The transdermal revolution

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Historically, developments in transdermal drug delivery have been incremental, focusing on overcoming problems associated with the barrier properties of the skin, reducing skin irritation rates and improving the aesthetics associated with passive patch systems. More-recent advances have concentrated on the development of non-passive systems to aid delivery of larger drug molecules, such as proteins and nucleotides, as the trend for discovering and designing biopharmaceuticals continues. Fundamentally, improvements in transdermal delivery will remain incremental until there is wider acceptance of this route of administration within the pharmaceutical industry. Only then will the transdermal revolution live up to its true potential.

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▼ The heightened focus on specialty pharmaceuticals that add value and patent protection in major pharmaceutical markets by providing better delivery (e.g. oral controlled-release, inhalation, implant and transdermal delivery systems) is increasing pressure to further push the boundaries of the practical applications of basic pharmaceutical research. Current transdermal drug delivery (TDD) relies primarily upon occlusive patches, and is now considered to be a mature technology. This method is capable of delivering drugs, the use of which would be limited through, for example, poor oral bioavailability, side effects associated with high peaks or poor compliance due to the need for frequent administration. However, the negatives of TDD have been skin irritation, relatively high manufacturing costs and less-than-ideal cosmetic appearance. Recent advances with traditional passive TDD systems have focused on reducing skin irritation and making products more aesthetically acceptable for patients. Alternative systems are in development that use physical enhancement, but they are more focused on the delivery of the larger molecules arising from research in the biotech sector, such as peptides and nucleotides. Regardless of the TDD system in development, the patient acceptability from an aesthetic and lack of irritation perspective will remain the main focus for the newer products entering the market.

The skin as a delivery target

The skin represents the largest and most easily accessible organ of the body and its use for topical and systemic delivery of drugs has been well documented [1,2]. Traditional preparations used include ointments, gels, creams and medicinal plasters containing natural herbs and compounds. The development of the first pharmaceutical transdermal patch for motion sickness (Alza Corporation; http://www.alza.com) in the early 1980s heralded acceptance of the benefits and applicability of this method of administration for modern commercial drug products.

The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved in the USA for the treatment of a wide variety of conditions including: hypertension, angina, motion sickness, female menopause, male hypogonadism, severe pain, local pain control, nicotine dependence, and recently, contraception and urinary incontinence. There are also several products in late-stage development that will further expand TDD usage into new therapeutic areas, including Parkinson's disease, attention deficit and hyperactivity disorder and female sexual dysfunction (Table 1).

The advantages of TDD have been well documented [3]. They include: therapeutic benefits such as sustained delivery of drugs to provide a steady plasma profile, particularly for drugs with short half-lives, and hence reduced systemic side effects; reducing the typical dosing schedule to once daily or even once weekly, hence generating the potential for improved patient compliance; and avoidance of the first-pass metabolism effect for drugs with poor oral bioavailability. Additionally, TDD represents a convenient, patient-friendly option for drug delivery with the potential for flexibility, easily allowing dose changes according

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Table 1. Examples of recently launched and developmental transdermal products, as detailed on Pharmaproject database (http://www.pjbpubs.com) at April 2004

Compound	Delivery System	Stage of Development	Company
Alprostadil	Gel – Alprox-TD	Launched in China	NexMed; http://www.nexmed.com/
Buprenorphine	Patch – Transtec	Launched in Europe	Grunenthal; http://www.grunenthal.com/
Dihydrotestosterone	Gel – Andractim	Launched in France and Netherlands	Unimed/Solvay; http://www.solvaypharmaceuticals-us.com/
Estradiol	MDTS	Phase II	Acrux; http://www.acrux.com.au/
Estradiol/progestogen	Gel	Phase II in USA	Antares; http://www.antarespharma.com
Ethinylestradiol & norelgestromin	Patch – Ortho Evra	Launched in USA	J&J; http://www.jnj.com/
Fentanyl	Patch – iontophoresis: E-TRANS	Pre-registration	Alza/J&J; http://www.alza.com/
	MDTS	Phase I	Acrux
Granisetron	MDTS	Preclinical	Acrux
hGH	Microneedle – Macroflux	Phase I	Alza/J&J
Hydromorphone	Patch – thermal	Phase I in USA	Altea; http://www.alteatherapeutics.com
Insulin	Sonophoresis	preclinical	Imarx; http://www.imarx.com/corporate.asp
	Patch – Thermal	Phase I in USA	Altea
Lidocaine	Patch – Lidoderm	Launched in USA	Endo; http://www.endo.com
Methylphenidate	Patch – Methypatch	Pre-registration in US	Noven; http://www.noven.com
Methyltestosterone	Patch	Phase II in USA	Noven
Oxybutynin	Patch – Oxytrol	Launched in USA	Watson/Theratech; http://www.theratech.com
Parathyriod hormone	Patch – Thermal	Phase I in USA	Altea
Rotigotine	Patch	Phase III in USA	Aderis/Schwarz; http://www.aderis.com/
Selegiline	Patch – STS	Pre-registration	Watson/Mylan; http://www.mylan.com/
Testosterone for males	Gel – Testim	Launched in USA	Auxilium/Bayer; http://www.auxilium.com
Testosterone for females	Patch	Phase III in USA	Watson/P&G; http://www.pg.com/main.jhtml
Vaccines	Patch	Preclinical	Alza

Abbreviations: MDTS, metered-dose transdermal system; TD, transdermal delivery

to patient needs and the capacity for self-regulation of dosing by the patient. Alternatively, TDD can be used in situations requiring minimal patient cooperation, that is, in situations involving administration of drugs by someone other than the patient. The non-invasive character of TDD makes it accessible to a wide range of patient populations and a highly acceptable option for drug dosing.

Limitations of skin as a delivery method

The barrier

It has been generally accepted that the main route of permeation through the skin for small molecules is via the intercellular pathway [4,5]. However, there is evidence that for some compounds the intracellular domain is also important [6] and often several mechanisms might be

working in parallel [7]. The intercellular space contains a mixture of lipids that can be organized to provide hydrophilic as well as lipophilic domains. It is thought that this organization of lipids will dictate the required physicochemical properties of a molecule to ensure that it can diffuse rapidly through the skin. Generally, suitable candidates for transdermal permeation are small molecules with good water and lipid solubility. These solubility characteristics are often also indicated by the possession of a low melting point, typically < 200°C [8].

Drug-related factors: partitioning

The two drug-related properties that influence flux across the skin are the concentration gradient of drug within the skin and the diffusivity, in accordance with Fick's Law. The concentration gradient, in turn, is influenced by the ability of the drug to partition into the skin [9] and its ability to partition out of the skin into the underlying tissues [10]. The octanol–water partition coefficient can be used to predict this partitioning behaviour within the skin. Thus, there is often a parabolic relationship between the octanol–water partition coefficient as expressed by logP and the penetration rate [11]. Compounds with low logP exhibit low permeability because there is little partitioning into the skin lipids. However, compounds with high logP also give low permeability due to their inability to partition out of the stratum corneum. The generally accepted range of logP for maximum permeation is between 1 and 3 [12,13].

The partitioning of the drug into the skin will also be influenced by its thermodynamic activity in the application vehicle. This can be improved by increasing the concentration of drug in the applied vehicle or by manipulating the vehicle to reduce drug solubility. The diffusivity of the drug can be enhanced by using permeation enhancers [14] or by physical enhancement methods such as iontophoresis. Whereas most work with enhancers has focused on mildly lipophilic drugs, a combination of the enhancers propylene glycol and lauric acid has demonstrated the potential to enhance the permeability of highly lipophilic drugs [15]. This is attributed to their synergistic lipid-fluidizing activity within the stratum corneum.

Drug-related factors: diffusivity

The chemical structure of the drug also influences the diffusivity [16,17], due to interactions between the polar head groups of the intercellular lipids with hydrogen-bond-forming functional groups present in the drug structure [18]. As a general rule, the number of hydrogen bonding groups in the permeant should not exceed two.

Although the skin represents a suitable target for drug delivery, as mentioned above, the functional properties that enable it to act as an excellent barrier also serve to limit the access of drugs into and across the epidermis. Whereas an initial consideration of the skin structure might suggest a simple barrier, a closer examination reveals a complex combination of a range of cell types. The outer layer, the stratum corneum, is a membrane ~20 μm thick, which represents the main contributor to the skin's impermeability. Much effort has been devoted to understanding the reasons for this impermeability as it is widely recognized that therein resides the answer to developing more efficient TDD products.

Occlusion

To improve the efficiency of TDD systems, traditional TDD products relied mainly on their occlusive nature to increase the permeability of the drug candidates. Although the mechanism by which occlusion increases the diffusivity of many drugs is not known, some of the effects of occlusion that might be important include: water accumulation within the skin leading to increased water content and swelling of the corneocytes and increased water content of the intercellular matrix [19]; increase in skin temperature and decreased evaporative loss of cosolvents [20]. However, occlusion often causes an increased propensity for skin irritation at the application site that could be due to the affects of the accumulated water [19] or to trapped sweat [21]. This represents a major hurdle to the patient acceptance of occlusive TDD systems and recent efforts have focused on the development of newer generation products with less potential for this reaction. Occlusive systems can also provide an environment for microbial proliferation.

Approaches to overcoming the barrier: physical

With the recent focus on the delivery of new protein-based and DNA-based therapeutic macromolecules generated by modern biotechnology, other tactics for overcoming the skin barrier have been explored. Although TDD enables administration of these compounds, thus avoiding degradation in the gastrointestinal tract and first-pass metabolism associated with oral delivery, it requires special enhancement techniques.

It is also important to consider whether delivery through the skin is likely to alter the activity or toxicity of the active agent. Recently, concern has been raised over transdermal vaccination because of the possibility of exacerbation of some autoimmune disorders [22].

Physical enhancement methods have been studied that involve the use of an energy source to overcome the barrier properties of the skin. These methods rely on providing a reservoir of drug on the skin surface, from which the

required levels of delivery can be achieved. The most notable advancements in product development in this area have used such approaches as iontophoresis and electroporation, typically for the delivery of large molecular weight or highly potent compounds. Low-frequency sonophoresis using ultrasound has also demonstrated the capacity to enhance drug delivery [23]. An alternative approach involves the use of microfabricated microneedles, which can be inserted into the skin, thereby producing a channel for drug transport across the stratum corneum [24]. The microneedles have been designed to penetrate only the outer layers of the skin, that is, the stratum corneum. The nerves reside much deeper within the skin and consequently this method has been projected as providing painless administration.

Alza Corporation has combined its Macroflux® technology (which comprises microprojections that create superficial pathways through the skin on application) with the electrotransport E-TRANS® technology to enable the delivery of recombinant human growth hormone (hGH). Preliminary studies demonstrated delivery of therapeutically relevant plasma levels of the hormone, but little has been reported about the further development of this product. Radio-frequency has also been used as a means of enabling the transdermal delivery of lipophilic drugs, through the generation of microchannels across the stratum corneum. Sintov *et al.* [25] describe significant *in vivo* enhancement of skin permeability for both of the poorly penetrating drugs granisetron and diclofenac after pretreatment of rat skin with radiofrequency electrodes. Powderject's technology (http://www.powderject.com/) takes a slightly different approach to breaching the barrier by the use of high velocities to force particles across the stratum corneum [26].

Approaches to overcoming the barrier: chemical

Chemical penetration enhancers have provided the basis for considerable research in the TDD area, as the search for the perfect enhancer continues, as reviewed by Barry [27] and Sinha and Pal Kaur [28]. The ideal candidate would provide a reversible reduction in the skin's barrier properties without long-term damage to the viable cells. Considerable effort has focused on the identification of chemicals or combinations of chemicals capable of acting as penetration enhancers and the prediction of their efficacy [29,30]. Despite the extensive studies performed, few compounds have been successfully incorporated into marketed products, partly because of the difficulty in predicting *in vivo* behaviour under conditions of use from the *in vitro* permeation tests that are normally used as screens for enhancement. It has also proved a difficult task to balance the formulation characteristics to ensure that the drug retains its tendency to partition from the vehicle in the presence of the permeation enhancer.

Permeation enhancers fall into two major categories: those that impact diffusion across the stratum corneum and those that alter partitioning into the stratum corneum. The former class generally comprises a long alkyl chain capable of intercalating with the long chains of the intercellular lipids, in addition to a polar head group that is capable of interacting with the lipid polar head groups [31]. This serves to disrupt the ordered nature of the skin lipids, increasing the fluidity and hence assisting permeation of the drug. The latter class of permeation enhancers works by affecting the solubility properties of the skin, thereby increasing the solubility of the drug within the stratum corneum.

Problems with existing technology

Existing TDD systems such as patches, creams and gels still suffer from some limitations. The precision of dosing is particularly an issue with creams and gels, especially as it has also been demonstrated that altering the dose applied per surface area can affect the systemic delivery profile, although conflicting effects have been observed when the area of application is increased [32,33]. Although precision of dosing might be less of an issue in patch systems, there is relatively little flexibility available for the dosing.

Variability of dosing has also been highlighted as an issue with TDD systems. Most studies have focused on the intra-site variability [34–36] of dosing that many have attributed to the different levels of skin hydration found at various anatomical sites [37]. It has also been shown that variations in temperature, possibly due to local microcirculation changes in the skin, can affect the drug delivery profile from TDD systems. Variability of dosing has also been observed between different skin types, skin of different aged patients [38] and diseased skin [39–42]. Psychological stress has also been shown to impact skin barrier recovery [43]. Variables that can account for the differences observed between sites in an individual and between individuals include: structural differences in the stratum corneum, such as thickness and lipid content, perfusion rate of the dermis, enzymatic activity in the skin, incidentally applied substances such as soaps, moisturizers and cosmetics

From the patient's perspective, the large surface area for application, particularly for gels and creams, that is required to produce adequate dosing levels can also translate into aesthetic concerns. It is crucial that formulators consider the aesthetics of the product after application, to avoid unpleasant stickiness or greasiness and to minimize residue on the skin.

The relatively high skin irritation rates that were associated with the earlier transdermal patches have been somewhat

reduced, but the inherent occlusive nature of the products still dictates that this remains an issue for TDD systems [44]. There have also been instances where contact sensitization to the drug has been identified after transdermal administration, as with the clonidine patch. The occurrence of sensitization reported has been up to 50% and seen to increase with time of exposure [45]. As consumers become increasingly educated about product options, their expectations regarding skin irritation rates and patch size have also been increased.

The majority of recently approved TDD systems in the USA use drug-in-adhesive technology, which afford improved aesthetic appeal and lower incidence of skin irritation than the solid matrix systems. Although the US market acceptance of the Vivelle-Dot™ estrogen patch (Noven; http://www.noven.com) substantiates that a reduced skin irritation profile and smaller patch are attractive to the patient, it should also be appreciated that even launch of a relatively large patch in a new therapeutic area, such as the Ortho-Evra™ contraceptive patch, can make a substantial impact on the market dynamics, demonstrating the attractiveness of this route of delivery to patients.

The potential for transfer of the dose from the patient to another person has been highlighted, particularly with gels and creams. This transfer can occur during application and afterwards, depending on how quickly the dose is absorbed into the stratum corneum and the degree of substantivity that the formulation exhibits for the skin. A measure of the formulation's substantivity can be determined by washing the application site after application. This has been shown to reduce estradiol delivery from the Sandrena® gel, with the degree of reduction affected by the surface area of application [33].

Existing TDD systems develop a gradient of drug across the various layers of the skin from the surface to the systemic circulation. This can generate issues where the drug delivery might need to be stopped suddenly because delivery can continue for some time after removal of the TDD system from the skin surface. This might not be such an issue for several of the non-passive TDD systems in development, where removal of the energy source will cease drug delivery.

Manufacturing of TDD systems has historically provided the formulator with some distinct challenges, particularly with the scale-up of multi-component patches. Additionally, there have also been issues with formulation stability and drug crystallization on longer-term storage.

The concept of evaporative delivery

A recent development that attempts to overcome some of the limitations of TDD systems described above involves application of the concept of evaporative delivery (Acrux; http://www.acrux.com.au). The system involves a solution of the drug in a mixture of volatile and non-volatile solvents. This formulation represents a micro-dose evaporative system that provides passive and non-occlusive delivery [46]. As a result of these characteristics, this system demonstrates very low skin irritation rates.

The system developed is a rapid-drying solution containing a volatile component that enables the volume per area of application to be precisely defined. This component also enables the formulation to have uniform distribution on the skin over a defined area after application, without leaving excess vehicle. Hence, this ensures that the dose can be administered in a precise and highly reproducible manner and that aesthetic and transferance issues are avoided. The evaporation of some of the vehicle leads to an increase in concentration of the active drug and hence enhanced partitioning into the stratum corneum [47].

The non-volatile component prevents the drug from precipitating from solution as the volatile solvent component evaporates. The physicochemical properties of the non-volatile component have been selected so that it partitions rapidly into the stratum corneum and aids partition of the drug into the stratum corneum, as well as serving to disrupt the ordered intercellular lipids and enhance permeation.

Hence, this type of delivery system creates an invisible depot of drug and enhancer in the stratum corneum from which the drug can be slowly absorbed into the systemic circulation (Figure 1). This can provide delivery over two to four days following a single application and sustained steady-state serum levels with chronic, once daily application. This system also has the flexibility to cater for a dial-a-dose concept, whereby the user can alter the dose delivered from a multi-dose product. Drug candidates for this concept would require a suitable safety and dose–response profile.

Drug products using this technology are being developed in a range of therapeutic areas and are typically administered using a Metered-dose Transdermal System, MDTS® (Acrux; http://www.acrux.com.au)

Conclusions

The future for transdermal drug delivery hinges on how it is perceived by companies involved in drug discovery. In the past it has been used as an alternative to oral delivery to overcome problems associated with that route. If transdermal delivery continues to be viewed in this context then future advances are likely to be incremental, as the drugs will not have been selected with a view to their suitability for transdermal delivery. The emphasis of the

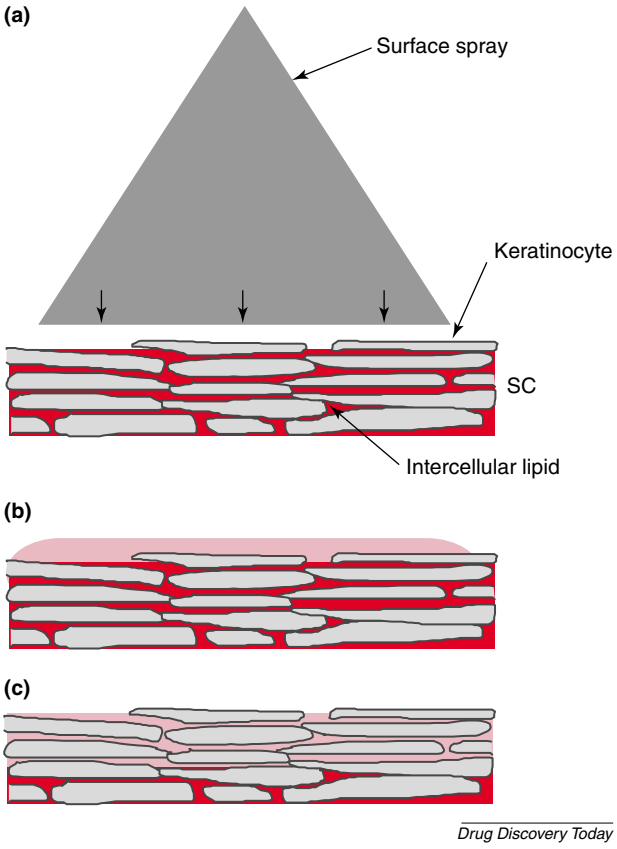

Figure 1. Schematic representation of time course of events with the metered-dose transdermal system (MDTS®; http://www.acrux.com). **(a)** Surface spray is applied to the stratum corneum (SC). **(b)** The 'forced partitioning' concept, involving the rapid evaporation of the volatile vehicle and then the partitioning of the drug and enhancer into the SC. **(c)** The drug and enhancer form a reservoir within the SC that is lipid in character and water resistant.

developments will be in overcoming the problems associated with the barrier properties of the skin. The approaches being taken to overcome these problems have been outlined in this review.

If, however, transdermal delivery was viewed as a desirable delivery route in its own right then new drugs might be selected deliberately for development based on their suitability for transdermal delivery (high potency, low melting points, low molecular weights and suitable logP). In this case we might expect to see a focus on improvements in the elegance, dosage flexibility and convenience of transdermal delivery systems. For example, dial-a-dose transdermal delivery is feasible for drugs with suitable properties by combining recent metered dose pump technology, such as that of Aptar Group (Aptar Group; http://www.aptar.com), with the MDTS® technology of Acrux. Drugs for which this type of approach is likely to be suitable include potent drugs where individualization of the dose is desirable.

Another factor that might be important for the future direction of transdermal delivery is the current surge in interest in nanotechnology. Application of developments in nanotechnology could lead to systems where a single device could monitor drug levels by sampling through the skin and thus provide controlled delivery of the drug [48]. The attractiveness of the transdermal route for application of this technology is obvious because of the accessibility of the device for adjustment, control and removal.

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