TRANSDERMAL DRUG DELIVERY SYSTEMS: SKIN PERTURBATION DEVICES.

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Human skin serves a protective function by imposing physicochemical limitations to the type of permeant that can traverse the barrier. For a drug to be delivered passively via the skin it needs to have a suitable lipophilicity and a molecular weight <500 Da. The number of commercially available products based on transdermal or dermal delivery has been limited by these requirements. In recent years various passive and active strategies have emerged to optimize delivery. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability. However passive methods do not greatly improve the permeation of drugs with molecular weights >500 Da. In contrast active methods, normally involving physical or mechanical methods of enhancing delivery have been shown to be generally superior. The delivery of drugs of differing lipophilicity and molecular weight including proteins, peptides, and oligonucletides has been shown to be improved by active methods such as iontophoresis, electroporation, mechanical perturbation, and other energy-related techniques such as ultrasound and needless injection. This chapter details one practical example of an active skin abrasion device to demonstrate the success of such active methods. The enhanced *in vitro* permeation of acyclovir through human epidermal membrane using a rotating brush abrasion device was compared to acyclovir delivery using iontophoresis. It was found that application of brush treatment for 10 seconds at a pressure of 300Nm^{-2} was comparable to 10 minutes of iontophoresis. The observed enhancement of permeability observed using the rotating brush was as a result of disruption of the cells of the stratum corneum causing a reduction of the barrier function of the skin. However, for these novel delivery methods to succeed and compete with those already on the market, the prime issues that require consideration include device design and safety, efficacy, ease of handling, and cost-effectiveness. This chapter provides a detailed review of the next generation of active delivery technologies.

Keywords Dermal, Drug Delivery, Permeability, Skin, Transdermal

INTRODUCTION

The skin barrier

Human skin has a multifunctional role primary among which is its role as a barrier against both the egress of endogenous substances such as water and the ingress of xenobiotic material (chemicals and drugs). This barrier function of the skin is reflected by its multilayered structure (Fig. 1). The top or uppermost layer of the skin known as the stratum corneum (SC) represents the end product of the differentiation process initially started in the basal layer of the epidermis with the formation of keratinocytes by mitotic division. The SC, therefore is comprised of dead cells (corneocytes) interdispersed within a lipid rich matrix. It is the "brick and mortar" architecture and lipophilic nature of the SC, which primarily accounts for the barrier properties of the skin (1,2). The SC is also known to exhibit selective permeability and allows only relatively lipophilic compounds to diffuse into the lower layers. As a result of the dead nature of the SC, solute transport across this layer is primarily by passive diffusion (3) in accordance with Fick's Law (4) and no active transport processes have been identified.

Typical delivery systems can be utilised to achieve transdermal drug delivery or dermal drug delivery. The former involves the delivery of drugs through the skin barrier in order that they exert a systemic effect where as the latter refers to delivery of drugs to particular locations within the skin so that they exert a local effect. This sort of dermal drug delivery approach is commonly used in the treatment of dermatological conditions such as skin cancer, psoriasis, eczema and microbial infections, where the disease is located in the skin. Like many alternative routes of delivery, the skin has both benefits and limitations (Table 1) when compared to more conventional methods such as oral drug delivery.

In the last twenty five years numerous methods of overcoming the skin barrier have been described but they can broadly be divided in to two main categories defined as either passive or active methods.

Passive methods for enhancing (trans)dermal drug delivery

The conventional means of applying drugs to skin include the use of vehicles such as ointments, creams, gels and "passive" patch technology. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. Such approaches include the use of penetration enhancers (5), supersaturated systems (6), prodrugs or metabolic approach (7, 8) liposomes and other vesicles (9, 10, 11, 12). However, the amount of drug that

can be delivered using these methods is still limited since the barrier properties of the skin are not fundamentally changed. As such there are still no medicines on the market in the US that contain a labelled penetration enhancer.

Active methods for enhancing (trans)dermal drug delivery

These methods involve the use of external energy to act as a driving force and/or act to reduce the barrier nature of the SC in order to enhance permeation of drug molecules in to the skin. Recent progress in these technologies has occurred as a result of advances in precision engineering (bioengineering), computing, chemical engineering and material sciences, which have all helped to achieve the creation of miniature, powerful devices that can generate the required clinical response. The use of active enhancement methods has gained in importance due to the advent of biotechnology in the later half of the 20th century, which has led to the generation of therapeutically-active, large molecular weight (>500 Da) polar and hydrophilic molecules, mostly peptides and proteins. However gastrointestinal enzymes often cause degradation of such molecules and hence there is a need to demonstrate efficient delivery of these molecules by alternative administration routes. Passive methods of skin delivery are incapable of enhancing permeation of such large solutes, which has led to studies involving the use of alternative active strategies such as those discussed here.

Electroporation

The use of electropermeabilization, as a method of enhancing diffusion across biological barriers, dates back as far as 100 years (13). Electroporation involves the application of high voltage pulses to induce skin perturbation. High voltages (≥100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect delivery include pulse properties such as waveform, rate and number (14). The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation (15). The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with a molecular weight greater that 7kDA, the current limit for iontophoresis (16).

Genetronics Inc (San Diego, California) have developed a prototype electroporation transdermal device, which has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics. Other transdermal devices based on electroporation have been proposed by various groups (17,18,19,20) however, more

clinical information on the safety and efficacy of the technique is required to assess the future commercial prospects.

Iontophoresis

This method involves enhancing the permeation of a topically applied therapeutic agent by the application of a low level electric current either directly to the skin or indirectly via the dosage form (21, 22, 23, 24, 25). Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms; electrorepulsion (for charged solutes), electro osmosis (for uncharged solutes) and electropertubation (for both charged and uncharged).

Parameters that affect design of an iontophoretic skin delivery system include; electrode type, current intensity, pH of the system, competitive ion effect and permeant type (24). The launch of commercialised systems of this technology has either occurred or is currently under investigation by various companies. Extensive literature exists on the many types of drugs investigated using iontophoretic delivery and the reader is referred to the following extensive reviews (13, 14, 26, 27, 28). The Phoresor^{TM} device (Iomed Inc.), was the first iontophoretic system to be approved by the FDA in the late 70's as a physical medicine therapeutic device. In order to enhance patient compliance the use of patient- friendly, portable and efficient iontophoretic systems have been under intense development over the years. Such improved systems include the Vyteris and E-TRANS iontophoretic devices. Previous work has also reported that the combined use of iontophoresis and electroporation is much more effective than either technique used alone in the delivery of molecules across the skin. (29, 30, 31).

The limitations of ionotophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA cm^{-2}) and the irreversible damage such currents could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of >7000 Da (32).

Ultrasound (sonophoresis and phonophoresis)

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. The proposed mechanism behind the increase in skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound

resulting in disruption of the SC (33). Ultrasound parameters such as treatment duration, intensity and frequency are all known to affect percutaneous absorption, with the latter being the most important (34). Although frequencies between 20 kHz-16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (< 100 kHz) are believed to have a more significant effect on transdermal drug delivery with the delivery of macromolecules of molecular weight up to 48 kDa being reported (33, 35, 36).

The SonoPrep ® device (Sontra Medical Corporation) uses low frequency ultrasound (55 kHz) for an average duration of 15 s to enhance skin permeability. This battery operated hand held device consists of a control unit, ultrasonic horn with control panel a disposable coupling medium cartridge, and a return electrode. The ability of the SonoPrep® device to reduce the time of onset of action associated with the dermal delivery of local anaesthetic from EMLA cream was recently reported (37). In the study by Kost *et al*.(37), skin treatment by ultrasound for an average time of 9 s resulted in the attainment of dermal anaesthesia within 5 min, which was comparable to the 60 min required in for non-treated skin. The use of other small, lightweight novel ultrasound transducers to enhance the *in vitro* skin transport of insulin has also been reported by a range of workers (35, 38, 39, 40).

Laser radiation and photomechanical waves

Lasers have been used in the clinical therapies for decades, therefore their effects on biological membranes are well documented. Lasers are frequently used for the treatment of dermatological conditions such as acne and to confer 'facial rejuvenation' where the laser radiation destroys the target cells over a short frame of time (~300 ns). Such direct and controlled exposure of the skin to laser radiation results in ablation of the SC without significant damage to the underlying epidermis. Removal of the SC via this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs (41, 42, 43). The extent of barrier disruption by laser radiation is known to be controlled by parameters such wavelength, pulse length, pulse energy, pulse number and pulse repetition rate (41).

A hand-held portable laser device has been developed by Norwood Abbey Ltd (Victoria, Australia). In a study involving human volunteers (44), the Norwood Abbey laser device was found to reduce the onset of action of lidocaine to 3-5 min, whilst 60 min was required to attain a similar effect in the control group. The Norwood Abbey system has been approved by the US and Australian regulatory bodies for the administration of a topically applied anaesthetic.

Pressure waves (PW), which can be generated by intense laser radiation, without incurring direct ablative effects on the skin have also been recently found to increase the permeability of the skin (45, 46, 47). It is thought that PW form a continuous or hydrophilic pathway across the skin due to expansion of the lacunae domains in the SC. Important parameters affecting delivery such as peak pressure, rise time and duration has been demonstrated (48, 49). The

use of PW may also serve as a means of avoiding problems associated with direct laser radiation.

Permeants that have been successfully delivered *in vivo* include insulin (50), 40 kDa dextran and 20 nm latex particles (45). A design concept for a transdermal drug delivery patch based on the use of PW has been proposed by Doukas & Kollias (47).

Radio-frequency

Radio-frequency involves the exposure of skin to high frequency alternating current (~ 100 kHz) resulting in the formation of heat-induced microchannels in the membrane similar to when laser radiation is employed. The rate of drug delivery is controlled by the number and depth of the microchannels formed by the device, which is dependent on the properties of the microelectrodes used in the device. The Viaderm device (Transpharma Ltd) is a hand held electronic device consisting of a microprojection array (100 microelectrodes/cm^2) and a drug patch. The microneedle array is attached to the electronic device and placed in contact with the skin to facilitate the formation of the microchannels. Treatment duration takes less than a second, with a feed back mechanism incorporated within the electronic control providing a signal when the microchannels have been created, so as to ensure reproducibility of action. The drug patch is then placed on the treated area. Experiments in rats have shown the device to enhance the delivery of granisetron HCL, with blood plasma levels recorded after 12 h rising to 30 times higher levels than that recorded for untreated skin after 24 h (51). A similar enhancement in diclofenac skin permeation was also observed in the same study (51). The device is reported not to cause any damage to skin with the radio-frequency-induced microchannels remaining open for less than 24 h. The skin delivery of drugs such as testosterone and human growth hormone by this device is also currently in progress.

Magnetophoresis

This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability. *In vitro* studies by Murthy (52) showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field. Other *in vitro* studies using a magnet attached to transdermal patches containing terbutaline sulphate (TS), demonstrated an enhancement in permeant flux which was comparable to that attained when 4% isopropyl myristate was used as a chemical enhancer (53). In the same paper the effect of magnetophoresis on the permeation of TS was investigated *in vivo* using guinea pigs. The preconvulsive time (PCT) of guinea pigs for those subjected to magnetophoretic treatment

was found to last for 36 h which was similar to that observed after application of a patch containing 4% IPM. This was in contrast to the response elicited by the control (patch without enhancer), when the increase in PCT was observed for only 12 h. In human subjects, the levels of TS in the blood was higher but, not significantly different to that observed with the patch containing 4% IPM. The fact that this technique can only be used with diamagnetic materials will serve as a limiting factor in its applicability and probably explains the relative lack of interest in the method.

Temperature ("thermophoresis")

The skin surface temperature is usually maintained at 32ºC in humans by a range of homeostatic controls. The effect of elevated temperature (non-physiological) on percutaneous absorption was initially reported by Blank *et al.*, (54). Recently, there has been a surge in the interest of using thermoregulation as means of improving the delivery profile of topical medicaments. Previous *in vitro* studies (55, 56) have demonstrated a 2-3 fold increase in flux for every 7-8˚C rise in skin surface temperature. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and an increase in drug diffusivity in the skin due to increased lipid fluidity (57). Vasodilation of the subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds (58, 59). The *in vivo* delivery of nitroglycerin (58), testosterone, lidocaine, tetracaine (60) and fentanyl (61) from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery. However, the effect of temperature on the delivery of penetrants over 500 Da has not been reported.

The controlled heat-aided drug delivery patch (CHADD) (Zars Inc, Salt Lake City, Utah) consists of a patch containing a series of holes at the top surface which regulate the flow of oxygen in to the patch. The patch generates heat chemically in a powder filled pouch by an oxidative process regulated by the rate of flow of oxygen through the holes in to the patch (62). The CHADD technology was used in the delivery of a local anaesthetic system (lidocaine and tetracaine) from a patch (S-Caine®) and found to enhance the depth and duration of the anaesthetic action in human volunteers when the results obtained in active and placebo groups were compared (63). Zars Inc together with Johnson and Johnson, recently submitted an investigational new drug (IND) application to the FDA for Titragesia™ (a combination of CHADD disks and Duragesic Patches, the latter contains fentanyl for treatment of acute pain). Kuleza & Dvoretzky (64), also describe a heat delivery patch or exothermic pad for promoting the delivery of substances into the skin, subcutaneous tissues, joints, muscles and blood stream, which may be of use in the application of drug and cosmetic treatments.

All the studies described above employed an upper limit skin surface temperature of 40 - 42 ^{o}C, which can be tolerated for a long period (> 1 h). In heat-patch systems where patient exposure to heat is ≤ 24 h, such an upper limit may be necessary for regulatory compliance. In addition, the issue of drug stability may also need to be addressed when elevated temperatures are used.

Thermopertubation refers to the use of extreme temperatures to reduce the skin barrier. Such perturbation has been reported in response to using high temperatures over a short duration (30 ms), with little or no discomfort, using a novel patch system (65). These investigators developed a polydimethylsiloxane (PDMS) patch for non intrusive transdermal glucose sensing via thermal micro-ablation. Ablation was achieved by microheaters incorporated within the patch. The heat pulse is regulated by means of a resistive heater, which ensures that the ablation is limited within the superficial of dead layers of the skin. Average temperatures of 130 ^{o}C are required for ablation to occur within 33 ms after which SC evaporation results. Other heat assisted transdermal delivery devices under development include the PassPort ® patch (Althea therapeutics) which ablates the SC via a similar manner as the above described PDMS patch. The exposure of skin to low (freezing) temperatures has been reported to decrease its barrier function (66, 67, 68) but has however not been exploited as means of enhancing skin absorption.

The final group of active enhancement methods entail the use of a physical or mechanical means to breach or bypass the SC barrier.

Microneedle based devices

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on this method (69). The device as described in the patent consists of a drug reservoir and a plurality of projections extending from the reservoir. These microneedles of length 50-110 µm will penetrate the SC and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel or solid particulates and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. As a result of the current advancement in microfabrication technology in the past ten years, cost effective means of developing devices in this area are now becoming increasingly common (70, 71, 72).

A recent commercialisation of microneedle technology is the Macroflux® microprojection array developed by ALZA Corporation. The macroflux® patch can either be used in combination with a drug reservoir (73) or by dry coating the drug on the microprojection array (74); the latter being better for intracutaneous immunization. The lengths of the microneedles have been estimated to be around 50-200 µm and therefore are not believed to reach the nerve endings in the

dermo-epidermal junction. The microprojections/ microneedles (either solid or hollow) create channels in the skin, hence allowing the unhindered movement of any topically applied drug. Clinical evaluations report minimal associated discomfort and skin irritation and erythema ratings associated with such systems are reportedly low (75). This technology serves as an important and exciting advance in transdermal technology due to the ability of the technique to deliver medicaments with extremes of physicochemical properties (including vaccines, small molecular weight drugs and large hydrophilic biopharmaceuticals) (76, 77, 78).

Yuzhakov *et al*., (72) describes, the production of an intracutaneous microneedle array and provides an account of its use (microfabrication technology). Various embodiments of this invention can include a microneedle array as part of a closed loop system 'smart patch' to control drug delivery based on feedback information from analysis of body fluids. Dual purpose hollow microneedle systems for transdermal delivery and extraction which can be coupled with electrotransport methods are also described by Trautman *et al*., (70); Down *et al*., (79); Allen *et al*., (80). These mechanical microdevices which interface with electronics in order to achieve a programmed or controlled drug release are referred to as microelectromechanical systems (MEMS) devices.

Skin puncture and perforation

These devices are similar to the microneedle devices produced by microfabrication technology. They include the use of needle-like structures or blades, which disrupt the skin barrier by creating holes and cuts as a result of a defined movement when in contact with the skin. Godshall and Anderson (81), described a method and apparatus for disruption of the epidermis in a reproducible manner. The apparatus consists of a plurality of microprotrusions of a length insufficient for penetration beyond the epidermis. The microprotrusions cut into the outer layers of the skin by movement of the device in a direction parallel to the skin surface. After disruption of the skin, passive (solution, patch, gel, ointment etc) or active (iontophoresis, electroporation etc) delivery methods can then be utilised. Descriptions of other devices based on a similar mode of action have been described by Godshall, (82); Kamen , (83); Jang, (84) and Lin *et al*., (85).

Needleless injection

Needleless injection is reported to involve a pain free method of administering drugs to the skin. This method therefore avoids the issues of safety, pain and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. Over the

years there have been numerous examples of both liquid (Ped-O-Jet®, Iject® Biojector2000® Medi-jector® and Intraject®) and powder (PMED™ device formerly known as powderject® injector) systems (78). The latter device has been reported to deliver successfully testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin (79, 86, 87).

Problems facing needless injection systems include the high developmental cost of both the device and dosage form and the inability, unlike some of the other techniques described previously, to programme or control drug delivery in order to compensate for inter-subject differences in skin permeability. In addition, the long-term effect of bombarding the skin with drug particles at high speed is not known thus, such systems may not be suitable for the regular administration of drugs. It may however be very useful in the administration of medicaments which do not require frequent dosing e.g. vaccines.

Suction ablation

Formation of a suction blister, involves the application of a vacuum (88) or negative pressure to remove the epidermis, whilst leaving the basal membrane intact. The cellpatch® (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism (89). It comprises a suction cup, epidermatome (to form a blister) and device (which contains morphine solution) to be attached to the skin this method which avoids dermal invasivity there by avoiding pain and bleeding is also referred to as skin erosion. Such devices have also been shown to induce hyperaemia in the underlying dermis in *in vivo* studies (90), which was detected via laser Doppler flowmetry and confirmed via microscopy, and is thought to further contribute to the enhancement of dextran and morphine seen with this method.

The disadvantages associated with the suction method include the prolonged length of time required to achieve a blister (2.5 h), although this can be reduced to 15-70 min by warming the skin to 38 ^{o}C (90, 91). In addition, whilst there is no risk of systemic infection compared to the use of intravenous catheters, the potential for epidermal infections associated with the suction method cannot be ignored even though the effects might be less serious (92).

Application of Pressure

The application of modest pressures (i.e. 25 kPa) has been shown to provide a potentially non-invasive and simple method of enhancing skin permeability of molecules such as caffeine (93). These workers attributed the increase in transcutaneous flux to either an improved transapendageal route or an increased partition of the compound into the SC when pressure was applied. This method may also work due to the increased solubility of caffeine in the stratum corneum caused by the increase in pressure.

Skin stretching

These devices hold the skin under tension in either a unidirectional or multidirectional manner (94, 95). The authors claim that a tension of about 0.01 to 10 mP results in the reversible formation of micropathways. The efficiency of the stretching process was demonstrated by monitoring the delivery of a decapeptide (1 kDa) across the skin of hairless guinea pigs using a microprotrusion array. The results of the study showed that the bi-directional stretching of skin after microprotrusion piercing, allowed the pathways to stay open (i.e. delayed closure) hence facilitating drug permeation to a greater extent (27.9 ± 3.3 μg/cm^2 h) than in the control group (9.8 ± 0.8 μg/cm^2 h), where the skin was not placed under tension after microneedle treatment. However, increased skin permeation in the absence of microneedle pre-treatment was found not to occur.

Other methods involving the use of skin stretching with subsequent use of delivery devices based on electrotransport, pressure, osmotic and passive mechanisms have also been suggested but the value of skin stretching alone without the benefit of a secondary active delivery device remains to be seen.

Skin abrasion

These techniques, many of which are based on techniques employed by dermatologists in the treatment of acne and skin blemishes (e.g. microdermabrasion), involve the direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied compounds. The delivery potential of skin abrasion techniques are not restricted by the physicochemical properties of the drug and previous work has illustrated that such methods enhance and control the delivery of a hydrophilic permeant, vitamin C (43) vaccines and biopharmaceuticals (96, 97, 98). One current method is performed using a stream of aluminium oxide crystals and motor driven fraises (99, 43) Sage & Bock (100, 101), also describe a method of pre-treating the skin prior to transdermal drug delivery which consists of a plurality of microabraders of length 50-200 μm. The device is rubbed against the area of interest, to abrade the site, in order to enhance delivery or extraction. The microabraders/microprotrusions terminate as blunt tips and therefore do not penetrate the SC. The device functions by removing a portion of the SC without substantially piercing the remaining layer. Some of these methods are claimed to offer advantages such as minimal patient discomfort, increased patient compliance, ease of use and less risk of infection compared to their more “invasive” predecessors such as ablation and the use of hypodermic needles/cannulas to deliver medicaments across the skin.

A practical example of a skin abrasion device

Introduction

Abrasion devices are generally expensive and usually require trained personnel to operate them, therefore limiting applicability of the technique. One novel strategy might be to employ a rotating brush to perturb the skin barrier. The potential of such a method was investigated and compared with more established methods of enhancing in vitro skin permeation. Acyclovir is interesting candidate for use in the development of active enhancement devices as it is poorly absorbed through the skin due to its hydrophilicity (102) This is thought to contribute to the low efficacy of commercial acyclovir formulations due to a delay in it reaching its intended target site in the basal epidermis (103, 104). Iontophoresis currently serves as one of the most effective skin permeation strategies of enhancing the therapeutic profile of ACV (104, 105, 106, 107) and as thus was used as a comparative method in the practical example of this review..

Methodology

In vitro experiments were conducted using excised human epidermal membrane. A rectangular section (~3 x 2 cm) of epidermal sheet was selected and a circular region (~1 cm^2) demarcated. Brush treatment of the skin was performed as previously described (108). In brief, the sample of epidermal sheet was inserted into the device clamp ensuring the demarcated region was exposed. The clamp was tightened and gently raised by means of the latch (lift) until the demarcated region of the epidermis was in into slight contact with bristles (surface area ~1 cm^2) of the brush. Pre-defined operational parameters (speed, applied pressure, treatment duration) of interest were then set on the control box for the abrasion process to occur.

Calibrated Franz cells of known surface area (~0.65 cm^2) and receptor volume (~2 mL) were used. The receptor chamber was filled with PBS (pH 7.4) and stirred throughout the duration of the experiment using a PTFE coated magnetic flea (5 x 2 mm). The treated membrane (using brush or positive controls) or untreated control was then clamped between the donor and receptor chambers of the Franz cell (with the stratum corneum (SC) facing upwards). A radiolabeled formulation was prepared by spiking Zovirax® cream with ^{3}H-ACV (ethanolic solution). A target finite dose of approximately 9 ± 1 mg cm^{-2} was applied to the epidermal membrane surface using a previously calibrated positive displacement pipette (Gilson Pipetman®, P20 Anachem UK Ltd) and carefully spread to cover the effective surface area by means of a tared syringe plunger. For iontophoresis the (anodal) treatment protocol employed was as described previously (106, 109). A 0.4 mA current limit and 10 min treatment duration was maintained to simulate “in use” conditions. A shorter iontophoretic treatment (0.4 mA for 10

min) was also employed, so as to reduce the likelihood of potential damage to the skin as a result of prolonged current exposure. All experiments were conducted in a water bath at 37°C over a minimum period of 4 h with sink conditions being maintained throughout. At certain time intervals 200 µl of the receiver fluid was carefully withdrawn from the receiver fluid. Approximately 4 ml of scintillation cocktail was added to each 200 µL sample and analysis was conducted using scintillation counting.

Results and discussion

The skin permeation of ACV (Zovirax cream) applied as a finite dose was promoted to a greater extent as the duration of brush treatment was extended (Fig. 2). A significant increase in ACV transport was observed following brush treatment ($p \leq 0.05$). The use of iontophoresis proved generally less effective than employing the rotating brush in enhancing permeation. For example the effect of 10 min anodal iontophoresis on the skin permeation of ACV proved to be comparable to that obtained after application of brush treatment at 300 Nm^{-2} for 10 s (Table 2). The iontophoretic method in this study employed optimum conditions (electrode type: anode, pH of buffer: 7.4, current intensity: ≤ 0.5 mA) which have been previously shown to enhance ACV permeation *in vitro* (105, 106, 109).

Findings from this present study support the effectiveness of a rotating brush applied to the skin, in enhancing the cutaneous permeability of acyclovir. The observed enhancement in permeability was a result of the disruption of the cells of the SC which compromises the principal barrier that skin provides to the absorption of applied compounds. Abrasion devices which allow the controlled removal of only the upper layers of the skin could be an important tool when attempting to generate a standardised skin treatment prior to the topical application of drugs. This pre-requisite is a limitation of previous research into this mode of skin penetration enhancement. The use of a rotating brush device as described in this study, may serve as an efficient and simple means of overcoming such a limitation. Further *in vitro* studies are warranted using other solutes to optimize further device parameters, as is an *in vivo* delivery feasibility study using such a prototype device.

The future

The market for transdermal devices has been estimated at US $2 billion (99) and this figure represents 10% of the overall US $28 billion drug delivery market. Such figures are surprising when it is considered that although the first transdermal patch was granted a licence by the FDA in 1979, only an additional nine drugs have been approved since this time. This short list of “deliverables” highlights the physicochemical restrictions imposed on skin delivery.

Transdermal drug delivery has recently experienced a healthy annual growth rate of 25%, which outpaces oral drug delivery (2%) and the inhalation market (20%) (110). This figure will certainly rise in the future as novel devices emerge and the list of marketed transdermal drugs increases. The emergence of such devices will increase the use of the skin as a route of administration for the treatment of a variety of conditions.

However, subjective and objective analysis of these devices is required to make sure both scientific, regulatory and consumer needs are met. The devices in development are more costly and complicated compared to conventional transdermal patch therapies. As such they may contain electrical and mechanical components which could increase the potential safety risks to patients due to poor operator technique or device malfunction. In addition, effects of the device on the skin must be reversible, since any permanent damage to the SC will result in the loss of its barrier properties and hence its function as a protective organ. Regulatory bodies will also require data to substantiate the safety of the device on the skin for either short or long term use. Thus, for any of these novel drug delivery technologies to succeed and compete with those already on the market, their safety, efficacy, portability, user-friendliness, cost-effectiveness and potential market has to be addressed.

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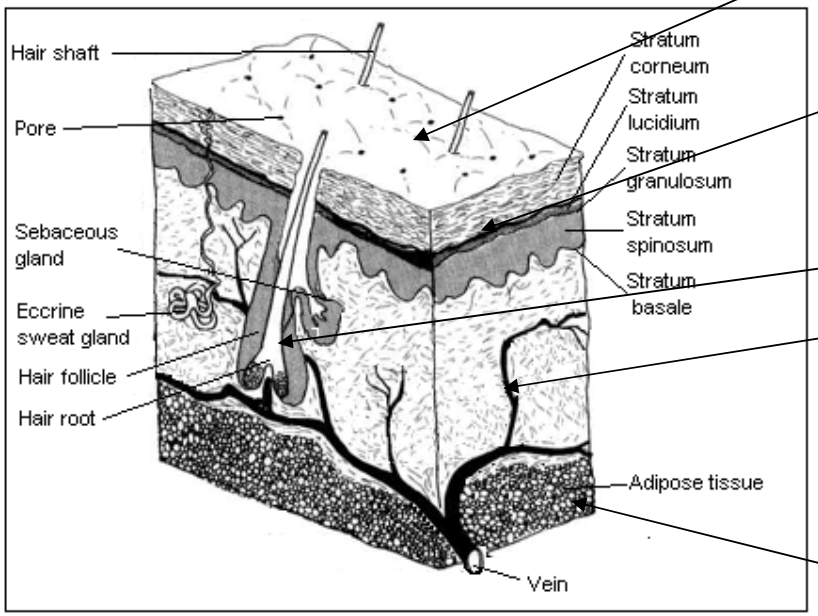
LIST OF FIGURES



Surface
Barriers/repellents,
Sunscreens
Antimicrobials
Antiseptics

Local
Corticosteroids
Cytotoxics
Antiviral
Antihistamines
Anaesthetics

Appendages
Antimicrobials
Depilatories

Systemic
Hormones
Antiemetics
Opiods
Antihypertensives
Anticoagulants
Antipsychotics
Antidepressants
etc

Deeper tissue
Non-steroidal
anti-inflammatory
agents (NSAIDs)

FIGURE 1

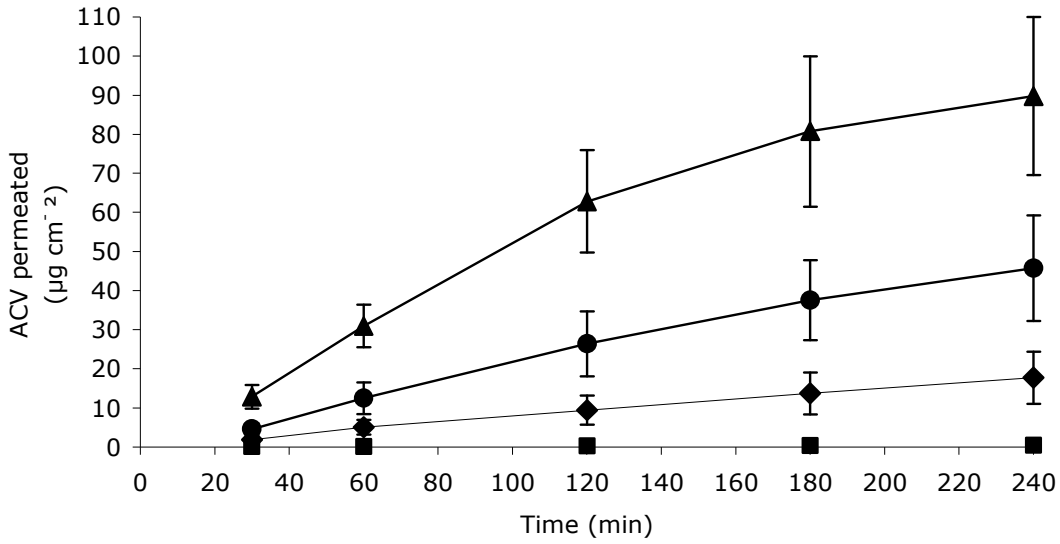

ACV permeated
(µg cm⁻²)
110
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
160
180
200
220
240
Time (min)

FIGURE 2

LIST OF TABLES

TABLE I.

BENEFITS	LIMITATIONS
• The avoidance of first pass metabolism and other variables associated with the GI tract such as pH, gastric emptying time. (112, 113, 114) • Sustained and controlled delivery over a prolonged period of time (115, 116) • Reduction in side effects associated with systemic toxicity i.e. minimisation of peaks and troughs in blood-drug concentration (117, 114) • Improved patient acceptance and compliance (118, 119, 120) • Direct access to target or diseased site e.g. treatment of skin disorders such as psoriasis, eczema and fungal infections (121) • Ease of dose termination in the event of any adverse reactions either systemic or local. • Convenient and painless administration (112, 113) • Ease of use may reduce overall healthcare treatment costs (122, 123) • Provides an alternative in circumstances where oral dosing is not possible (in unconscious or nauseated patients) (114)	• A molecular weight less than 500 Da is essential to ensure ease of diffusion across the SC (124), since solute diffusivity is inversely related to its size. • Sufficient aqueous and lipid solubility, a Log P (octanol/water) between 1-3 is required for the permeant to successfully traverse the SC and its underlying aqueous layers for systemic delivery to occur (125) • Intra-and inter-variability associated with the permeability of intact and diseased human skin. This implies that there will be fast, slow and normal skin absorption profiles resulting in varying biological responses (126, 127). The barrier nature of intact SC ensures, that this route is only applicable for very potent drugs that require only minute concentrations (e.g. 10-30 ng/ml for nicotine) in the blood for a therapeutic effect (112) • Pre-systemic metabolism; the presence of enzymes in the skin such as peptidases, esterases etc. might metabolise the drug into a form which is therapeutically inactive, thereby reducing the efficacy of the drug (128). • Skin irritation and sensitisation; referred to as the “Achilles heel” of dermal and transdermal delivery. The skin as an immunological barrier may be provoked by exposure to certain stimuli, this may include drugs, excipients, or components of delivery devices resulting in erythema, oedema etc (129, 130, 131, 132).

Table II

Treatment type	Amount in receptor (μg cm^{-2}) after 60 min	Enhancement Factor
Untreated	0.14 ± 0.08	-
10s brush treatment^{+}	5.06 ± 1.88*	36.17
30s brush treatment^{+2}	12.5 ± 4.02*	89.29
60s brush treatment^{+}	30.91 ± 5.45*	220.76
Ionotophoresis (anodal)	4.95 ± 2.35*	35.42