Breaching the skin barrier through temperature modulations

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Abstract

The impermeability of the stratum corneum often hinders the transport of molecules across the skin. Temperature modulations in the skin and the application of local heat both have the potential of circumventing this problem temporarily and reversibly and when applied, may aid in enhancing drug diffusion through the skin. A controlled and precise application of heat has the ability to create a cascade of events in the skin and thus aids in facilitating a faster movement of molecules into and across the skin. Possible mechanisms of enhancing drug permeation include: a) increase in drug diffusivity in the vehicle and/or in the skin, b) increase in partitioning and diffusion, c) disturbance in the lipid structure of the stratum corneum, and d) increased local blood flow. These mechanisms may operate individually or concurrently. The creation of micropores or channels in response to exposure to very high heat energy for a fraction of time is another technique that can facilitate the transport, known as thermal ablation. These micropores then serve as channels from where drug molecules can escape from formulations into the skin at a much faster rate than through passive diffusion. This review, therefore, summarises the effects that temperature modulations may have on the permeability of the skin. Physical techniques of heat induced skin ablation, such as chemical heating, thermoporation, radiofrequency induced thermal ablation, and laser induced thermal ablation are also presented in this review.

Keywords: Stratum corneum; Temperature; Permeability; Heat; Micropores; Thermal ablation; Safety

Contents

1. Introduction

The skin, together with the mucosal linings of the digestive and respiratory tracts comprises the largest organs in the human body, with their role being the protection of internal structures from external hostility such as micro-organisms and radiation, whilst also limiting the undesirable loss of water from the body [1, 2]. As a result of its easily accessible large surface area, the skin continues to attract much research interest as a minimally invasive to non-invasive and an alternative route for drug delivery to conventional oral and intravenous drug administration techniques [3-6].

The advantages of drug delivery through the skin include a needleless administration of drug (i.e. no pain to the patient), the reduction of possible infections, reduced compliance issues, and most notably [7] the possibility of delivering drugs for a prolonged period of time at a constant rate, by avoiding the hepatic first-pass metabolism that can otherwise lead to significant drug loss [8, 9]. The administration of drugs through the skin, however, has many challenges, including overcoming the variability in penetration among individuals and among the different locations on the skin of an individual [10], and the excellent barrier function of the outer membrane of the skin itself, the stratum corneum (SC) [11], that limits the ingress of chemicals. The poor penetration of drugs through the skin hence often limits the efficacy of topically applied drugs [12], which is why physical and chemical enhancement approaches are actively sought and adopted to enhance drug delivery [13].

Some approaches to enhance percutaneous absorption may involve the use of an energy source to compromise the SC barrier, or even the complete removal of the SC. The use of heat energy as a strategy to enhance the uptake of an active pharmaceutical ingredient (API) into the skin was originally reported by Fritsch and Stoughton [14]. A number of other researchers have subsequently demonstrated enhanced drug [15-17], or vaccine [18, 19] percutaneous absorption at elevated skin temperatures. This contribution, therefore, aims at reviewing the impact of temperature on the skin's permeability to compounds, with special reference to various techniques that employ heat energy for promoting drug transport across the skin.

2. Skin physiology

The physiology of the skin has been excellently described in previous publications [20-22], and an overview thereof is presented here.

The skin is the largest organ in the human body and roughly accounts for 15% of the total bodyweight, with a surface area of 1.5 - 2.0 m^2 of varying thickness, depending on anatomical site and gender [21, 23]. The skin is a multi-layered organ, in which all of the layers differ from each other with regards to morphology and function.

Traditionally, skin is divided into three discrete layers, i.e. the epidermis, the dermis and the subcutaneous fat layer, or hypodermis. The epidermis is the outermost layer of the skin and is characterised as the thinnest part of the skin, with its thickness varying, depending on the location on the skin. From histological point of view, the epidermis is a stratified squamous epithelial layer, within which keratinocytes are organised in five different strata [24, 25]. Protection of the skin is primarily provided by the superficial layer of the epidermis, the SC, which is only 10 - 20 μm in thickness and represents the main barrier to percutaneous absorption and water loss from the body [26]. The SC is composed of compact, dehydrated and keratinised, multi-layered cells that are

embedded within a matrix of lipid lamellae that descend from the secreted content of the lamellar bodies, giving the SC a brick and mortar organisation [27, 28]. Beneath the SC is the living epidermis (50 - 100 μm) also called as viable epidermis, which has an important function of regeneration of the SC. The viable epidermis is further divided into four distinct layers, i.e. the stratum lucidum, the stratum granulosum, the stratum spinosum and the stratum basale. The dermis (1 - 2 mm) is directly alongside the viable epidermis and provides the mechanical properties of the skin [29]. The dermis is made up of collagen, elastins and glycosaminoglycans, collectively called the extracellular matrix, as well as fibroblasts that extend the extracellular matrix. The highly vascular dermis also contains the pilosebaceous glands, sweat glands, dermal adipose cells, mast cells and infiltrating leucocytes [21].

3. Process and routes of percutaneous absorption

Percutaneous absorption generally refers to the penetration of foreign entities into different layers of the skin and subsequently permeating across the skin thus leading to systemic absorption. The percutaneous absorption depends upon various events. When a drug is applied to the skin, it passively diffuses from the formulation and partitions into the SC. The concentration gradient is the primary driver for transdermal delivery through the SC. The route that the drug follows after entering the SC depends on the affinity, fractional areas and ease of diffusion through the respective component features [30].

From an anatomic point of view, there are three possible macro-routes of drug permeation across the intact skin. Firstly, the transport *via* intracellular route through corneocytes. Corneocytes provide aqueous environment due to the presence of hydrated keratin, thus allowing for the transport of hydrophilic or polar solutes. However, corneocytes are surrounded by a lipid envelope, thus connecting cells with the lipid bilayer [31]. Secondly, the transport *via* intercellular spaces, which allow diffusion of lipophilic or non-polar solutes through the continuous lipid matrix. Intracellular and intercellular routes are collectively called as the transepidermal route (Fig. 1). On a micro-scale, both polar and non-polar substances diffuse *via* these first two routes through different mechanisms [15, 32]. After reaching steady state condition, bulk diffusion through the lipid region dominates. Siddiqui *et al*. [33] compared the diffusion of steroids across the SC and silicone membranes, and found that their penetration kinetics was independent of aqueous channels. Thirdly, the transappendageal or shunt route considers transport *via* the sweat ducts (eccrine route) and hair follicles (follicular route), as well as their associated sebaceous glands. The transappendageal route is considered to play a negligible role, because of the relatively small area it represents (less than 0.1% of total surface), although difference in opinion exists among different research groups. This route has, however, been recommended as a possible minor transport route for large polar compounds [34].

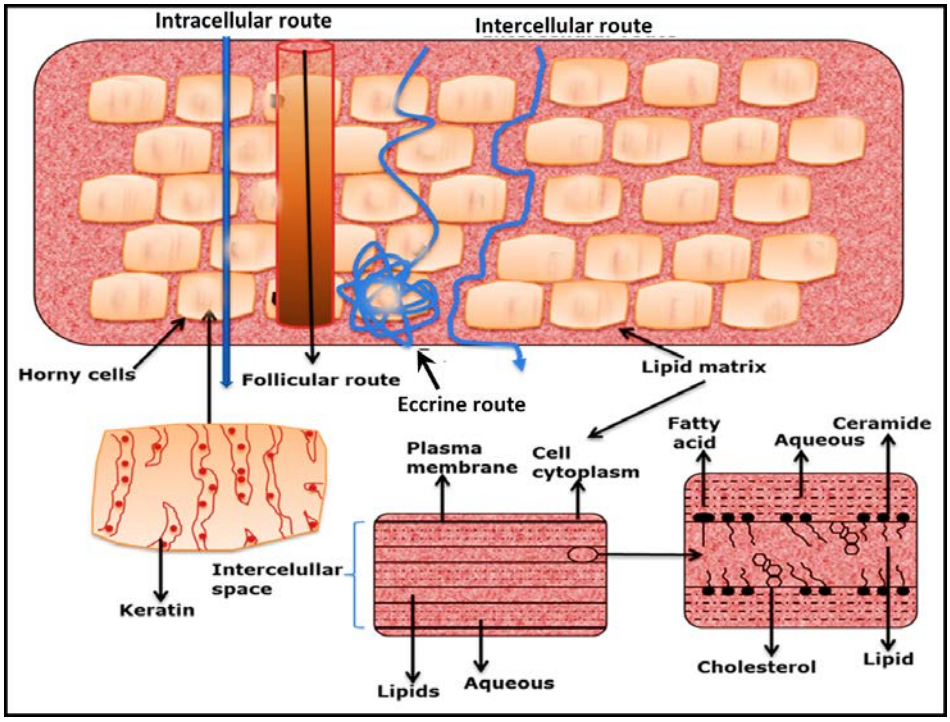

Fig. 1: Possible drug penetration routes across human skin. Modified with permission from [22].

4. Thermal effects on the skin physiology

This is an established fact that the diffusion of substances across a homogenous membrane increases with increasing temperature [35]. This may be applied to the skin, and it is envisaged that a positive relation would exist between skin temperature and the penetration of topically applied chemicals. Variations in skin temperature may therefore significantly influence the transport of active substances from transdermal drug delivery devices [36]. It is important, though, to understand the thermal effects on the skin's homeostasis. The thermoregulatory centre of the human body controls the internal (core temperature) and skin temperature through the blood circulation. Excessive heating elevates internal and skin temperatures, which are countered by cutaneous vasodilation as a result of neural mechanisms coupled with the local effects of higher temperatures on the skin vessels themselves. As the core temperature reaches the threshold, cutaneous blood flow increases, which tends to deliver heat to the body surfaces, where it is dissipated to the environment, along with the evaporation of sweat. Cutaneous blood flow thus protects the skin from damage from excessive heat. The exact mechanism of cutaneous vasodilation has, however, remained somewhat enigmatic. Conversely, temperature levels below normal body temperature cause cutaneous vasoconstriction through combined neural and local mechanisms to conserve heat, or energy [37].

Recently, different transient receptor potential (TRP) receptors have been identified to act as sensors of temperature, or other physical or chemical factors [38] that control the skin barrier homeostasis. TRPV1, TRPV3 and TRPV4 are believed to be activated by heat to then recover the disrupted barrier function of the skin [38]. A more recent study, however, suggests that TRPV4 is indeed associated with the epidermal permeability barrier homeostasis, but not TRPV3 [39].

Since temperature can modify the structure of the skin layers, thermal techniques are routinely used to investigate the physical properties of the SC. Differential scanning calorimetry (DSC) has been used by several investigators to study the thermally induced structural changes in the human SC. Several thermal transitions have been identified at approximately 10°C, 35 - 40°C, 65 - 75°C, 80°C and 100°C [40, 41]. The first three transitions are assigned to the SC lipids, while transition at 80°C represents lipids that are associated with proteins. The transition at 100°C is associated with the denaturation of proteins. Fig. 2 represents thermal events in various skin samples. The transition at 35 - 40°C is small, thermally reversible and varies from sample to sample, thus suggesting that the lipids are not tightly associated with the SC and may arise from the sebaceous fats that are still adhering to the SC after washing. In the reheated SC samples, 65 - 75°C and 80°C transitions reappear, whilst the transition at 100°C has disappeared, indicating that lipid transitions are reversible, whilst those of proteins are irreversible.

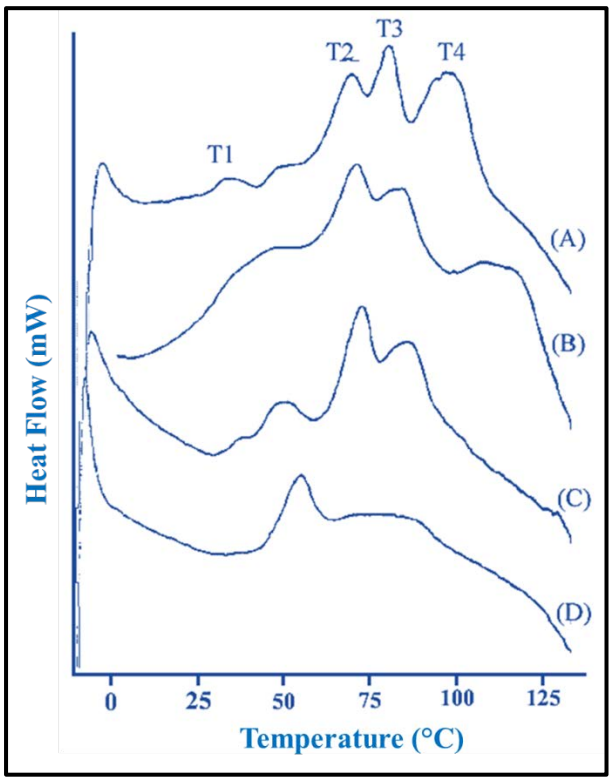

Fig. 2: DSC traces of (A) 20 - 40% hydrated stratum corneum, (B) reheated sample, (C) de-lipidised stratum corneum (20 - 40% hydrated), and (D) de-lipidised stratum corneum (dry). Endothermic transitions appear as peaks. T1, T2, T3 and T4 represent 35 - 40°C, 65 - 75°C, 80°C and 100°C, respectively. Adapted with permission from [42].

Park *et al*. examined the histology of the human skin with respect to temperature modulations after exposing the skin to a temperature range of 25 - 315°C for 100 ms, as shown in Fig. 3 [43]. This study revealed a three zone influence of temperature within the experimental range on skin permeability. Zone 1 represents heating from 100 - 150°C, where a minor-fold increase in skin permeability of a hydrophilic compound was observed. However, two- and three-fold enhancements in skin permeation were observed at temperature increases from 150 - 250°C (zone 2) and above 300°C (zone 3), respectively. Higher temperatures had brought about changes in the SC keratin network, which ultimately led to decomposition and vaporisation of the SC, thus

facilitating drug transport. These structural changes are visible in the histological illustrations in Fig. 3.

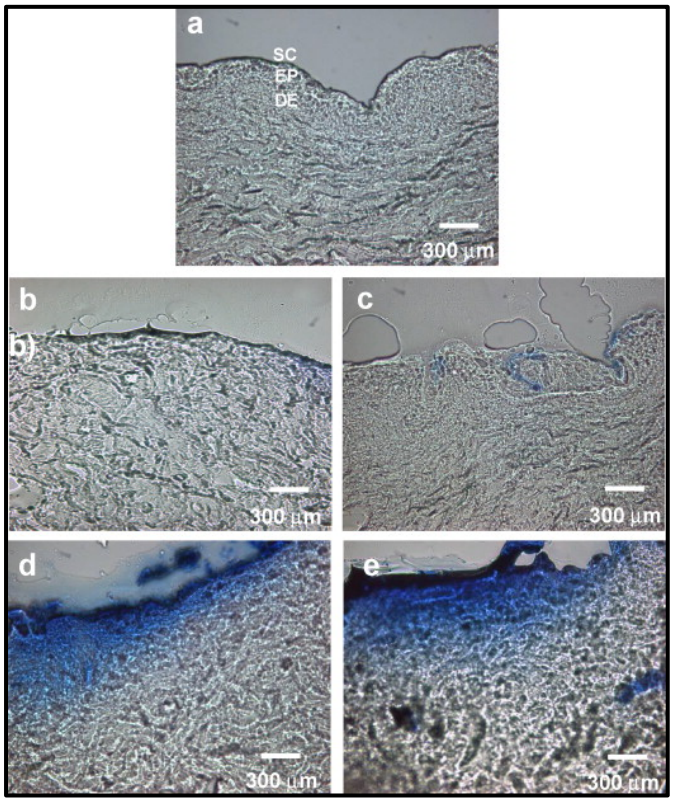

Fig. 3: Histological representations of human skin after a 100 ms exposure to (a) no treatment, (b) 260°C, (c) 315°C, (d) 368°C, (e) 415°C. Trypan blue was used as a marker and hematoxylin and eosin (H&E) for staining. SC, EP and DE represent stratum corneum, epidermis and dermis, respectively. Reproduced with permission from [43].

Conclusively, thermal analyses of the SC demonstrated that main lipid transitions had appeared at and above 40°C. These outcomes also confirmed that temperature variations above 40°C may disturb the lipid lamellae and facilitate faster permeation. However, care should be taken during exposure to higher temperatures, since long-term exposure to heat well above the skin's tolerance threshold may lead to the denaturation of proteins and the burning of the deeper skin tissues.

5. Mechanisms through which temperature variations affect skin permeation

Although the use of heat energy as a means of enhancing drug permeability has been reported for several solutes [14, 43, 44], such possibilities are far from being fully exploited. The exact mechanism in which heat aids with enhancing skin permeation remains poorly understood, despite the fact that the effect of heat on the skin's homeostasis has been extensively studied. The United States Food and Drug Administration (FDA) has already warned about the possibility of toxicity because of the enhanced percutaneous absorption of topically applied formulations (fentanyl patch), resulting from an increase in body temperature (e.g. during physical exercise, sauna baths) and the associated exposure to UV radiation from the sun [45]. Table 1 summarises various studies focussing on temperature effects on the skin permeation.

Table 1: A summary of temperature/heat effects on the permeation of drugs

Drug/formulation	Experiment type	Membrane	Exposed temperature/heating source	Transport mechanism/reason	Reference
Saturated solutions of parathion	*In vitro*	Porcine skin	37°C and 41°C	Structural changes in the SC	[46]
Terodiline gel formulation containing propylene glycol and ethanol	*In vitro*	Wistar rat full thickness skin and SC	25-50°C	Fluidity of lipids in SC and drug penetrated through lipoidal pathway	[47]
Dihydrotestosterone solutions in: ethanol/water (50:50); propylene glycol; oleic acid (10% v/v in propylene glycol); limonene (2% v/v in propylene glycol); Transcutol® and oleic acid (10% v/v in Transcutol®)	*In vitro*	Hairless rat skin	28.6°C, 35.1°C and 38.2°C	Increased SC lipid fluidity due to heating and disturbance of lipid organisation by penetration enhancers	[36]
Saturated solutions of methyl paraben, ethyl paraben and caffeine	*In vitro*	Cellulose and human epidermis	23-45°C	Increased drug diffusivity in vehicle and the membrane, and fluidity of the SC lipids	[44]
Saturated lidocaine solution	*In vitro*	Cellulose, silicone and human epidermis	27-45°C	Increased drug diffusivity and partitioning, and structural changes in the epidermis	[48]
Aqueous solutions of various alcohols (polar and non-polar)	*In vitro*	Human epidermis	5-50°C	Polar molecules diffused through polar pathway, while non-polar through intercellular lipidic pathway	[15]
Aqueous solutions of urea, mannitol, triethylammonium ion and corticosterone	*In vitro*	Human epidermis	27°C and 30°C	Hydrophilic solutes diffused through porous pathway, while corticosterone through intercellular lipidic pathway	[17]
Nitroglycerin	*In vivo*	Healthy volunteers	Infrared heating	Presumably because of cutaneous or subcutaneous drug reservoir build-up and changes in regional blood flow	[49]
Nitroglycerin	*In vivo*	Healthy volunteers	Sauna bath (90°C)	Same as above	[50]
Nicotine	*In vivo*	Healthy volunteers who smoke	Sauna bath (82°C)	Same as above	[51]
Testosterone	*In vivo*	Healthy volunteers	Heat patch	Same as above	[52]
Fentanyl	*In vivo*	Healthy volunteers	Heating patch and unspecified device used (42°C)	No reason mentioned	[53]
Methyl salicylate	*In vivo*	Healthy volunteers	40°C	Increased skin temperature, cutaneous blood flow, and skin hydration	[54]

As discussed earlier (Section 3), the process of permeation can be divided into a series of steps such as the release of permeant from the formulation, partitioning of permeant into the SC and diffusion through it, and finally partitioning from SC to the viable epidermis from where a permeant can escape into the general circulation. It would be interesting to capture an overall scenario of influence of temperature variations on the formulations, and on the skin, in order to compromise its barrier properties. Therefore, we aim to address the influence of temperature variations on these steps for a better understanding of the temperature dependent permeation process.

5.1. Influence of temperature on formulation vs. skin

It is important to understand when temperature is varied during skin permeation experiments, exactly what changes occur that may possibly increase the escape of compounds from the formulations (more specifically from the vehicle) into the skin. Generally, at laboratory scale, temperature variations are controlled by using a water bath that is coupled with the *in vitro* permeation system. This method, however, is unable to distinguish between penetration enhancement being as a result of the effect of temperature modulations on the applied formulations, or due to changes in the skin itself. Also, these experiments are usually conducted at controlled receptor temperature and therefore, it is difficult to decouple the exact temperature effects on the donor side where the formulation is present. Now the question arises, what happens if a subject wearing a transdermal patch is exposed to heat or high temperature? An excellent example of this scenario is the transdermal fentanyl patch which was ranked number two in terms of the death toll during 1998 – 2005 in the United States [55]. Many death cases were reported due to the overdoses of fentanyl, and one of the reasons of overdose was enhanced temperature, which possibly accelerated the drug release from the patch and may also have increased the skin permeability. Consequently, FDA issued cautions for the use of fentanyl transdermal patch, which also include avoidance of exposure to the environmental heat such as sun-bath, sauna and hot tubs, or the exposure of heat from heating pads, heated blankets, or even hyperthermia [56]. However, there are many instances such as chronic pain associated with cancer where an increased dose of fentanyl is required over extended period of time and application of controlled and precise heat at the application site can quickly increase the drug penetration. Once again, the question arises, does the application of heat bring changes in the formulation properties or an enhanced temperature affects the skin? To answer this, we will focus our discussion on both factors.

The effect of temperature on formulation/SC partitioning is a function of both the formulation solubility and the SC solubility, both of which change with temperature. Enhanced solubility of a drug in the given formulation or a vehicle as a result of temperature modulations can lead the system away from saturation or supersaturation state, thus changing the thermodynamic activity negatively which is the driving force for the compounds to escape the formulation/vehicle and enter into the skin [57]. According to Fick's second law of diffusion, the permeation of a compound across the skin is directly proportional to the concentration of permeant in top layer of the SC [58].

Chang & Riviere [46] demonstrated influence of environmental temperature on the *in vitro* transport of parathion across the porcine skin. The temperature of the donor phase was controlled using a flow-through diffusion chamber. Relative humidity (20% and 90%) and dose (4 μg, 40 μg and 400 μg in 10 μL of ethanol) as variables were also

introduced in the experiments. The environmental conditions (air temperature = 42°C and perfusate (receptor media) temperature = 37°C; air temperature = 42°C and perfusate temperature = 42°C) studied in this experiment revealed a significant effect on the rate of parathion transport. More interestingly, 4 µg dose with both the air and perfusate temperature set at 42 °C resulted in more than two-fold increase in the parathion penetration when compared with 40 µg (over one-fold) and 400 µg (less than one-fold). Relative humidity at 90% significantly enhanced the drug absorption at all dose levels. The authors concluded that the enhanced absorption of the drug was due to the structural changes in the skin barrier as a result of temperature and humidity modulations regardless of dose. Similar finding were reported in other studies by Ogiso *et al*. [47] and Clarys *et al*. [36]. They concluded that the rapid penetration of the permeants was due to the partially melted SC lipids.

Given that one can argue if temperature mediated changes in the skin barrier properties are the sole contributor of this enhancement. Most of the prior work employed permeation enhancers (ethanol, propylene glycol and terpenes) in the formulations, which are known to disturb the SC lipid organisation. Therefore, it is not easy to decouple the temperature effects on skin permeability from these studies.

Later, Akomeah *et al*. [44] studied the release of methylparaben (MP), butylparaben (BP) and caffeine (CF) from their aqueous saturated solutions across a non-rate limiting cellulose membrane, by employing varying temperatures. This experimental setup ensured a precise study of the effects of temperature on the formulation in the absence of the skin. The release rates of MP, BP and CF through cellulose membrane were found to be slightly higher with a factor of 1.53, 1.55 and 1.66, respectively, with each 7 - 8°C rise in receptor temperature starting from 23 - 45°C. This increase in release rate was attributed to the dependence of diffusivity of the permeants on the temperature and not on the concentration of saturated solutions. Although saturated solubility was increased with increasing temperature. Following the release study, they compared these permeation outcomes with those of the same three compounds through human epidermis. A two- to three-fold increase in steady state flux for all three compounds across human epidermal tissue was observed with increase in receptor temperature (23 - 45°C). The relative increase in diffusivity with temperature of three penetrants (MP, BP, and CF) accounted for 66%, 68% and 81% (averaged values), respectively, in the enhancement. These results also show that the skin barrier properties are partially affected when exposed to higher temperature such as 45°C, and diffusion across the SC remains the rate-limiting step i.e. only ≤ 35% increased permeation was observed when heat changed the barrier properties. Therefore, an increase in the fluidity of the SC lipids at experimental temperature was not the sole contributor in enhanced epidermal permeability [41], and that the molecular diffusivity at the vehicle/skin interface had contributed more. Recently, Otto & De Villiers [59] performed computer simulations to investigate the effect of heat on diffusion kinetics of ketoprofen from gel formulation. Molecular dynamics simulation revealed an increase in diffusion coefficients of water and ketoprofen with a 10°C rise in temperature. This increase in drug mobility resulted in effective release of drug from the gel system and an enhanced permeation of ketoprofen was achieved.

From literatures cited above, it can be concluded that increasing temperature can have effects on both the penetrant in the vehicle and the skin. Relative contribution of effects of heat on the vehicle and the skin is difficult to decouple from such laboratory

investigations. Nonetheless, changes in the drug diffusivity in the vehicle are more pronounced and would largely have contributed to the enhancement of drug transport. However, one can't ignore the reversible structural changes of the SC barrier with moderate rise in temperature (≈45°C) whilst maintaining its rate-limiting property. Additionally, vehicle composition may also influence the permeation in response to the supplied heat. Certain formulations (i.e. gels or lotions) can quickly dry at the surface of the skin, thus forming a barrier film at the skin/vehicle interface which could halt the permeation process [60].

5.2. Influence of temperature on partitioning and diffusion

To date, there is no clear link between temperature-induced changes in the formulation and/or in the skin barrier properties and the percutaneous absorption of drugs. This is because temperature can bring changes to formulation stability, drug diffusivity in the vehicle, partitioning in the skin and diffusion across the rate-limiting barrier. Theoretically, a positive relationship between temperature and the percutaneous penetration of topically applied products is expected. The percutaneous penetration of topically applied products can be explained by Fick's law of diffusion [61].

$$J = k_p.\Delta C \qquad \text{(Eq. 1)}$$

Where J is the flux (g.cm^{-2}.s^{-1}); k_p is the skin permeability coefficient (cm.s^{-1}); and ΔC is the difference in concentration across the membrane with the permeability coefficient.

$$k_p = \frac{D \times P}{h} \qquad \text{(Eq. 2)}$$

Where P is the partition coefficient of solute between membrane and vehicle; D is the diffusion constant (cm^2.s^{-1}); and h is the thickness of the membrane (cm). Clearly, the process of percutaneous absorption is principally based on partitioning and diffusion, which occur in parallel.

The partition coefficient is the solubility of the drug in the membrane relative to the vehicle when equilibrium ensues. In many cases, the partition coefficient is the primary factor in determining drug permeation across the skin. Although log P values of neutral immiscible liquids correlate well with their water solubilities, the solubilities of solids also depend on the energy required to break the crystal structure. Since the SC has a significant proportion of lipids (10-16%), thus, partitioning of a drug into the skin would be dependent on its solubility in the lipids [62, 63]. Determination of membrane/vehicle partition coefficient is not straight forward and hence partitioning in aqueous immiscible solvents such as octanol is routinely modelled as a surrogate for the SC/vehicle partitioning. Often, skin permeation is modelled using skin mimics, such as silicone membranes, because of their lipid-like properties [64]. Many studies have, therefore, utilised silicone membranes to investigate the basic mechanisms involved in the partitioning and diffusion of compounds from formulations and to examine the influence of external stimuli, such as temperature, on the transport of compounds [65-68]. Wood *et al*. [48] recently undertook such investigation of the mechanisms of heat facilitated drug transport across regenerated cellulose membrane (RCM), silicone membrane and human epidermis. A controlled temperature water bath, maintained at 27°C, 32°C, 37°C and 45°C was used as a heating source. Three factors were considered,

i.e. drug release from the formulation, molecular mobility or partitioning, and the diffusivity of the human epidermis in response to temperature changes up to 45°C. A linear relationship between lidocaine transport and temperature was attributed to a direct consequence of heat increasing the molecular diffusivity of drug in the RCM membrane. These results echoed the findings of Akomeah *et al*. [44], where they demonstrated increased molecular mobility of three penetrants across RCM. RCM can form a polymeric barrier and may retard the diffusion for hydrophilic and hydrophobic compounds, therefore, only silicone and epidermal membranes were used in partitioning studies. The partition coefficient of lidocaine base across silicone membrane and human epidermis increased with increasing temperature. This demonstrates increasing affinity of lidocaine for the components of both barriers, similar to what has been reported previously [69]. Oliveira *et al*. demonstrated thermodynamics of vehicle-membrane partitioning of solutes and associated changes in the enthalpy were determined by applying Van't Hoff's analysis [67]. A change in enthalpy of the solute-membrane partitioning of MP was observed at various temperatures, suggesting a temperature dependant interaction between the solute and the membrane. For permeation through the skin, from the second law of thermodynamics, the Gibbs free energy (ΔG) for that process must be negative, as expressed by the following equation.

$$\Delta G = \Delta H - T\Delta S \qquad \text{(Eq. 3)}$$

A change in enthalpy (ΔH) values will determine the effect of temperature on the partitioning process. According to Le Chaterlier's principle, partitioning will increase as temperature decreases for systems with a negative enthalpy value. For systems with positive enthalpy, partitioning will increase when more heat is generated [70].

More recently, Waters *et al*. demonstrated the transport of parabens across silicone membranes at various experimental temperatures [65]. Thermodynamic data has, however, not been captured during this study, but temperature dependant increased transport of compounds have been demonstrated at a range of experimental temperatures.

Continuing with the findings of Wood *et al.* [48], unlike RCM and silicone membranes, where a linear increase in the transport of the drug had been observed because of an increased molecular motion in the formulation, skin diffusivity was not linearly related to temperature changes. Instead, a two phase relationship was observed in the human epidermis. The diffusion coefficient of drug had decreased at a temperature range between 27 - 32°C, whilst it dramatically increased (519%) with a rise in temperature between 32 - 45°C. According to the authors, this sharp change in drug diffusion was attributed to the fluidity of the lipids, and orthorhombic to hexagonal lipid transitions in the human epidermal tissue [71]. This study concluded that modifications in the lipid organisation of the SC had mainly been responsible for enhancing drug transport in the human epidermis, compared with the changes associated with the formulation as a result of temperature variations [48].

An important determinant in transdermal drug delivery that also influence the mechanical properties of the skin is the sorption of water by the SC. Hydration of skin tend to increase the diffusivity of drugs in the skin. This fact is well used by the cosmeceuticals in claiming the cosmetic skin benefit derived from moisturisers. Biophysical evidence suggests that the SC lipid domains comprise the primary barrier to

transepidermal water loss [72] and to the penetration of small compounds into the skin. Extraction of lipids from the SC demonstrated to have led to a thousand-fold increase in water permeability. The role of the SC lipids in regulating water loss is hence well founded and well known [73].

The dependence of water diffusion through the SC on water content was confirmed *in vitro* on intact SC by Blank *et al*. [74]. They demonstrated that increased relative humidity can increase water contents of the SC, which resulted in increased permeability and diffusion coefficients of skin.

The dependence of the level of water sorption on temperature was reviewed by Potts [75]. He concluded, based upon isothermic analytical outcomes that the number of water-binding sites within the SC had increased with temperature. Although the binding energy of sorbed water should be decreased by an increase in temperature, a higher number of available binding sites seemed to have dominated the process. The temperature induced increase in the number of water binding sites may have been the result of protein unfolding, or of changes in the diffusion coefficient of water through the SC, or both.

The mechanisms through which water diffused across the SC, or any other lamellar lipid phase, is somewhat enigmatic. Most researchers working in this domain have suggested that water permeates through lipid lamellae *via* free-volume voids, created as a result of random fluctuations in alkyl chain packing. Findings by Potts & Francoeur [73] showed a strong correlation between water permeability and the SC lipid alkyl-chain disorder, which therefore confirmed the free volume hypotheses.

5.3. Temperature variations and permeation pathways

Evidence from data presented by Flynn et al. [76] suggests that the effect of temperature on the diffusion process is a result of the positive change in the diffusion coefficient with an increase in temperature. Therefore, the transport of a solute at different experimental temperatures can offer mechanistic insights into the diffusion process of a solute across membranes and has been shown to be related to the activation energies of the membranes' permeability [77]. In general, the activation energy (E_a) is a kinetic function of the characteristics of both the diffusing molecule and the diffusion pathway. A molecule needs to be raised to a certain energy level so that it can break the restraining bonds and diffuse across the membrane [15]. The following equation [76] expresses the Arrhenius relationship between diffusivity and temperature:

$$D_i = D_0 e^{(-E_a)/RT} \qquad \text{(Eq. 4)}$$

where D_i is the diffusion coefficient, D_0 is the Arrhenius factor, R is the gas constant and T is the absolute temperature in Kelvin.

When $\log D_i$ is plotted against $1/T$, a straight line is expected, the slope of which would then be proportional to the activation energy. Linearity in this relationship also tells if there is an unchanged mechanism of permeation across the experimental temperature range. Early work of Roberts *et al*. [78] and Blank *et al*. [15] demonstrated that polar molecules would diffuse through a polar pathway consisting of 'bound water', and considerably high activation energy would be needed compared with diffusing through 'free water'. On the other hand, non-polar substances would diffuse much easily

through the lipidic intercellular spaces because of their better lipid solubility with a minimal requirement of activation energy. These conclusions were based on the permeation data obtained for aliphatic alcohols and phenolic compounds. However, Peck *et al.* [17] concluded opposite to what has been reported earlier. They studied temperature dependant permeability of polar solutes such as urea, mannitol and tetraethyl ammonium ion (TEA), and compared with the transport of lipophilic solute, namely corticosterone. They observed an increased permeability of hydrophilic permeants across the human epidermal membrane (HEM), however, the required activation energy was much lower than that for the corticosterone. Thus, the permeation of urea, mannitol and TEA is likely through the porous pathway, and corticosterone permeated through the intercellular lipidic pathway. The slight increase in the permeability of polar solutes may result from the temperature mediated reversible structural changes which increase the porosity of the HEM or decrease the tortuosity of the polar pathway. Increase in temperature may also have altered the water binding sites in the porous pathway, thus increasing the diffusion coefficients of the permeants [75].

These contradictory reports were the basis of Mitragotri's investigation into the role of activation energies in explaining the mechanism of permeation [77]. He qualitatively reviewed temperature dependency of skin permeability to hydrophilic and hydrophobic solutes [77]. Hydrophobic solutes largely diffuse through the SC lipids [79], while the transport route for hydrophilic solutes is not fully understood and believed to permeate through the intracellular pathway [80]. Skin permeability to hydrophobic and hydrophilic compounds and their temperature dependencies have previously been described by using the following equations [81]:

$$\frac{E_a}{R} = r^2 \frac{\partial A}{\partial (1/T)} + \frac{E_o^D}{R} + 0.7\frac{E_{o/w}^P}{R} \qquad \text{(Eq. 5) (for hydrophobic solutes)}$$

$$E_a = E_w^D - R\frac{\partial}{\partial (1/T)}\ln(\lambda) \qquad \text{(Eq. 6) (for hydrophilic solutes)}$$

Where E_a is the activation energy of the skin's permeability; r is the van der Waal's solute radius in Å; A is a constant whose value is related to the structure of lipid chains in the SC; R is the universal gas constant; E_o^D is the activation energy of a solute's diffusion in an aprotic solvent; $E_{o/w}^P$ is the activation energy of the solute octanol-water partition coefficient; E_w^D is the activation energy of a solute's diffusion in water; and λ is the hydrodynamic radius of the solute.

Based on this qualitative study, Mitragotri concluded that high activation energies of strongly hydrophobic solutes had been due to the direct dependency of their permeabilities on their sizes, whilst no correlation had been observed between activation energies and the sizes of hydrophilic permeants. Although this model, furthermore, assumed that hydrophilic solutes would diffuse through permeable pores in the impermeable membrane, thermal expansion of these pores had not accounted for a higher diffusion of hydrophilic solutes, since the pore sizes were relatively larger than those of the solutes [77].

The temperature dependency of permeation pathways has shown complexity and many factors such as porosity, tortuosity and pore size may influence the diffusion of lipophilic and hydrophilic permeants across the epidermal membrane. However,

detailed mechanistic investigations are still lacking and more importantly, current techniques do not accommodate the transappendageal or shunt pathway as a potential contributor of temperature mediated skin permeation. Therefore, there is a substantial knowledge gap exists and thus warrants further exploration of permeation process with respect to temperature modulations.

5.4. Influence of temperature on in vivo drug absorption

We have already discussed that temperature can enhance skin permeability through multiple factors such as effects on: formulation, vehicle/membrane partitioning, drug's diffusivity, and can reversibly compromise the rate-limiting barrier. In addition to these, as discussed earlier (Section 4), the heat mediated increase in skin penetration and subsequent absorption of chemicals is also associated with changes in the local blood flow. Important considerations of such variations in transdermal therapy, for example, include occlusion of the skin to elevate the skin temperature [82], temperature variations within different body regions [83], and physical exercise and exposure to the sun [84]. Rabkin & Hunt [85] demonstrated a three-fold increase in local perfusion with an increase in subcutaneous temperature by 4°C. This increased local blood flow can quickly clear the drug that is accumulated in the skin after application of transdermal formulation at elevated temperatures. Several studies have demonstrated an improved transdermal absorption and distribution of nitroglycerine [49], testosterone [52] and fentanyl [53] as a result of changes in the skin temperature.

Klemsdal *et al*. demonstrated the temperature effects on the *in vivo* permeation of nitroglycerine from a patch (Transderm-Nitro® CIBA GEIGY), applied to nineteen healthy volunteers each, releasing 10 mg/24 h drug for 2 h [49]. Ten out of nineteen volunteers received local heating for 15 min using an infrared source to the skin area surrounding the patch, whilst cooling with ice bags was applied for the same duration to the remaining nine volunteers. An increase in plasma concentration from 3.1 to 7.6 $nmol.L^{-1}$ was observed among those who were exposed to heating. Increased local blood flow was confirmed using photoplethysmography, which caused increased clearance of drug from the area where the patch was applied. Conversely, cooling had decreased the plasma concentration from 2.1 to 1.4 nmol. L^{-1}. This study concluded that changes to local blood flow may increase *in vivo* drug absorption.

Exposure to heat during sauna bath or physical exercise can escalate body's core temperature, which in turn, increase the cutaneous blood flow by 3 $L.\ min^{-1}.°C^{-1}$ [86]. This is almost 10- to 12-fold increase in the cutaneous flow and one can expect a faster uptake of drug from the site of application. This was practically demonstrated by Barkve *et al*. [50]. Twelve healthy volunteers, each wearing 10 mg nitroglycerine patch, were exposed to heating during a 20 min sauna session (air temperature, 90°C; peak skin temperature, 39°C). This resulted in an increased plasma concentration of nitroglycerine from 2.3 nmol. L^{-1} to 7.1 nmol. L^{-1}, compared with the control session at room temperature. This enhancement was attributed to the increased body temperature followed by vasodilation of blood vessels, which resulted in increased cutaneous blood flow. Similar findings were reported by Vanakoski *et al*. [51] where an enhanced absorption and subsequent increased plasma concentration of transdermal nicotine was achieved after a 10 min sauna session (mean temperature, 82°C) in twelve healthy volunteers who smoke. They further noticed that mean plasma concentration was decreased after the sauna session, which possibly indicates a decreased blood flow when the body was cooled down to the normal temperature.

Based on the studies cited here, one can argue if the temperature-induced change in blood flow rate affect the skin accumulation of drug enough to change the diffusion-driving concentration gradient across the skin? A discreet investigation may warrant this hypothesis to stand true. A closer approach to test this hypothesis would be the escape of drugs into systemic circulation after hypodermal injection. Ronnemaa and Koivisto [87] studied the influence of temperature and physical exercise on the absorption of insulin post subcutaneous injection. A 3- to 5-fold increase in insulin plasma concentration was associated with warm temperature (30°C), compared with cold temperature (10°C). Physical exercise further increased absorption up to 22% and 28% with warm and cold temperatures, respectively. This study concluded that the higher insulin absorption at warm temperature may be due to the higher skin temperature and local blood flow.

The studies discussed here indicate importance of local blood flow in increasing the plasma concentration of topically and/or transdermally applied drugs. This is practically important to be aware of the factors that can influence the uptake of drugs, which may lead to overdose. Such considerations are crucial when designing transdermally delivered drug patches.

6. Physical heating techniques for enhancing skin drug delivery

A significant change in skin temperature for short duration is one way of enhancing drug permeation across biological membranes and is this method generally known as thermophoresis, or thermal ablation. Permeation enhancement through thermal ablation is achieved by heating the skin surface, until tissues are vaporised and removal of the SC occurs at the site of heating [88], thus causing the skin barrier to be compromised. Such exposure could continue for a long time at a moderate temperature (≤ 100°C), or for a short period at a very high temperature (≥ 100°C) [43]. Brief exposure to heat ensures that the temperature of the skin surface (SC) is sufficiently high, while the viable epidermis and deeper skin tissues experience a minimum rise in temperature [88], with no damage being caused to the deeper tissues [89].

Devices which directly use heat energy to increase the transport of drugs into, and across the skin have become increasingly popular over the past two decades. The fact that microporation, associated with controlled thermal energy could augment the influx of drugs, has led to the development of more advanced and precise devices, of which some of them have shown promise in reaching clinical trial phases and in ultimately making it to the market. Some of the FDA approved products and those which are under development are enlisted in Table 2.

This next section reviews thermal techniques that have been used in enhancing topical and transdermal drug delivery, i.e. chemical heating, thermoporation, radio-frequency induced thermal ablation, and laser induced thermal ablation.

Table 2: FDA approved and pipeline products utilising physical heating techniques

		Clinical trial phase	Company	Energy source/ type	Drug	Disease condition
Marketed products	Synera®, Rapydan® (in Europe)		Nuvo Research Inc., Canada (Galen Inc., US have exclusive rights of marketing in the US, and Eruocept Pharmaceuticals, Netherland is responsible in Europe)	Iron oxide reaction/CHADD	Lidocaine/tetracaine	Pain
	ViaDor® (formerly ViaDerm®)		Syneron Medical Ltd., Israel	Radio-frequency	-	-
Pipeline products	Passport-Insulin™	Phase 1 and 2	Nitto Denko, Japan	Heat energy to cause thermoporation	Insulin	Diabetes
	hGh-ViaDor® System	Phase 1	Teva Neuroscience Inc., US	Radio-frequency	Human growth hormone or somatropin	Growth hormone deficiency
	Teriparatide-ViaDor® System	Phase 2	Syneron Medical Ltd., Israel and Eli Lilly and Company	Radio-frequency	Teriperatide	Osteoporosis
	Matrix Transdermal Ketoprofen/CHADD™	Phase 2	Zars Pharma, acquired by Nuvo Research Inc., Canada	CHADD	Ketoprofen	Osteoarthritis
	Matrix Transdermal Fentanyl/CHADD™	Phase 2	Zars Pharma, acquired by Nuvo Research Inc., Canada	CHADD	Fentanyl	Pain
	ViaDor®-GLP1 System	Phase 1	Syneron Medical Ltd., Israel	Radio-frequency	GLP-1 (glucagon-like peptide-1)	Diabetes
	ViaDor®-Calcitonin System	Phase 1	Syneron Medical Ltd., Israel	Radio-frequency	Calcitonin	Osteoarthritis

6.1. Transdermal drug delivery using chemical heating

Locally applied, chemically generated heat has been used as a non-invasive technique to speed up the transdermal transport of anaesthetics [90]. Although control of the exothermic reaction at the skin surface is complex, the iron oxidation reaction could offer an elegant means of generating heat [91]. The FDA has approved the lidocaine/tetracaine transdermal patch (Synera®; Nuvo Research Inc., Canada) that employs CHADD™ heating POD based on an iron oxidation reaction as a source of heat energy (Fig. 4) [92]. It had already been established that application of mild temperature would only enable an enhanced transport of small molecular weight molecules. A different formulation strategy may, however, generate different results, even for similar compounds. A lidocaine/tetracaine patch, for example, offered significantly better local anaesthesia, compared to lidocaine/prilocaine (EMLA) cream after 10, 20 and 30 min of application [93].

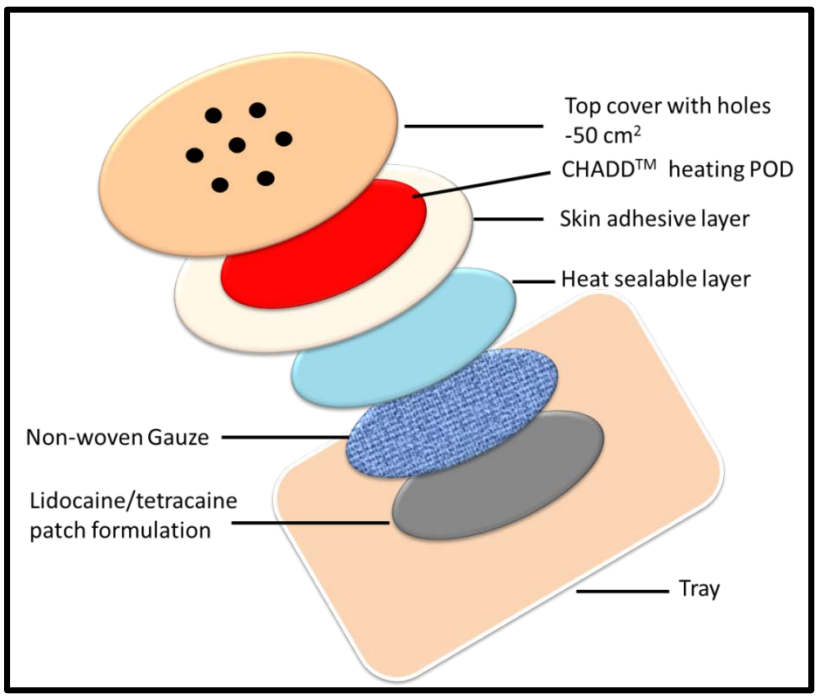

Fig. 4: Synera® Lidocaine/Tetracaine patch with CHADD™ technology, adapted from [93].

The reaction mixture used in commercial skin patches is packed in an air permeable pouch, which is placed on the skin surface. Upon mixing of oxygen with the reaction mixture, heat is generated, which can maintain the skin surface temperature at approximately 42°C for up to 4 h, or even longer. However, a reaction being initiated by oxygen is deemed slower and inefficient, compared with the more recently reported reaction that utilises water as the reaction initiator [91]. Wood *et al*. compared both oxygen and water types of initiated reactions and demonstrated their effects on the release of lidocaine at saturated and sub-saturated levels from a carboxymethyl cellulose (CMC) hydrophilic matrix Fig. 5 [91]. A short, sharp temperature variation (up to 65 °C) could result in the rapid diffusion of lidocaine through the CMC matrix, compared with the slow and more extensive one driven by the oxygen controlled oxidation reaction. The authors concluded that the improved lidocaine penetration could have been ascribed to an iron oxidation reaction that may have altered the structure of the membrane, resulting in the so-called regenerated cellulose membrane (RCM). Alteration in the membrane, however, could not have been the sole contributor

to this enhancement, as there had also been the possibility of an increase in thermodynamic activity of lidocaine within the polymer matrix, or a change in the inherent molecular diffusion. These effects were difficult to decouple, and thus warrants a more thorough investigation at revealing the exact mechanism of heat facilitated drug transport.

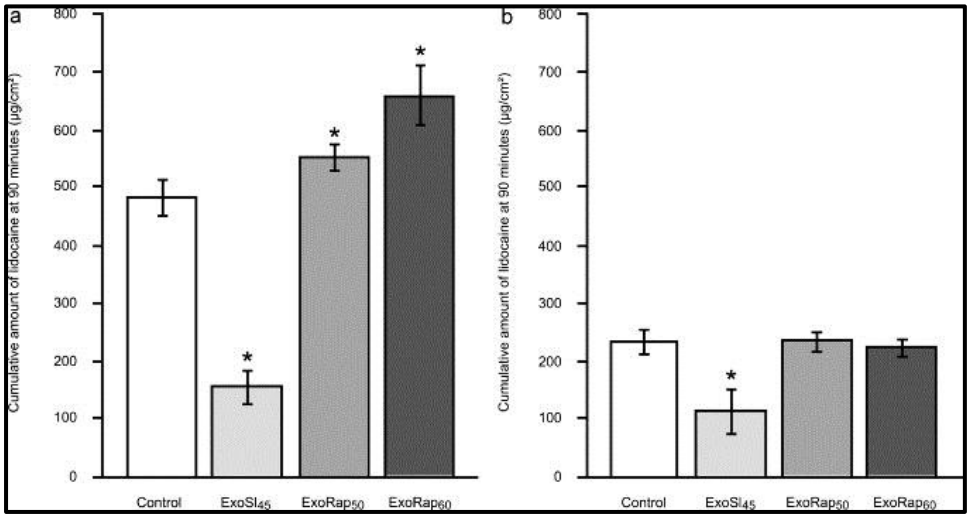

Fig. 5: Comparison of the release of lidocaine during 90 min (T_{90}) from a (a) saturated and (b) sub-saturated CMC based hydrophilic matrix. $ExoSI_{45}$ is the commercial oxygen initiated reaction, whilst $ExoRap_{50}$ and $ExoRap_{60}$ are water initiated reaction mixes. Asterisks (*) represent statistically significant differences. Reproduced with permission from [91].

6.2. Transdermal drug delivery using thermoporation

Thermoporation, also known as microporation, refers to a method that involves heating to vaporise small openings in the SC. Heat is produced by an array of metallic filaments, which are temporarily in contact with the skin. An activation electric pulse induces heating of the filaments, which creates small pores on the skin surface, thus causing aqueous pathways across the SC. This is followed by applying the drug, or vaccine to these pores *via* an adhesive patch for treatment [94], as depicted in Fig. 6. This method has only been tested for the topical delivery of drugs, since excess heat can induce thermohaemolysis [95].

Paranjabe *et al*. [89] developed a polydimethylsiloxane (PDMS) patch, integrated with micro-heaters, for a controlled and non-intrusive transdermal glucose delivery, using thermoporation. The generation of heat is controlled by a resistive heater, which restricts thermal ablation to the superficial layers of the skin. An average temperature of 130°C for more than 33 ms is required, after which SC evaporation results and small pores are formed, thus allowing for the diffusion of bio-molecules, such as glucose, into the skin surface. Later, Altea Therapeutics Corporation (www.alteatherapeutics.com) patented a patch system, called PassPort™ (Altea Therapeutics Corp., Atlanta, GA), which thermally ablates the SC to create aqueous micropores in the SC. Later, Nitto Denko (Japan) acquired assets of Altea in 2012. The insulin PassPort™ patch is currently under development by Nitto Denko, after which it will be evaluated for possible approval by the FDA, before being released into the market [96]. Initial evaluation during Phase 1 clinical setup indicates that sustained insulin therapeutic levels were achieved for up to a twelve hours application period, using the PassPort™ system [97, 98]. Badkar *et al*. assessed the feasibility of the PassPort™ system for the *in vivo*

transdermal delivery of interferon alpha-2b (INFα2b) [99]. This study concluded that microporation, using the PassPort™ system coupled with iontophoresis, showed potential for enhancing INFα2b delivery in hairless rat skin. Grag *et al*. also demonstrated a needle free transdermal vaccine (recombinant H5 hemagglutinin) delivery in mice, using the PassPort™ system against a pandemic influenza virus, whilst an enhanced immunogenicity was also recorded that had protected the mice against a lethal exposure to a highly pathogenic avian H5N1 influenza virus [100].

Microporation devices also offer additional benefits such as elimination of the risk of blood-borne pathogens' transmission because of the use of disposable and sterilisable metal filaments that facilitate microporation on the skin surface [100]. Nevertheless, excessive heating can damage deeper tissues and electric field limitations may be applied here since the device filaments are connected electrically.

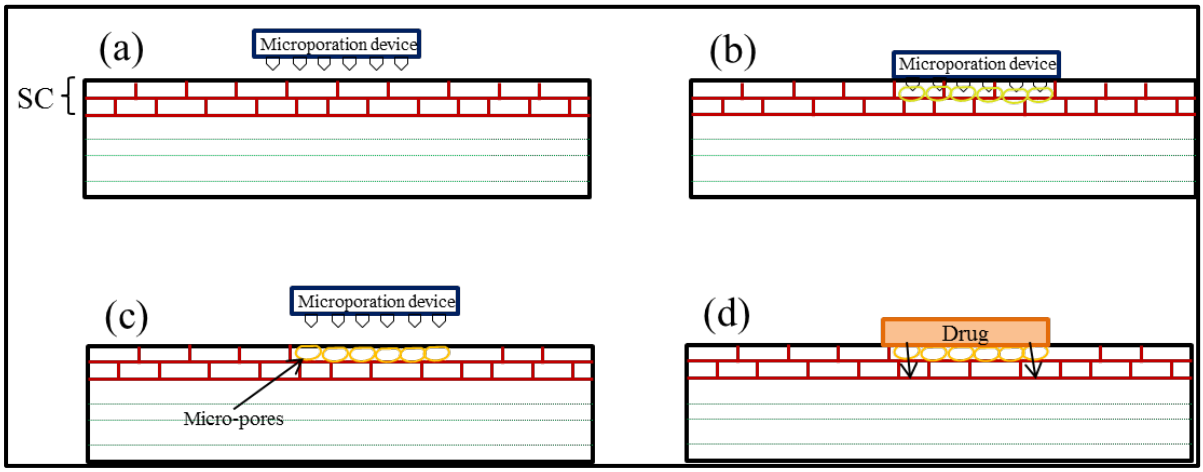

Fig. 6: Schematic representation of thermal ablation: (a) micro-electrodes traverse the skin, (b) skin thermal ablation using resistive heating or radio-frequency energy, (c) micropore formation across the SC, and (d) drug patch applied over the pores to deliver the drug.

6.3. Radiofrequency induced thermal ablation for enhancing transdermal delivery

Radiofrequency (RF) induced thermal ablation is a promising technique for possible application in electro-surgery and in the ablation of malignant tissues [101], and has been extensively used in cosmetology for skin tightening, rejuvenation and body contouring [102]. RF induced thermal ablation involves a mechanism that is somewhat similar to microporation, during which resistive heating is used. Devices are equipped with an array of micro-electrodes capable of generating an electric current into the skin in the radio frequency range (100 - 500 kHz), thus inducing localised heating, liquid evaporation and the removal of cells [103, 104]. This results in the creation of transient aqueous micro-channels across the SC, which augment the transport of water soluble entities through the skin [103]. Transpharma Medical, which has now been acquired by Syneron Medical (Yokneam, Israel) developed the ViaDor® RF device (formerly known as ViaDerm®) (Fig. 7) for the transdermal delivery of compounds, which has been evaluated for the delivery of small hydrophilic compounds, genes and peptides [18, 101, 105]. Sintov *et al*. adapted the RF technique as an option in their pioneering study of the transdermal delivery of hydrophilic compounds and achieved a thirty-fold higher plasma concentration of test compounds, compared with passive diffusion [101]. Levin *et al*. administered human growth hormone (hGH) to rats and Guinea pigs using ViaDor® and recorded a 75% higher bioavailability, compared to subcutaneous

injection [18]. A subsequent study demonstrated the feasibility of using this technology in augmenting the delivery of gene expression vectors across the excised human skin [105].

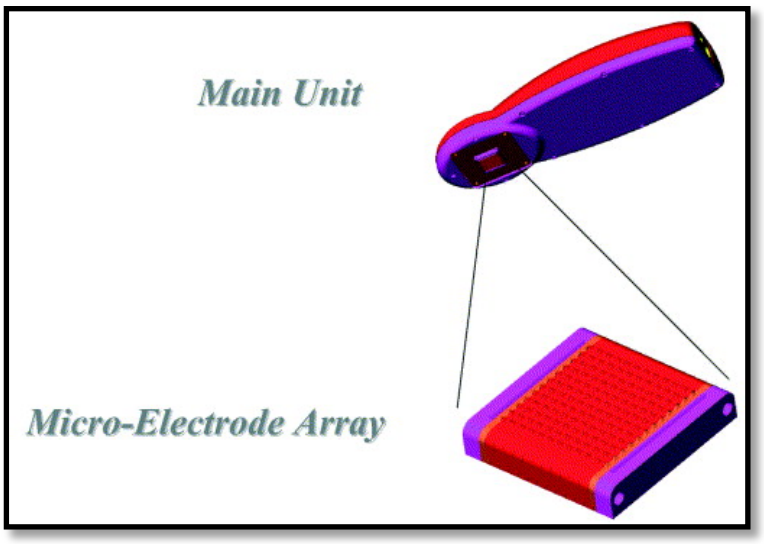

Fig. 7: Illustration of the ViaDor® device (Syneron Medical Ltd., Israel) for enhancing transdermal drug delivery. Reproduced with permission from [101].

The technique has proven safe with limited untoward effects, for instance, only mild erythema has been reported. Since, the energy is only applied to the upper epidermis and it does not reach the dermal pain receptors and therefore, the procedure is almost painless. However, serious skin damage may occur when the contact between the applicator and the tissue is not ideal or the applicator is lifted. But with the advancement in the technique and the development of new computerised circuitry, energy is immediately cut off when sudden impedance changes are detected. Also the micro-electrodes are not disposable, therefore, some contamination is possible which may result in skin infections.

6.4. Laser ablation for enhancing skin permeation

Laser induced skin ablation is another promising technique for circumventing the impermeability of the SC to enhance topical and transdermal delivery of small and large drug molecules. A high energy laser beam can disrupt the SC to facilitate the transport of compounds through the skin. The use of laser in drug delivery had been derived from dermatological [106] and cosmetic applications. A safe use of the procedure has been reported for treating certain medical conditions and for reinforcement of the skin, by removing wrinkles, and it is, therefore, used as an anti-aging skin therapy [107]. Although laser induced skin ablation does not entirely rely on heat energy, but it can be used as a source of energy. Drug permeation enhancement, using laser as a source of heat energy, has recently been reviewed [108] and therefore, a brief description is provided in this section. Nelson *et al*. first reported the application of laser energy, emitted at 2,790 nm, for enhancing the permeability of interferon gamma (INF-γ) across pig skin [109]. Generally, three mechanisms are associated with laser induced skin ablation, i.e. direct ablation, optical breakdown by photochemical waves and photothermal effects. Exposing skin to laser irradiations can illicit skin fragmentation, causing these fragments to move away from the skin surface, because of the pressure waves which can disrupt the skin in a mechanism similar to that induced by ultrasound

[110]. As a result, small pores form in the SC, which facilitate the transport of molecules across the skin. Broadband, unipolar and compressible photomechanical waves are generated by lasers [111] that can induce lipid disruption in the SC and allow for the transport of molecules to the deeper strata. When exposing the skin to the laser light, the absorbed energy can be converted into heat, which would instantly vaporise water in the skin and create micro-channels, thereby facilitating drug transport across the skin [112, 113]. Thermal effects are induced in four different phases, i.e. heating of the skin (from 37 - 60°C), followed by coagulation (60 - 65°C), drying (90 - 100°C) and finally vaporisation (> 100°C). The intensity of laser should be controlled as such that the micro-channel depth is limited to less than 200 μm to avoid pain and bleeding, associated with deep tissue damage of the skin [113].

The use of laser as an aid to enhance the skin permeation of drugs is a relatively new subject of investigation and the safety, reliability and reversibility of this technique is yet to be established within the clinical scope.

7. Safety concerns with short and long term application

There are certain questions which still needed to be answered. Are the thermal techniques safe enough for short and long term transdermal applications? What is the maximum tolerability and frequencies of applications? Will such techniques be ready to replace existing strategies in the near future?

Generally, thermal techniques for transdermal delivery are deemed safe, their short and long term safety is an area open for investigation. Current laboratory investigations revealed that a controlled and precise temperature can be administered using existing thermal techniques, and it is plausible that there is no fear of significant health issues associated with the use of heat mediated transdermal drug delivery. Such devices are programmable and heat released per unit area is controlled by the system, thus allow for better regulation of drug permeation rates.

Thermal techniques such as thermoporation, radiofrequency and laser are usually applied before the application of drugs, therefore, heat labile drugs can be used for transdermal applications. Heat produced by chemical mixture is generally less than 50°C, thus ensuring safe use of heat sensitive drugs in the transdermal patches.

8. Conclusions and future perspectives

Transdermal drug delivery has attracted research interest for decades, as an alternative drug delivery method, with compelling opportunities for the painless delivery of low molecular weight and lipophilic drugs. Only a limited number of drugs have, however, reached the market to date, because of the difficulty in traversing the skin barrier, presented by the SC. The SC's impermeability has been successfully compromised, using various physical and chemical techniques that enable the disruption of the SC, without disturbing the deeper tissues, thus providing the opportunity for an increasingly widespread impact on medicines.

The use of physical energy methods, such as the use of heat energy, has shown promise for the targeted delivery of drugs. Controlled heat energy is effective in facilitating the transport of small and possibly macro-molecules to pass through the skin more efficiently, compared with traditional techniques. Temperature modulations could bring about a series of reversible physiological events within the skin in favour of

molecule transfer, and thus provide a minimal invasive to non-invasive and more efficacious method for drug delivery. The studies discussed in this review have shed some light on various aspects of temperature mediated enhanced skin permeability. We have identified various events that influence the skin permeation associated with changes in the skin temperature and are summarised here;

A. Temperature can enhance drug diffusivity in the formulation and the skin.
B. Increased temperature can improve drug partitioning and diffusion in various skin layers.
C. Temperature can bring structural changes to the skin which reversibly decrease the impermeability of the SC.
D. Cutaneous and subcutaneous drug reservoir build-up during transdermal treatment may be cleared quickly with an increase in local blood flow associated with modulations in the skin temperature.

We believe multiple factors were involved, either individually or in combination, that aided enhanced skin permeation. However, a controlled and precise temperature alteration is required at the skin surface in order to compromise the SC barrier reversibly.

Among the various physical techniques discussed here, the thermoporation technique stands as an ideal alternative to micro-needles based devices, which require sterilisation prior to their application. Contactless ablation, using laser energy, also presents potential opportunities in enhancing drug permeation across the skin. The extension of such physical techniques for the delivery of drugs to paediatrics would be an additional benefit, if successfully translated.

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