonged local analgesic action. Pharm Res 2012;29:170–7.
[177] Pegoraro C, MacNeil S, Battaglia G. Transdermal drug delivery: from micro to nano. Nanoscale 2012;4:1881–94.
[178] Daddona PE, Matriano JA, Mandema J, Maa Y-F. Parathyroid hormone (1–34)-coated microneedle patch system: clinical pharmacokinetics and pharmacodynamics for treatment of osteoporosis. Pharm Res 2011;28:159–65.
[179] Ita K. Transdermal delivery of drugs with microneedles – potential and challenges. Pharmaceutics 2015;7:90–105.
[180] Samad A, Ullah Z, Alam MI, Wais M, Shams MS. Transdermal drug delivery system: patent reviews. Recent Pat Drug Deliv Formul 2009;3:143–52.
[181] Norman JJ, Arya JM, McClain MA, Frew PM, Meltzer MI, Prausnitz MR. Microneedle patches:usability & acceptability for self-vaccination against influenza. Vaccine 2014;32:1856–62.
[182] Nicolas J-F, Guy B. Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice. Expert Rev Vacc 2008;7:1201–14.
[183] Laurent PE, Bonnet S, Alchas P, Regolini P, Mikszta JA, Pettis R, et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. Vaccine 2007;25:8833–42.
[184] Gardeniers HJ, Luttge R, Berenschot EJ, De Boer MJ, Yeshurun SY, Hefetz M, et al. Silicon micromachined hollow microneedles for transdermal liquid transport. J Microelectromech Syst 2003;12:855–62.
[185] Hong X, Wu Z, Chen L, Wu F, Wei L, Yuan W. Hydrogel microneedle arrays for transdermal drug delivery. Nano-Micro Lett 2014;6:191–9.
[186] Martanto W, Moore JS, Kashlan O, Kamath R, Wang PM, O'Neal JM, et al. Microinfusion using hollow microneedles. Pharm Res 2006;23:104–13.
[187] Gupta J, Felner EI, Prausnitz MR. Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedles. Diabetes Technol Ther 2009;11:329–37.
[188] Amirouche F, Zhou Y, Johnson T. Current micropump technologies and their biomedical applications. Microsys Technol 2009;15:647–66.
[189] Larrañeta E, McCrudden MT, Courtenay AJ, Donnelly RF. Microneedles: a new frontier in nanomedicine delivery. Pharm Res 2016;33:1055–73.
[190] Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. J Pharm Pharmacol 2012;64:11–29.
[191] Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. J Control Release 2012;164:26–40.
[192] Walters KA. Dermatological and Transdermal Formulations. Boca Raton, FL, USA: CRC Press; 2002.
[193] Donnelly RF, Singh TRR, Garland MJ, Migalska K, Majithiya R, McCrudden CM, et al. Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery. Adv Func Mater 2012;22:4879–90.
[194] Watanabe T, Hagino K, Sato T. Evaluation of the effect of polymeric microneedle arrays of varying geometries in combination with a high-velocity applicator on skin permeability and irritation. Biomed Microdev 2014;16:591–7.
[195] Wang Q, Yao G, Dong P, Gong Z, Li G, Zhang K, et al. Investigation on fabrication process of dissolving microneedle arrays to improve effective needle drug distribution. Eur J Pharm Sci 2015;66:148–56.
[196] Yang S, Feng Y, Zhang L, Chen N, Yuan W, Jin T. A scalable fabrication process of polymer microneedles. Int J Nanomed 2012;7:1415–22.
[197] Ashraf MW, Tayyaba S, Afzulpurkar N, Nisar A, Punyasai C, Saejok K, et al. Optimization of fabrication process for MEMS-based microneedles using ICP etching technology. Adv Mater Res 2012;403:4611–6.
[198] Choi H-J, Yoo D-G, Bondy BJ, Quan F-S, Compans RW, Kang S-M, et al. Stability of influenza vaccine coated onto microneedles. Biomaterials 2012;33:3756–69.
[199] Vrdoljak A, McGrath MG, Carey JB, Draper SJ, Hill AV, O'Mahony C, et al. Coated microneedle arrays for transcutaneous delivery of live virus vaccines. J Control Release 2012;159:34–42.
[200] Demir YK, Akan Z, Kerimoglu O. Sodium alginate microneedle arrays mediate the transdermal delivery of bovine serum albumin. PLoS One, 2013;8:e63819.
[201] Kolli CS, Xiao J, Parsons DL, Babu RJ. Microneedle assisted iontophoretic transdermal delivery of prochlorperazine edisylate. Drug Dev Ind Pharm 2012;38:571–6.
[202] Singh ND, Banga AK. Controlled delivery of ropinirole hydrochloride through skin using modulated iontophoresis and microneedles. J Drug Target 2013;21:354–66.
[203] Pikal MJ. The role of electroosmotic flow in transdermal iontophoresis. Adv Drug Deliv Rev 2001;46:281–305.
[204] Sieg A, Guy RH, Delgado-Charro MB. Electroosmosis in transdermal iontophoresis: implications for noninvasive and calibration-free glucose monitoring. Biophys J 2004;87:3344–50.
[205] Mitragotri S, Blankschtein D, Langer R. Transdermal drug delivery using low-frequency sonophoresis. Pharm Res 1996;13:411–20.
[206] Johnson ME, Mitragotri S, Patel A, Blankschtein D, Langer R. Synergistic effects of chemical enhancers and therapeutic ultrasound on transdermal drug delivery. J Pharm Sci 1996;85:670–9.
[207] Katsumi H, Liu S, Tanaka Y, Hitomi K, Hayashi R, Hirai Y, et al. Development of a novel self-dissolving microneedle array of alendronate, a nitrogen-containing bisphosphonate: evaluation of transdermal absorption, safety, and pharmacological effects after application in rats. J Pharm Sci 2012;101:3230–8.
[208] Simonin J-P. On the mechanisms of in vitro and in vivo phonophoresis. J Control Release 1995;33:125–41.
[209] Skauen DM, Zentner GM. Phonophoresis. Int J Pharm 1984;20:235–45.
[210] Levy D, Kost J, Meshulam Y, Langer R. Effect of ultrasound on transdermal drug delivery to rats and guinea pigs. J Clin Invest 1989;83:2074–8.
[211] Park D, Park H, Seo J, Lee S. Sonophoresis in transdermal drug deliverys. Ultrasonics 2014;54:56–65.
[212] Azagury A, Khoury L, Enden G, Kost J. Ultrasound-mediated transdermal drug delivery. Adv Drug Deliv Rev 2014;72:127–43.
[213] Singer AJ, Homan CS, Church AL, McClain SA. Low-frequency sonophoresis: pathologic and thermal effects in dogs. Acad Emerg Med 1998;5:35–40.
[214] Lee S, McAuliffe DJ, Flotte TJ, Kollias N, Doukas AG. Photomechanical transdermal delivery: the effect of laser confinement. Lasers Med Surg 2001;28:344–7.
[215] Lee S, McAuliffe DJ, Flotte TJ, Kollias N, Doukas AG. Photomechanical transcutaneous delivery of macromolecules. J Invest Dermatol 1998;111:925–9.

[216] Wong TW. Electrical, magnetic, photomechanical and cavitational waves to overcome skin barrier for transdermal drug delivery. J Control Release 2014;193:257–69.
[217] Haine AT, Koga Y, Hashimoto Y, Higashi T, Motoyama K, Arima H, et al. Enhancement of transdermal protein delivery by photothermal effect of gold nanorods coated on polysaccharide-based hydrogel. Eur J Pharm Biopharm 2017;119:91–5.
[218] Lee JW, Gadiraju P, Park J-H, Allen MG, Prausnitz MR. Microsecond thermal ablation of skin for transdermal drug delivery. J Control Release 2011;154:58–68.
[219] Levin G, Gershonowitz A, Sacks H, Stern M, Sherman A, Rudaev S, et al. Transdermal delivery of human growth hormone through RF-microchannels. Pharm Res 2005;22:550–5.
[220] Badkar AV, Smith AM, Eppstein JA, Banga AK. Transdermal delivery of interferon alpha-2B using microporation and iontophoresis in hairless rats. Pharm Res 2007;24:1389–95.
[221] Bramson J, Dayball K, Evelegh C, Wan YH, Page D, Smith A. Enabling topical immunization via microporation: a novel method for pain-free and needle-free delivery of adenovirus-based vaccines. Gene Ther 2003;10:251–60.
[222] Hoffman P, Abuknesha R, Andrews N, Samuel D, Lloyd J. A model to assess the infection potential of jet injectors used in mass immunisation. Vaccine 2001;19:4020–7.
[223] Rathbone MJ, Hadgraft J, Roberts MS, Lane ME. Modified-Release Drug Delivery Technology. Boca Raton, FL, USA: CRC Press; 2008:5–50.
[224] Loyd V, Allen J, Nicholas G, Popovich HC. Ansel Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th ed. New Delhi: Wolters Kluwer Publishers; 2005:298–9.
[225] Murthy SN, Sammeta SM, Bowers C. Magnetophoresis for enhancing transdermal drug delivery: mechanistic studies and patch design. J Control Release 2010;148:197–203.
[226] The WT: Wearable Technologies. 2015 Market Assessment on Smart Patches. Available from: https://www.wearable-technologies.com/wt-wearable-technologies-2015-market-assessment-smart-patches/, accessed on June 10, 2019.
[227] Petersen KK, Rousing ML, Jensen C, Arendt-Nielsen L, Gazerani P. Effect of local controlled heat on transdermal delivery of nicotine. Int J Physiol Path Pharmacol 2011;3:236–42.
[228] Barkve TF, Langseth-Manrique K, Bredesen JE, Gjesdal K. Increased uptake of transdermal glyceryl trinitrate during physical exercise and during high ambient temperature. Am Heart J 1986;112:537–41.
[229] Nelson JS, McCullough JL, Glenn TC, Wright WH, Liaw L-HL, Jacques SL. Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. J Invest Dermatol 1991;97:874–9.
[230] Baron ED, Harris L, Redpath WS, Shapiro H, Hetzel F, Morley G, et al. Laser-assisted penetration of topical anesthetic in adults. Arch Dermatol 2003;139:1288–90.
[231] Dhamecha DL, Rajendra V, Rathi A, Ghadlinge S, Saifee M, Dehghan M. Physical approaches to penetration enhancement. Int J Health Res 2010;3:57–70.
[232] Wang KH, Fang JY, Hu CH, Lee WR. Erbium: YAG laser pretreatment accelerates the response of Bowen's disease treated by topical 5-fluorouracil. Dermatol Surg 2004;30:441–5.
[233] Lin C-H, Aljuffali IA, Fang J-Y. Lasers as an approach for promoting drug delivery via skin. Expert Opin Drug Deliv 2014;11:599–614.
[234] Kappes RS, Schönfeld F, Li C, Golriz AA, Nagel M, Lippert T, et al. A study of photothermal laser ablation of various polymers on microsecond time scales. SpringerPlus 2014;3:489–503.
[235] Hussain A, Wahab GMKA, Ur-Rahman MAS, Altaf H, Akhtar N, Qayyum MI. Potential enhancers for transdermal drug delivery: a review. Int J Basic Med Sci Pharm 2014;4:19–22.
[236] Schlupp P, Weber M, Schmidts T, Geiger K, Runkel F. Development and validation of an alternative disturbed skin model by mechanical abrasion to study drug penetration. Results Pharma Sci 2014;4:26–33.
[237] von Moos S, Johansen P, Tay F, Graf N, Kündig TM, Senti G. Comparing safety of abrasion and tape-stripping as skin preparation in allergen-specific epicutaneous immunotherapy. J Allerg Clin Immunol 2014;134:965–7.
[238] Lipper C. Promotional hang-tag with integral removable tattoo. US Patent, 1998, US-5776586-A.
[239] Rahimi IA, Eberhard I, Kasten E. TATTOOS: what do people really know about the medical risks of body ink? J Clin Aesthet Dermatol 2018;11:30–5.
[240] American Institute of Medical Sciences and Education. 10 Medical Tattoo Ideas for Healthcare Professionals and Enthusiasts. Available at: https://www.aimseducation.edu/blog/medical-tattoo-ideas-for-healthcare-professionals/; Mayo Clinic. Tattoos: understand risks and precautions; available at www.mayoclinic.org/healthy-lifestyle/adult-health/in-depth/tattoos-and-piercings/art-20045067, accessed on June 10, 2019.
[241] Korting HC. Carriers in the topical treatment of skin disease. In: Schäfer-Korting M, editor. Drug Delivery. Berlin, Heidelberg: Springer; 2010:435–68.
[242] Madheswaran T, Baskaran R, Thapa RK, Rhyu JY, Choi HY, Kim JO, et al. Design and in vitro evaluation of finasteride-loaded liquid crystalline nanoparticles for topical delivery. AAPS PharmSciTech 2013;14:45–52.
[243] Lapteva M, Mondon K, Möller M, Gurny R, Kalia YN. Polymeric micelle nanocarriers for the cutaneous delivery of tacrolimus: a targeted approach for the treatment of psoriasis. Mol Pharm 2014;11:2989–3001.
[244] Goebel AS, Neubert RH, Wohlrab J. Dermal targeting of tacrolimus using colloidal carrier systems. Int J Pharm 2011;404:159–68.
[245] Doktorovová S, Araújo J, Garcia ML, Rakovský E, Souto EB. Formulating fluticasone propionate in novel PEG-containing nanostructured lipid carriers (PEG-NLC). Colloid Surf B Biointerfaces 2010;75:538–42.
[246] Marchiori M, Lubini G, Dalla Nora G, Friedrich R, Fontana M, Ourique A, et al. Hydrogel containing dexamethasone-loaded nanocapsules for cutaneous administration: preparation, characterization, and in vitro drug release study. Drug Dev Ind Pharm 2010;36:962–71.
[247] Siddique MI, Katas H, Amin MCIM, Ng S-F, Zulfakar MH, Jamil A. *In-vivo* dermal pharmacokinetics, efficacy, and safety of skin targeting nanoparticles for corticosteroid treatment of atopic dermatitis. Int J Pharm 2016;507:72–82.
[248] Ourique A, Pohlmann A, Guterres S, Beck R. Tretinoin-loaded nanocapsules: preparation, physicochemical characterization, and photostability study. Int J Pharm 2008;352:1–4.
[249] Ourique AF, Melero A, da Silva CdB, Schaefer UF, Pohlmann AR, Guterres SS, et al. Improved photostability and reduced skin permeation of tretinoin: development of a semisolid nanomedicine. Eur J Pharm Biopharm 2011;79:95–101.
[250] Bessar H, Venditti I, Benassi L, Vaschieri C, Azzoni P, Pellacani G, et al. Functionalized gold nanoparticles for

topical delivery of methotrexate for the possible treatment of psoriasis. Colloids Surf B Biointerfaces 2016;141:141–7.
[251] Srisuk P, Thongnopnua P, Raktanonchai U, Kanokpanont S. Physico-chemical characteristics of methotrexate-entrapped oleic acid-containing deformable liposomes for in vitro transepidermal delivery targeting psoriasis treatment. Int J Pharm 2012;427:426–34.
[252] Lin YK, Huang ZR, Zhuo RZ, Fang JY. Combination of calcipotriol and methotrexate in nanostructured lipid carriers for topical delivery. Int J Nanomed 2010;5:117–28.
[253] Avasatthi V, Pawar H, Dora CP, Bansod P, Gill MS, Suresh S. A novel nanogel formulation of methotrexate for topical treatment of psoriasis: optimization, in vitro and in vivo evaluation. Pharm Dev Technol 2016;21:554–62.
[254] Singka GSL, Samah NA, Zulfakar MH, Yurdasiper A, Heard CM. Enhanced topical delivery and anti-inflammatory activity of methotrexate from an activated nanogel. Eur J Pharm Biopharm 2010;76:275–81.
[255] Romero GB, Arntjen A, Keck CM, Müller RH. Amorphous cyclosporin A nanoparticles for enhanced dermal bioavailability. Int J Pharm 2016;498:217–24.
[256] Kim ST, Jang D-J, Kim JH, Park JY, Lim JS, Lee SY, et al. Topical administration of cyclosporin A in a solid lipid nanoparticle formulation. Die Pharm 2009;64:510–4.
[257] Keck C, Anantaworasakul P, Patel M, Okonogi S, Singh K, Roessner D, et al. A new concept for the treatment of atopic dermatitis: silver–nanolipid complex (sNLC). Int J Pharm 2014;462:44–51.
[258] Ilves M, Palomaki J, Vippola M, Lehto M, Savolainen K, Savinko T, et al. Topically applied ZnO nanoparticles suppress allergen-induced skin inflammation but induce vigorous IgE production in the atopic dermatitis mouse model. Part Fibre Toxicol 2014;11:38–50.
[259] Ilinskaya A, Dobrovolskaia M. Immunosuppressive and anti-inflammatory properties of engineered nanomaterials. Br J Pharmacol 2014;171:3988–4000.
[260] Fontana M, Rezer J, Coradini K, Leal D, Beck R. Improved efficacy in the treatment of contact dermatitis in rats by a dermatological nanomedicine containing clobetasol propionate. Eur J Pharm Biopharm 2011;79:241–9.
[261] Shah PP, Desai PR, Patel AR, Singh MS. Skin permeating nanogel for the cutaneous co-delivery of two anti-inflammatory drugs. Biomaterials 2012;33:1607–17.
[262] Depieri LV, Borgheti-Cardoso LN, Campos PM, Otaguiri KK, de Carvalho Vicentini FTM, Lopes LB, et al. RNAi mediated IL-6 in vitro knockdown in psoriasis skin model with topical siRNA delivery system based on liquid crystalline phase. Eur J Pharm Biopharm 2016;105:50–8.
[263] Hansen S, Lehr CM. Nanoparticles for transcutaneous vaccination. Micro Biotech 2012;5:156–67.
[264] Azeem A, Ahmad FJ, Khar RK, Talegaonkar S. Nanocarrier for the transdermal delivery of an antiparkinsonian drug. AAPS PharmSciTech 2009;10:1093–103.
[265] Sack M, Alili L, Karaman E, Das S, Gupta A, Seal S, et al. Combination of conventional chemotherapeutics with redox-active cerium oxide nanoparticles-A novel aspect in cancer therapy. Mol Cancer Ther 2014;13:1740–9.
[266] Saar BG, Contreras-Rojas LR, Xie XS, Guy RH. Imaging drug delivery to skin with stimulated Raman scattering microscopy. Mol Pharm 2011;8:969–75.
[267] Ploetz E, Laimgruber S, Berner S, Zinth W, Gilch P. Femtosecond stimulated Raman microscopy. Appl Phys B 2007;87:389–93.
[268] Freudiger CW, Min W, Saar BG, Lu S, Holtom GR, He C, et al. Label-free biomedical imaging with high sensitivity by stimulated Raman scattering microscopy. Science 2008;322:1857–61.
[269] Ozeki Y, Dake F, Kajiyama Si, Fukui K, Itoh K. Analysis and experimental assessment of the sensitivity of stimulated Raman scattering microscopy. Opt Express 2009;17:3651–8.
[270] Nandakumar P, Kovalev A, Volkmer A. Vibrational imaging based on stimulated Raman scattering microscopy. New J Phys 2009;11:033026.
[271] Saar BG, Freudiger CW, Reichman J, Stanley CM, Holtom GR, Xie XS. Video-rate molecular imaging in vivo with stimulated Raman scattering. Science 2010;330:1368–70.
[272] Herkenne C, Alberti I, Naik A, Kalia YN, Mathy FX, Préat V, et al. *In vivo* methods for the assessment of topical drug bioavailability. Pharm Res 2008;25:87–103.
[273] Kim KW, Kim K-S, Kim H, Lee SH, Park J-H, Han J-H, et al. Terahertz dynamic imaging of skin drug absorption. Opt Express 2012;20:9476–84.
[274] Hong I, Gabay M, Lodolce A. Safety concerns involving transdermal patches and magnetic resonance imaging (MRI). Hosp Pharm 2010;45:771–8.
[275] Shi H, Magaye R, Castranova V, Zhao J. Titanium dioxide nanoparticles: a review of current toxicological data. Particle Fibre Toxicol 2013;10:15–48.
[276] Yang G, Chen Q, Wen D, Chen Z, Wang J, Chen G, et al. A Therapeutic microneedle patch made from hair-derived keratin for promoting hair regrowth. ACS Nano 2019;13:4354–60.
[277] Petchsangsai M, Wonglertnirant N, Rojanarata T, Opanasopit P, Ngawhirunpat T. Microneedles-mediated transdermal delivery. World Academy of Science, Engineering and Technology, Int J Med, Health Biomed Bioeng Pharm Eng 2012;6:439–42.
[278] Yao W, Tao C, Zou J, Zheng H, Zhu J, Zhu Z, et al. Flexible two-layer dissolving and safing microneedle transdermal of neurotoxin: a biocomfortable attempt to treat rheumatoid arthritis. Int J Pharm 2019;563:91–100.
[279] Albash R, Abdelbary AA, Refai H, El-Nabarawi MA. Use of transethosomes for enhancing the transdermal delivery of olmesartan medoxomil: *in vitro, ex vivo*, and *in vivo* evaluation. Int J Nanomed 2019;14:1953–68.
[280] Sadarani B, Majumdar A, Paradkar S, Mathur A, Sachdev S, Mohanty B, et al. Enhanced skin permeation of Methotrexate from penetration enhancer containing vesicles: in vitro optimization and in vivo evaluation. Biomed Pharmacother 2019;114:108770.
[281] Park D, Won J, Shin UC, Park H, Song G, Jang J, et al. Transdermal drug delivery using a specialized cavitation seed for ultrasound. IEEE Trans Ultrason Ferroelectric Freq Control 2019;66:1057–64.
[282] Mofidfar M, O'Farrell L, Prausnitz MR. Pharmaceutical jewelry: earring patch for transdermal delivery of contraceptive hormone. J Control Release 2019;301:140–5.
[283] Yu T, Zhang S, Cao X, Liu C. Iontophoretic delivery of transdermal patches containi. Acta Biochim Pol 2019;66:167–72.
[284] Charoensumran P, Ajiro H. Cationic moieties in polystyrene gels swollen with D-limonene improved transdermal delivery system. Polymers 2018;10:E1200.

[285] Svenskaya YI, Genina EA, Parakhonskiy BV, Lengert EV, Talnikova EE, Terentyuk GS, et al. A simple non-invasive approach toward efficient transdermal drug delivery based on biodegradable particulate system. ACS Appl Mater Interface 2019;11:17270–82.
[286] Sharma CS, Khandelwal M. A novel transdermal drug-delivery patch for treating local muscular pain. Ther Deliv 2018;9:405–7.
[287] Kaur R, Sharma A, Puri V, Singh I. Preparation and characterization of biocomposite films of carrageenan/locust bean gum/montmorillonite for transdermal delivery of curcumin. BioImpacts 2019;9:37–43.
[288] Mahajan NM, Zode GH, Mahapatra DK, Thakre S, Dumore N, Gangane PS. Formulation development and evaluation of transdermal patch of piroxicam for treating dysmenorrhea. J Appl Pharm Sci 2018;8:35–41.
[289] Mendes I, Ruela A, Carvalho F, Freitas J, Bonfilio R, Pereira G. Development and characterization of nanostructured lipid carrier-based gels for the transdermal delivery of donepezil. Colloids Surf B Biointerfaces 2019;177:274–81.
[290] Sabri AH, Ogilvie J, Abdulhamid K, Shpadaruk V, McKenna J, Segal J, et al. Expanding the applications of microneedles in dermatology. Eur J Pharm Biopharm 2019;140:121–40.
[291] Parhi R, Swain S. Transdermal evaporation drug delivery system: concept to commercial products. Adv Pharm Bull 2018;8:535–50.
[292] Szunerits S, Boukherroub R. Heat: a highly efficient skin enhancer for transdermal drug delivery. Front Bioengg Biotechnol 2018;6:1–15.
[293] Verma A, Jain A, Hurkat P, Jain SK. Transfollicular drug delivery: current Perspectives. Res Report Transderm Drug Deliv 2016;5:1–17.
[294] Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics 2015;7:438–70.
[295] USP Performance Tests. Topical and transdermal dosage forms. Pharmacopoeial Forum 2009;35:750–64.
[296] General Drug Release Standards-Transdermal Delivery Systems: USP29-NF 24, Pharmacopoeial Forum 2013;31:198. Available from: http://ftp.uspbpep.com/v29240/usp-29nf24s0_c724s30.html. Accessed on December 23, 2018.
[297] European Medicines Agency: guideline on quality of transdermal patches: Committee for Medicinal Products for Human Use (CHMP). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-transdermal-patches_en.pdf. Accessed on December 23, 2018.
[298] Hillery AM, Park K. Drug Delivery: Fundamentals and Applications. 2nd ed. Boca Raton, FL, USA: CRC Press; 2016.
[299] Wang B, Hu L, Siahaan TJ. Drug Delivery: Principles and Applications. 2nd ed. NJ, USA: John Wiley & Sons, Inc.; 2016.
[300] Bhowmik D, Kumar KPS, Bhanot R. Recent Advances in Transdermal Drug Delivery System. Mauritius: LAP Lambert Academic Publishing; 2017.
[301] Benson HEA, Watkinson AC, editors. Topical and Transdermal Drug Delivery: Principles and Practice. NJ, USA: Wiley & Sons; 2011.
[302] Hao Y, Li W, Zhou X, Yang F, Qian Z. Microneedles-based transdermal drug delivery systems: a review. J Biomed Nanotech 2017;13:1581–97.
[303] Watkinson AC, Kearney M-C, Quinn HL, Courtenay AJ, Donnelly RF. Future of the transdermal drug delivery market – have we barely touched the surface? Expert Opin Drug Deliv 2016;13:523–32.