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Transdermal Drug Delivery: 30+ Years of War and Still Fighting!

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Abstract

By any measure, transdermal drug delivery (TDD) is a successful controlled release technology. Over the last 30+ years, a steady flux of transdermal products have received regulatory approval and reached the market. For the right compounds, TDD is an effective and preferred route of administration; for others, delivery across the skin makes no sense at all. Currently, the “rules” that govern (passive) TDD feasibility are clearly understood, and research activity is focused on novel approaches that strive to subvert skin’s excellent barrier function, and broaden the range of active species amenable to percutaneous administration.

Keywords: Transdermal drug delivery; skin barrier function; controlled release

Introduction

Prior to 1980, transdermal drug delivery (TDD) was limited to very few compounds (including nitroglycerin and estradiol) formulated in relatively simple ointments and gels. The latter, conventional vehicles were inelegant, inefficient and suffered from poor control of both the quantity of drug applied and the area of skin exposed. The outcome of this less than ideal situation was significant variability in the extent and duration of drug effect.

The field was therefore primed for the concept, pioneered in large part by the Alza Corporation in Palo Alto, California, of a transdermal patch in which system design and explicit control of surface area were combined to create a technology capable of passive drug delivery to the systemic circulation at a predetermined rate [1].

Consequently, a clear, perceived advantage of TDD was the provision of a prolonged period of administration, during which drug levels would be maintained within the therapeutic window, offering thereby a extended duration of action and, for compounds of short biological half-life, a reduced frequency of dosing. It was further argued, not unreasonably, that achieving these aims would lower variability, both within and between patients and substantially improve, as a result, compliance and adherence with drug use [1-3].

Two further key benefits were also immediately apparent. The first addressed an important problem for a number of (up until the advent of TDD) orally administered drugs; specifically, those subject to a large, pre-systemic first-pass effect. Such compounds typically have very low (or even non-existent, in some cases) oral bioavailability, particularly inconvenient dosing regimens, and significant incidences of adverse effects, often the result of the high levels of metabolite(s) formed on their first passage through the liver. In contrast, by administering such drugs transdermally, the classic first-pass effect is avoided and these major drawbacks are circumvented [1-4].

The second is self-evidently practical in nature: in situations where drug input is no longer desirable (due, for instance, to an important change in a patient's status), transdermal administration can be stopped by removal of the patch. Apart from an intravenous infusion, there is no other route of drug delivery for which this is instantaneously possible¹ [4, 5].

Taken together, the potential benefits of TDD led, in the early days, to some frankly 'hallucinogenic' claims about the future breadth of application of the administration route. However, it did not take long before reality reasserted its grip on the field and it became clear that the systemic delivery of drugs across the skin would be subject to a number of limitations. Most importantly, given that the skin's principal function is to act as a protective barrier, and that the rate of molecular transport through (in particular) the outermost layer, the stratum corneum, is highly constrained and very slow, it follows that TDD is suitable only

¹ Of course, drug, which has been released from the patch and is diffusing across the skin, but has not yet been 'resorbed' into the blood circulation, will ultimately be absorbed (albeit at a reduced rate as the driving concentration gradient will have been removed).

for very potent drugs [1]. Indeed, the daily dose of those compounds, which have reached the market, is measured typically in terms of a few milligrams (Table 1).

Furthermore, given the relationship between molecular properties and skin permeability, there have emerged certain (Lipinski-like) 'rules' that a drug must satisfy, in addition to potent pharmacological activity, to become a feasible candidate for TDD [6]; specifically: (a) modest molecular weight ($MW < 400$ to 500 Da), (b) a balanced lipophilicity ($\log\{\text{octanol-water partition coefficient}\}$, $\log P$, ideally around 2 to 3), and (c) a measurable solubility both in oil and in water (given that TDD requires both breaching the lipophilic stratum corneum and resorption into the aqueous central compartment of the systemic circulation).

The combination of the right physicochemical properties to enable skin penetration, and the ability to elicit the desired therapeutic effect at very low concentration, means that TDD can be achieved from a patch of reasonable size: currently, there are few transdermal systems in use of area greater than 50 cm^2 (about the size of a credit card). Should either skin permeability or pharmacological potency be insufficient, then TDD becomes impossible without an impracticably large patch [1, 3]. Testosterone, for example, has walked this fine line with the result that the present approach of choice to deliver this compound is a gel formulation, which can be applied over a larger surface area².

A further limitation of considerable relevance is skin tolerability. Because skin sensitivity varies widely among individuals, all transdermal systems on the market include skin irritation in their list of adverse effects; indeed, merely occluding the skin with a patch can be enough to cause obvious reddening of the application site [1]. However, some drugs are themselves irritating and the careful, early testing of skin irritation (and sensitisation) due to the active agent is a key component of TDD development. For the moment, while there are clues to the chemical structure – skin sensitisation relationship, it remains difficult to predict *a priori* whether a drug will provoke a degree of irritation sufficient to cause cessation of further development: *in vivo* evaluation is essential. It is almost certainly true that many transdermal projects have fallen at the skin tolerability hurdle.

² In the case of testosterone, the therapeutic window is relatively large, meaning that the inherent inaccuracy in dosing a conventional formulation over a less than precisely defined surface area of skin is acceptable.

Table 1: Daily dose ranges and selected physicochemical and pharmacokinetic properties of currently approved transdermally delivered drugs.

Drug (year of approval)	Dose/day (mg)	MW (Da)	log P ^a	Cl (L/hr)	t _½ (hr) ^b	F (%) ^c	C _{p,eff} (ng/mL) ^e
Scopolamine (1979)	0.3	303	0.98	672	2.9	27	0.04
Glyceryl trinitrate (1981)	2.4 - 15	227	1.62	966	0.04	< 1	0.1 - 5
Clonidine (1984)	0.1 - 0.3	230	2.42 ± 0.52	13	6 - 20	95	0.2 - 2.0
Estradiol (1986)	0.025 - 0.100	272	4.01	615 - 790	0.05	3-5	0.04 - 0.06
Fentanyl (1990)	0.288 - 2.400	337	4.05	27 - 75	3 - 12	32	1.0
Nicotine (1991)	7 - 21	162	1.17	78	2	30	10 - 30
Testosterone (1993)	0.3 - 5	288	3.32		0.17 - 1.7	< 1	10 - 100
Estradiol & Norethisterone Acetate (1998)	0.025 - 0.050	272	4.01		2 - 3	3 - 5	0.04 - 0.07
	0.125 - 0.250	340	3.99		6 – 8 ^d	64	0.8 - 1.1
Norelgestromin & Ethinyl Estradiol (2001)	0.2	327	3.90 ± 0.47		28	40	0.8
	0.034	296	3.67		17 ^d		0.05
Estradiol & Levonorgestrel (2003)	0.050	272	4.01		3	3 - 5	0.03 - 0.05
	0.007 - 0.015	312	3.72 ± 0.49		28 ^d		0.1 - 0.2
Oxybutynin (2003)	3.9	357	4.02 ± 0.52		2	6	1.0 - 5.0
Selegeline (2006)	6 - 12	187	2.90	84	10	10	2.0 - 3.0
Methylphenidate (2006)	26 - 80	233	2.15 ± 0.42	20	2 - 3	5 - 20	5.0 - 25
Rotigotine (2007)	1 - 3	315	4.58 ± 0.72	600	5 – 7 ^d	n/a	~1.0
Rivastigmine (2007)	4.6 - 9.5	250	2.34 ± 0.16	108	1.5	40	~10
Granisetron (2008)	3.1	312	2.55 ± 0.28	33-76 healthy 15-34 patients	4 – 6 healthy 9-12 patients	60	0.7 - 9.5
Buprenorphine (2010)	0.12 - 1.68	468	4.98	55	22 – 36 ^d	n/a	0.1 - 0.4

^aLog{octanol-water partition coefficient (P)}: either experimental or calculated (mean ± SD) values.

^bTerminal half-life post-oral or IV dosing.

^cOral bioavailability.

^dTerminal half-life following transdermal delivery.

^ePharmacologically effective plasma concentration.

Current state-of-the-art

The presently approved drugs in the U.S.A. and Europe for passive transdermal delivery are listed in Table 1 (in the chronological order of approval by the Food & Drug Administration). The limited number of compounds seen in this list reflects the difficulty of meeting the dual challenge of high pharmacological potency and skin permeability necessary for successful TDD. Over the last 30+ years, therefore, approval for a new compound to be administered as a transdermal patch has occurred approximately once every two years.

Nevertheless, TDD today represents annually a multi-billion (US) dollar market and a true controlled drug release success story [7]. It's fair to say that, apart from the field of oral administration, TDD's 'return on investment', from the standpoint of the translation of research to clinical application, is second to none. Indeed, transdermal fentanyl, for at least the last 5 years, may be considered a pharmaceutical "blockbuster", with annual sales exceeding US\$ 1Billion! The transdermal patch concept is well-known and accepted by the general public, and it is now possible to purchase nicotine patches over-the-counter from a pharmacy or supermarket.

Further examination of Table 1 reveals that all of drugs approved for transdermal delivery, with the single exception of rotigotine, were previously available to patients by another route of administration (such as oral, sublingual, injection, etc.). Rotigotine was the first and, for the moment, the only new chemical entity to be developed and approved by the regulatory authorities specifically for transdermal delivery [8]. It remains to be seen whether this bold approach becomes a seriously considered alternative by the pharmaceutical industry for potent development candidates deemed unsuitable for oral administration because of metabolic (first-pass effect) sensitivity.

Typically, the strategy is to formulate the drug in a suitable, adhesive polymer matrix, or in two such layers (Figure 1), at a loading close to saturation, thereby providing the maximum driving force for passive diffusion across the skin (see following section) [4]. Variation of the patch area can then be used to titrate the dose delivered in a direct proportion (Figure 2), or to transfer a degree of drug input rate control from the skin to the delivery system [9].

Figure 1: Schematic diagrams of typical “matrix” passive transdermal drug delivery systems. For clarity, the release liner, which contacts the drug-in-adhesive layer, and which is removed before patch application, is not shown.

Figure 2: Steady-state plasma concentrations of three drugs after transdermal delivery as a function of patch area (redrawn from ref [4]).

Transdermal drug delivery – feasibility and control

Assuming that a suitably potent drug candidate has been identified for which a convenient oral dosing regimen proves impossible (e.g., due to high first-pass effect, short biological half-life, etc.), then the feasibility of transdermal delivery requires an assessment of the molecule's skin penetrability. A default starting position is to estimate the compound's maximum flux across the skin (J_{max} , typically in units of $\mu\text{g}/\text{cm}^2/\text{hr}$) and to evaluate whether this value is sufficient to satisfy the steady-state, "rate in = rate out" equation below where Q (mg) is the anticipated daily dose and with A (cm^2), the patch area, being no greater than 50 cm^2 :

$$\left(\frac{1000}{24}\right) \times Q = A \times J_{max} \quad (\text{Eq. 1})$$

Equation (1) can also be written, of course, in terms of the drug's systemic clearance (Cl in L/hr) and effective steady-state plasma concentration ($C_{p,eff}$ in $\mu\text{g}/\text{L}$); i.e., $Cl \times C_{p,eff} = A \times J_{max}$ [10].

The maximum steady-state flux across the skin is given by Fick's 1st law of diffusion

$$J_{max} = \left(\frac{D}{h}\right) \times K_{SC/v} \times C_{v,sat} = k_{p,v} \times C_{v,sat} \quad (\text{Eq. 2})$$

where D is the compound's diffusivity across (most typically) the stratum corneum (SC), h is the diffusion path-length through the barrier, $K_{SC/v}$ is the drug's partition coefficient between the SC and the vehicle in which it is applied, and $C_{v,sat}$ is its saturation solubility in the vehicle. The permeability coefficient of the drug from the vehicle ($k_{p,v}$, which has units of velocity, e.g., cm/hr) is a convenient shorthand that brings together three parameters that are difficult to uniquely determine by experiment.

For TDD, the vehicle is most usually a patch (e.g., like those in Figure 1) and neither $k_{p,v}$ nor $C_{v,sat}$ are routinely available. However, at least in theory, Equation (2) should be valid for any vehicle, which does not alter the SC barrier, or change the drug's solubility therein [11]. Assuming that water satisfies these criteria, the corresponding permeability coefficient ($k_{p,w}$) and aqueous solubility ($C_{w,sat}$) can then be used to estimate J_{max} using Equation (2). While water solubilities are typically measured experimentally in drug development, or can be derived from established algorithms, skin permeability coefficients from water may be accessed from Franz-type diffusion cell studies or predicted (in units of cm/hr) from the empirical relationship derived by Potts & Guy [12]:

$$\log k_{p,w} = -2.7 + 0.71 \times \log P - 0.0061 \times MW \quad (\text{Eq. 3})$$

(where P is the drug's octanol-water partition coefficient (again, typically known or easily calculated) and MW is its molecular weight) and corrected for the contribution of the underlying viable skin for more lipophilic compounds by Cleek & Bunge [13]:

$$k_{p,w}^{corr} = \frac{k_{p,w}}{1 + \frac{k_{p,w} \sqrt{MW}}{2.6}} \quad (\text{Eq. 4})$$

This approach has been adopted for the 18 drugs approved for transdermal delivery (and identified in Table 1) and the results are presented in Table 2. Lipophilicities (i.e., $\log P$ values) and water solubilities were either obtained from readily accessible databases [14, 15], or were estimated using freely available algorithms [14, 15]. In general, while the latter produced estimates of $\log P$ with little variability, the calculated values of $C_{sat,w}$ were less consistent, especially for drugs of poor aqueous solubility.

It is immediately apparent that the ability of approved transdermal drugs to penetrate the skin varies widely from the extremely permeable nicotine to compounds, such as buprenorphine and the progestins, which have very low predicted fluxes. Given, as mentioned above, that the ‘default’ position in developing a transdermal patch is to create a polymer matrix, which is saturated with a sufficient payload of the drug to ensure delivery for the duration of application, it is informative to compare the estimated J_{max} values in Table 2 with the labelled *in vivo* delivery rates of the products on the market. This information is collected in Table 3, and the ratios of the clinical input rates to the estimated maximum fluxes is illustrated graphically in Figure 3.

If all transdermal systems were formulated to provide the maximum thermodynamic driving force for passive diffusion across the skin, the ratios in Figure 3 should all be equal to 1. Given the inherent uncertainty in the parameters used in Equation (2) to determine J_{max} , it has been proposed [16] that ratios falling within an order of magnitude of this ideal value are reflective of patches in which the drug’s activity is at or close to optimal.

In those cases where the *in vivo* delivery rate falls well below J_{max} , for example with nicotine, it is clear that the transdermal systems have been formulated with a lower loading of the drug (i.e., below the saturation concentration) and that they have assumed a degree of rate control so as to prevent a potentially excessive exposure of the patient to the active compound. Nicotine, self-evidently, permeates the skin very quickly, to an extent which is far greater than necessary for its use in smoking cessation patches.

The situations in which the achieved delivery rates exceed J_{max} significantly can, more often than not, be attributed to the presence in the patch formulations of excipients recognised to be skin penetration enhancers, either through perturbation of SC lipid organisation thereby increasing drug diffusivity, or via their ability to promote drug solubilisation within the barrier and provide a steeper concentration gradient to drive the flux to a higher level. Examples in the former category include MinitranS (glyceryl trinitrate), which contains glycerol monolaurate and ethyl oleate, and Andropatch (testosterone), which includes glycerol monooleate, methyl laurate and ethanol. In the latter group, the effect may be achieved somewhat indirectly in the manufacturing process where the drug is typically and

initially dissolved with a polymeric adhesive in an organic solvent(s). Once cast on the release liner or backing film, a controlled drying process evaporates solvent, resulting, in certain cases, to supersaturation of drug within the patch. If this metastable state persists until application to the skin, then a concomitant supersaturation of the active agent can be produced in the SC and a greater-than-anticipated flux will result. Neupro (rotigotine) adopts a different approach to improve drug solubility in the SC: incorporation into the patch of the excipient, povidone (or polyvinylpyrrolidone, PVP), causes water to be taken up from the skin into the delivery system, shifting the partition coefficient of the lipophilic drug more favourably towards the SC. A similar strategy is used in other transdermal products (such as those containing buprenorphine and norethisterone acetate), sometimes in combination with an additional excipient that acts on the SC lipid organisation.

Transdermal delivery has also benefitted from advances in adhesive science, an excellent illustration being the so-called DOT-MatrixTM (delivery-optimised thermodynamics) technology [17], which allows increased drug loading per unit quantity of adhesive and the use of a smaller patch area. In a matrix patch based on the DOT technology, an acrylic adhesive, for example, is loaded with the drug and then dispersed into a silicone adhesive in which the active compound is less soluble. The supply of drug from the 'encapsulated' acrylic "cells" maintains its thermodynamic activity in the silicone adhesive at the maximum level ensuring the most efficient delivery possible. The technology is used in various patches at present, most impressively perhaps in the Daytrana (methylphenidate) system for the treatment of ADHD in children.

Table 2: Predictions of the maximum fluxes of drugs currently approved for transdermal delivery in Europe and the USA.

Drug	MW (Da)	log P ^a	± SD	C _{w,sat} (mg/cm ³) ^b	± SD	log k _{p,w}	k _{p,w} (cm/h) ^c	k _{p,w} ^{corr} (cm/h) ^d	J _{max} (µg/cm ² /h) ^e
Nicotine	162.2	1.17		1000		-2.843	1.44E-03	1.43E-03	1425
Selegilene	187.3	2.90		1.14		-1.765	1.72E-02	1.58E-02	18.0
Scopolamine	303.4	0.98		100		-3.825	1.50E-04	1.49E-04	14.9
Rivastigmine	250.3	2.34	0.16	3.37	1.18	-2.540	2.88E-03	2.83E-03	9.53
Clonidine	230.1	2.42	0.52	1.60	2.34	-2.362	4.34E-03	4.23E-03	6.77
Methylphenidate	233.3	2.15	0.42	1.14	1.04	-2.573	2.67E-03	2.63E-03	2.99
Fentanyl	336.5	4.05		0.20		-1.844	1.43E-02	1.30E-02	2.60
Glyceryl trinitrate	227.1	1.62		1.38		-2.912	1.22E-03	1.21E-03	1.67
Granisetron	312.4	2.55	0.28	0.61	0.81	-2.764	1.72E-03	1.70E-03	1.04
Oxybutynin	357.5	4.02	0.52	0.034	0.036	-1.991	1.02E-02	9.50E-03	0.32
Rotigotine	315.5	4.58	0.72	0.0091	0.0006	-1.341	4.56E-02	3.47E-02	0.32
Testosterone	288.4	3.32		0.023		-2.073	8.44E-03	8.00E-03	0.18
Ethinyl estradiol	296.4	3.67		0.011		-1.873	1.34E-02	1.23E-02	0.14
Estradiol	272.4	4.01		0.0039		-1.487	3.25E-02	2.70E-02	0.11
Buprenorphine	467.6	4.98		0.0067	0.0073	-1.970	1.07E-02	9.84E-03	0.07
Norethisterone acetate	340.5	3.99		0.0053		-1.910	1.23E-02	1.13E-02	0.06
Norelgestromin	327.5	3.90	0.47	0.0036	0.0019	-1.896	1.27E-02	1.17E-02	0.04
Levonorgestrel	312.5	3.72	0.49	0.0015	0.0014	-1.934	1.16E-02	1.08E-02	0.02

^aWhen available, experimental values are given; otherwise, the average of calculated estimates – in italics - are provided (with SD in the following column); see text for details.

^bWhen available, experimental values are given; otherwise, the average of calculated estimates – in italics - are provided (with SD in the following column); see text for details.

^cCalculated using Equation (3).

^dCalculated using Equation (4).

^eCalculated using Equation (2) using the values of $k_{p,w}^{corr}$ and $C_{w,sat}$ in the Table.

Table 3: *Delivery rates and active areas of commercialised transdermal products and comparison of labelled in vivo input fluxes across the skin with the corresponding maximum values (J_{max}) estimated theoretically.*

Product - Drug	Delivery rate	Active area (cm ²)	$J_{in\ vivo}^a$ µg/cm ² /hr	J_{max} µg/cm ² /hr	$J_{in\ vivo}/J_{max}$
Transderm Scop - Scopolamine	1 mg/72 h	2.5	5.6	14.9	0.38
Nitroderm TTS - GTN ^b	5-15 mg/24 h	10 - 30	20	1.67	12
Deponit TTS - GTN ^b	5, 10 mg/24 h	9, 18	23		14
MinitranS - GTN ^b	5 mg/24 h	6.7	31		19
Catapres-TTS - Clonidine	0.1 - 0.3 mg/24 h	3.5 - 10.5	1.2	6.77	0.18
Dermestril/Alora - Estradiol	25-100 µg/24 h	9 - 36	0.12	0.11	1.1
Estradot/Vivelle-Dot - Estradiol	25-100 µg/24 h	2.5 - 10	0.42		3.8
Dermestril Septem - Estradiol	25 µg/24 h	11.25	0.09		0.84
Fem7 - Estradiol	50-100 µg/24 h	15 - 30	0.14		1.3
Menorest - Estradiol	37.5-100 µg/24 h	11 - 29	0.14		1.3
Estrapatch - Estradiol	40-80 µg/24 h	14.25 - 28.5	0.12		1.1
Esclim - Estradiol	25-100 µg/24 h	11 - 44	0.09		0.86
Climara - Estradiol	25-100 µg/24 h	6.5 - 25	0.17		1.5
Sequidot Phase I - Estradiol	50 µg/24 h	5	0.42		3.8
Fem7 Combi/Conti - Estradiol ^c	50 µg/24 h	15	0.14		1.3
Climara Pro - Estradiol ^c	45 µg/24 h	22	0.09		0.77
Sequidot Phase II - Estradiol ^c	50 µg/24 h	16	0.13		1.2
Estragest - Estradiol ^c	25 µg/24 h	10	0.10		0.95
Combipatch - Estradiol ^c	50 µg/24 h	9	0.23		2.1
Durogesic SMAT - Fentanyl	12-100 µg/h	25 - 42	2.4	2.60	0.92
Fentadolon - Fentanyl	25 µg/h	15	1.7		0.64
Matrifen - Fentanyl	25 µg/h	8.4	3.0		1.1
Fentalis Reservoir - Fentanyl	25 µg/h	10	2.5		0.96
Nicorette TX - Nicotine	10-25 mg/16 h	9 - 22.5	69	1425	0.05
NiQuitin CLEAR - Nicotine	7-21 mg/24 h	7 - 22	42		0.03
Nicotinell/Habitrol - Nicotine	7-21 mg/24 h	10 - 30	29		0.02
Intrinsa - Testosterone	0.3 mg/24 h	28	0.45	0.18	2.5
Testopatch - Testosterone	1.2-2.4 mg/24 h	30 - 60	1.7		9.3
Testoderm TTS ^d - Testosterone	5 mg/24 h	60	3.5		19
Andropatch - Testosterone	2 mg/24 h	32	2.6		14
Sequidot Phase II – Nor’acetate ^e	250 µg/24 h	16	0.65	0.06	11
Estragest – Nor’acetate ^e	125 µg/24 h	10	0.52		8.7
Combipatch – Nor’acetate ^e	140 µg/24 h	9	0.65		11
Evra - Norelgestromin	203 µg/24 h	20	0.42	0.04	11
Evra – Ethinyl estradiol	33.9 µg/24 h	20	0.07	0.14	0.50
Fem7 Combi - Levonorgestrel	10 µg/24 h	15	0.03	0.02	1.4
Fem7 Conti - Levonorgestrel	7 µg/24 h	15	0.02		0.97
Climara Pro - Levonorgestrel	15 µg/24 h	22	0.02		0.95

Kentera/Oxytrol - Oxybutynin	3.9 mg/24 h	39	4.2	0.32	13
Emsam - Selegeline	6-12 mg/24 h	20 - 40	13	18	0.69
Daytrana - Methylphenidate	1.1-3.3 mg/h	12.5 - 37.5	88	2.99	29
Neupro - Rotigotine	1, 3 mg/24 h	5, 15	8.3	0.32	26
Exelon - Rivastigmine	4.6, 9.5 mg/24 h	5, 10	38	9.53	4.0
Sancuso - Granisetron	3.1 mg/24 h	52	2.5	1.04	2.4
BuTrans/Norspan - Buprenorph ^f	5-20 µg/h	6.25 - 25	0.8	0.07	11
Transtec Pro - Buprenorph ^f	35-70 µg/h	25 - 50	1.4	0.07	20

^aDeduced from the labelled delivery rate and active area of the patch.

^bGTN = glyceryl trinitrate.

^cEstradiol present in combination patches with either norethisterone acetate or levonorgestrel.

^dPatch is for application to the scrotum.

^eNor'acetate = norethisterone acetate.

^fBuprenorph = buprenorphine.

Figure 3: Graphical illustration of the ratio of drug fluxes across the skin in vivo from marketed transdermal patches to theoretical estimates of the corresponding J_{max} values.

Future perspectives for transdermal drug delivery

Despite the important achievements of TDD over the past three decades or so, it remains an undeniable fact that the route of administration is limited to a relatively small subset of highly potent, low molecular weight and moderately lipophilic drugs. Even with the enhancement of delivery possible via the use of different excipients, and combinations thereof, or by the clever 'tweaking' of the thermodynamics involved, only modest degrees of increased flux can be practically achieved. As soon as one becomes more aggressive, for example by using more of an enhancer or more enhancers in a mixture, then unacceptable skin irritation (i.e., deal-breaking in terms of product development) is pretty much the inevitable result.

Nonetheless, this has not deterred a cohort of determined transdermal scientists from continuing to carry the battle to the skin, attempting not only to persuade other small molecules of less attractive properties across the barrier, but also to explore more orthogonal ideas which may allow even macromolecular drugs to be administered transdermally.

Inevitably, some of these battles have ended in resounding victories for the skin (and, in many cases, for common sense as well, it must be said), with forays involving liposomes, electroporation, the 'gene gun', to name but a few, ending up much like the Charge of the Light Brigade in 1854. Others, in contrast, while yet to 'deliver' in a commercial sense, have shown more tenacity and have opened up new areas of research in which real advances have already been achieved.

One of the most intensively studied approaches has been iontophoresis, and the use of the past tense reflects the fact that the level of activity is presently less than it was just before the new millennium. Iontophoresis, of course, has been known and studied for over 100 years and it remains, to all intents and purposes, the only 'physical' transdermal technology to have received regulatory approval and for which commercial products have been marketed³. This mature technology is one for which an excellent mechanistic understanding has been defined and a more than reasonable safety profile exists. It is recognised that the use of a small electric current to enhance TDD is not going to enable hundreds of drugs to become deliverable across the skin and, even though small proteins have been coaxed across the barrier with this approach [18], the scope for applying iontophoresis to the delivery of monoclonal antibodies, for example, is simply not going to happen. Nevertheless, products containing lidocaine, fentanyl and, most recently, sumatriptan have surmounted the regulatory hurdles and been commercialised. Equally, transdermal iontophoresis formed the basis for the only noninvasive glucose monitor (the GlucoWatch BiographerTM) to have ever been approved by the U.S. FDA. However, at the time of writing,

³ In contrast, for example, to sonophoresis, which is yet to realise its original promise [Azagury A, Khoury L, Enden G, Kost J. Ultrasound mediated transdermal drug delivery. *Adv Drug Deliv Rev.* 2014. doi: 10.1016/j.addr.2014.01.007].

the lidocaine, fentanyl and glucose monitoring systems are unavailable, having suffered a mix of commercial and technical setbacks, leading to their withdrawal from the market.

It goes without saying that this has significantly undermined confidence in the future of iontophoresis as a viable transdermal technology and provides a real (and keenly observed) challenge for the sumatriptan product to overcome this difficult situation. The experience with iontophoresis illustrates that the 'marriage' between a drug and its delivery system, particularly one that involves complex (and, almost always, more expensive) technology is never going to be an easy one. There has to be an important unmet medical need, which is intractable to established, simpler (and, almost always, cheaper) approaches. Had the three unsuccessful iontophoretic devices, which made it to the finishing line, worked absolutely as envisaged, then they may well have been of significant benefit and delivered a substantial financial return on investment. In not meeting this bar, however, they rather quickly succumbed to a bad press that only highlighted their deficiencies while ignoring their very attractive attributes.

What lies ahead for iontophoresis, then? Clearly, the technology needs a commercial success and, as mentioned already, the launch of the newly approved sumatriptan system is a cause for great anticipation. The field also needs to identify the best possible drug-disease combination to address with the technology. One area, for example, in which extremely promising clinical data emerged a few years ago, involved the delivery of a peptide (MW = ~1200 Daltons) used in fertility treatment. The ability of short iontophoretic pulses to mimic the delivery of this compound that is typically given in a series of uncomfortable subcutaneous injections was quite remarkable (see Figure 4). Finally, interest continues in the monitoring applications of iontophoresis, where glucose remains the Holy Grail of the field.

As the highs and lows of iontophoresis played out on either side of the millennium, a new research effort became progressively more vocal and visible in the transdermal world, and the concept of "skin poration" moved squarely onto centre stage. The almost heretical premise of this new wave was (i) to acknowledge the unconquerability of the SC (especially towards the delivery of biopharmaceuticals), and (ii) to devise means with which to circumvent the skin's barrier. The latter specifically involves creating new pathways through the SC using technologies that are minimally invasive, essentially painless and reversible.

The skin permeabilisation methods are varied, with microneedles (of one sort or another) leading the way, followed by thermal and laser-assisted ablation. The number of publications addressing these technologies, especially microneedles, is growing exponentially and recent, authoritative reviews are available in the literature [19-24]. In each approach, new, aqueous pathways are created across the outer few hundred microns (give or take) of the skin allowing the barrier function of the SC to be 'short-circuited' and relaxing two key limitations of passive transdermal delivery:

- (1) The requirement for the drug to be lipophilic (to enable its partitioning into the SC) is lifted; indeed, delivery through 'porated' skin is best suited for molecules which have decent water solubility and, in the case of conventional, low MW compounds, use of the (frequently more stable) salt form of a drug is therefore preferred.
- (2) The constraint of low molecular weight for TDD is removed; these technologies create openings in the skin which are measured in tens of microns, meaning that pretty much any biopharmaceutical (peptide, protein, antibody, vaccine, siRNA, oligonucleotide, DNA) can gain access following poration of the barrier.

These widened boundary conditions, however, do not mean that TDD is suddenly possible for all conceivable drugs! It remains the case that the route of administration is best suited to potent compounds, the dose requirements of which are modest; that is, it will still be impossible, for example, to deliver a drug requiring a dose of, say, 500 mg a day. The practicality of such a challenge, in terms of delivery system design, is unclear and the skin's reaction to the presence of the resulting large quantity of xenobiotic, which must flow through it per unit time, is unlikely to be a happy one.

To illustrate the potential of, and the challenges facing, the skin poration field, we focus our attention on microneedles. As stated above, this approach has been subject to the most intensive research effort and it is the most advanced in terms of progress with respect to clinical evaluation. Although the idea of microneedles had been around for quite some time, the step change in microfabrication technology at the end of the 20th Century provided the trigger for the concomitant focus on applications in TDD. Since then, enormous diversity in microneedle design and use, materials, fabrication methods, and potential therapeutic applications has been seen. Table 4 attempts to capture this very broad spectrum of activity.

In terms of progress towards clinical application of the microneedle technology, there are a number of human trials underway, with the majority focused on vaccine delivery. As a first demonstration of the potential of the skin poration approach, vaccination is a very attractive option: the dose required is very low, administration is not needed on a continuous basis, the therapeutic window is relatively large, and the skin provides an excellent 'amplification' system for the desired immune response. There would appear to be an excellent chance, therefore, that microneedle-based vaccinations will ultimately become generally available, both for immunisation against (e.g.) the influenza virus, but also to combat a range of diseases in sub-Saharan Africa, for example, where the delivery (in all senses of the word) of conventional vaccine formulations remains a significant challenge. A more interesting, and less easily answered, question is what comes after vaccines? Where is the obvious unmet medical need that microneedles (or indeed any of the poration approaches) can address better, more reliably and safer than a conventional needle-and-syringe?

Figure 4: *In vivo* plasma concentration versus time profiles of a ~1200 Dalton peptide delivered systemically by either 3 subcutaneous injections or 3 x 5-minute pulses of transdermal iontophoresis (personal communication, Vyteris, Inc.).

Table 4: *Summary of the microneedle technology field.*

Materials^a	Silicon, metals, polymers, ceramics.
Fabrication methods	Lithography; wet and dry etching; laser cutting; micromolding.
Mechanism	Solid μ needles pre-treatment followed by drug formulation/patch application. Metal/polymer μ needles coated with drug-containing matrix which dissolves on insertion, releasing drug. Drug incorporated into polymer μ needles, which dissolve on insertion, releasing the active compound. Hollow μ needles through which liquid drug formulations can be infused.
Medical applications	Low MW drugs, including naltrexone, lidocaine, PDT applications. Biopharmaceuticals, including parathyroid hormone, insulin and other peptide and protein drugs. Vaccines, e.g., influenza, West Nile virus, HPV, etc. Sampling of interstitial fluid in viable skin for monitoring/diagnosis applications.
Practical issues	Sharpness, length, insertion force, velocity. Infusion through hollow μ needles depends on geometry, infusion pressure, partial retraction. Skin recovery post- μ needle insertion is rapid (within hours) if skin not occluded or treated with inhibitors of skin repair. Biopharmaceutical drug stability in μ needles. Pain on μ needle insertion appears minimal, but transient erythema observed. No increased risk of infection at poration site is yet apparent. Attractive to patients and healthcare workers.

^aNote that the fabrication methods, mechanism, medical applications and practical issues listed are not necessarily specific to one particular microneedle material.

Concluding comment

In a little over 30 years, transdermal delivery has been transformed from an interesting new idea to a multi-billion US dollar per year industry. As a controlled release technology, TDD has, in many ways, out-performed by some distance most of its “sexier” competitors and appears likely to continue to do so in the foreseeable future. For most of its lifetime, TDD has kept to its relatively modest ambitions, recognising its limitations and batting away a variety of upstart ideas that showed no respect to the formidable bioengineering of the skin barrier. While forays into more exotic territory, such as iontophoresis, have offered seductive promises that have yet to deliver any tangible, economic return, the most recent explorations of what might be possible when new openings are made in the skin are now in the vanguard of research and future development. The next 5-10 years will reveal the extent to which the TDD landscape may be reconfigured by this work.

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