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Review

TRANSDERMAL DRUG DELIVERY: A PERSPECTIVE

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The current status of transdermal drug delivery is reviewed. The advantages and drawbacks of systemic drug input via the skin are detailed. Specific examples of transdermally delivered drugs are considered and the delivery systems employed are described. A kinetic analysis of transdermal drug delivery and percutaneous absorption is presented and its application to the prediction of plasma drug concentration versus time profiles following topical administration is demonstrated. Finally, the outstanding unknowns and areas requiring further research are identified and the prognosis for the future utility of this mode of drug administration is addressed.

INTRODUCTION

Since the introduction of the transdermal delivery system for scopolamine [1], there has been a proliferation of interest in this route of drug administration. This may be attributed to a number of reasons which will be discussed in this review. Little attention has been paid to the limitations of transdermal drug delivery and these will also be addressed in this article. To date a number of drug candidates have been investigated but information in the literature is only available for a few. Most research has been concentrated on nitroglycerin but other published data exist for scopolamine, clonidine, estradiol, timolol and nicotine. On the basis of these results it is possible to produce guidelines concerning transdermal delivery. It is also feasible to predict the rates of percutaneous absorption based on the physicochemical properties of the drug and use this information to assess the optimal conditions for successful transdermal delivery [2].

The advantages of this route for systemic drug delivery may be identified. Of least scientific interest but of practical relevance is good patient compliance. The systems are easy to self-administer and removal provokes an immediate reduction in the plasma levels of the drug. Current transdermal devices provide therapy for periods between one and seven days, thus minimizing repeat dosing intervals. This reduction in dose interval gives an associated decrease in potential side effects. Another advantage is the production of sustained and controllable levels of drug in the plasma. First-pass metabolism is avoided

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although biotransformation can be mediated by either micro-organisms present on the skin surface [3] or enzymes within the epidermis [4]. In certain circumstances, enzymatic transformation may be used to advantage; for example, when the active species is presented to the skin as a prodrug [5].

The limitations of transdermal drug delivery (TDD) are functions of skin physiology and drug bio-activity. The excellent barrier properties of skin are well known [6, 7], and currently limit TDD to only the most potent drugs. In terms of dosage, this criterion implies that drugs, the daily dose of which is 10—20 mg or less, are potential candidates for TDD. There are, in addition, further constraints determined by the physicochemical properties of the drug. For a drug molecule to reach the cutaneous microvasculature, and, hence, the systemic circulation, it must traverse both the lipophilic stratum corneum and the much more hydrophilic viable epidermis (Fig. 1) [8]. Therefore, drugs with a reasonable partition coefficient and possessing solubility both in oil and in water are most ideal. A highly lipophilic compound, for example, may readily enter and diffuse within the stratum corneum but be unable to penetrate deeper into the skin. Its ultimate appearance in the plasma will then be determined by the very slow partitioning process at the stratum corneum--viable tissue interface. There remains no simple relationship between percutaneous penetration and drug molecular weight (M). It is likely that, for essentially simple drug moieties ($M < 600$ daltons), molecular weight has little effect because the partitioning and solubility characteristics dominate. More complex molecules of higher molecular weight ($M > 1000$ daltons), for example peptides and small proteins such as insulin, may be limited in part by their bulk; however, the extremes of lipid solubility manifested by these substances are probably the principal factors. The other major disadvantage of TDD is the potential elicitation of either allergic or irritant responses by the drug or the adhesive of the device. At the present time, there is no way to predict *a priori* the possible inflammatory effects of the drug from its chemical structure and/or properties, although efforts to do so are underway [9].

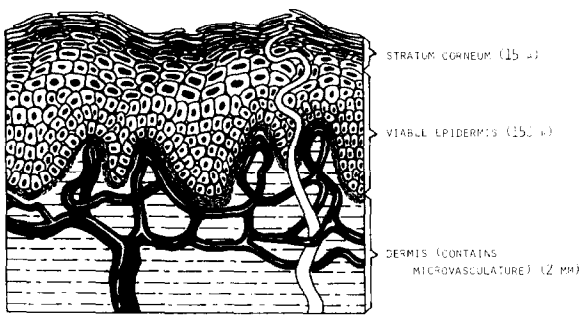

Fig. 1. Skin structure — schematic.

TRANSERMALLY DELIVERED DRUGS

Currently there are four drugs approved in the US for the transdermal route of administration: clonidine, estradiol, nitroglycerin and scopolamine. Other drugs (nicotine, timolol) have also been examined. In this section we review briefly the details of the approaches taken to deliver these agents across the skin of man.

Transdermal delivery of the drugs listed has been accomplished by one of three formulation approaches: (a) using a membrane-moderated device [3, 10], (b) with a matrix system [11, 12], and (c) from a more conventional ointment dosage form. In the former system, a reservoir containing the drug is enclosed on three sides by an impermeable laminate; the remaining side is covered by a polymeric membrane which meters the transport of drug out of the reservoir through an adhesive layer which holds the system to

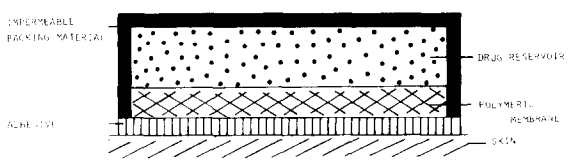

Fig. 2. Diagram of a membrane-moderated transdermal drug delivery system.

the skin (Fig. 2). For the matrix device, the drug reservoir is manufactured by dispersing in some way the drug within a polymeric matrix; transport through the polymeric network controls the release of active agent to the skin. In this type of approach the adhesive may be incorporated between the matrix reservoir and the skin or it may form a non-medicated ring around the periphery of the matrix. Alternatively, in its most recent form, the adhesive itself constitutes the medicated matrix [13]. Initial transdermal delivery of nitroglycerin was achieved using a conventional topical formulation, which acted as a convenient means for keeping a supply of the drug in contact with the skin. In general, little rate control is provided by such a formulation.

1. Clonidine

Clonidine is a potent beta-adrenergic antihypertensive agent which has been incorporated into a membrane-controlled delivery system. The device has been manufactured such that it releases clonidine in a controlled fashion over a seven-day period. In order to achieve the therapeutic levels of clonidine desired (approximately 0.6—1.2 ng/ml) devices with surface areas of 3.5, 5.0 and 10.5 cm^2 have been investigated [14—16]. The release rate of clonidine from these devices has been set between 1.5 and 2.0 $\mu g/cm^2$ h. The 5-cm^2 patch contains 5 mg of drug, of which approximately 0.5 mg is distributed in the adhesive and forms a loading dose delivered initially after application. The system leads to steady-state plasma concentrations being maintained at the target level between, on average, three and seven days post-application (Fig. 3). The rather slow rise to steady state is a function of the biological half-life of clonidine (ca. 9 hours) and the suspected reservoir effect of clonidine in the stratum corneum. Once target therapeutic levels have been attained, removal of the patch and reapplication of a new device to a different skin site leads to maintenance of the appropriate

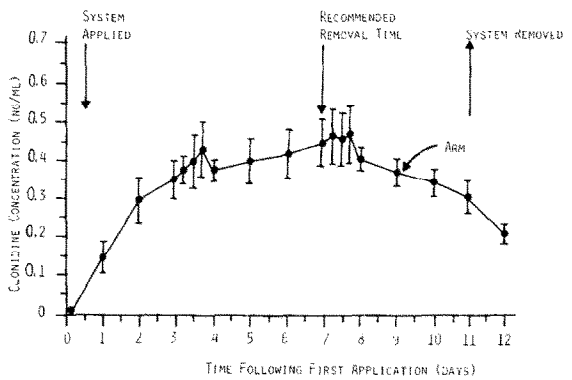

Fig. 3. Clonidine plasma concentrations (mean ± s.e., n = 17) during seven-day application and three days post-removal of a single transdermal device. (Adapted from Ref. [16].)

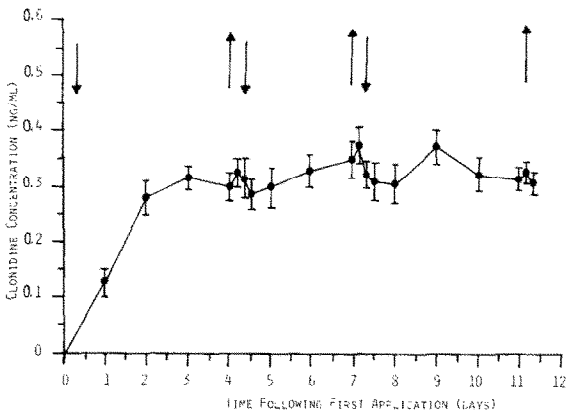

Fig. 4. Clonidine plasma concentrations (mean ± s.e., n = 8) following multidose transdermal delivery. Systems were applied at t = 0, t = 4 days and t = 7 days. (Adapted from Ref. [15].)

plasma concentration (Fig. 4) [15].

Pharmacodynamic assessment of clonidine following transdermal drug delivery shows that efficacy equivalent to that provided by conventional dosing regimens (Catapres tablets, 0.15 mg every 12 hours or Catapres Perlongets, 0.25 mg every 24 hours) can be obtained. Two days after application of the transdermal device, mean arterial blood pressure is consistently reduced and only marginal dry mouth and sedative side-effects are apparent [16–19].

An as yet unresolved issue with respect to transdermally delivered clonidine is the effect

of the agent on the skin. Initial reports [15] indicate that 15—20% of patients treated show local cutaneous reactions. These responses include irritation and sensitization typical of contact dermatitis. Where problems have occurred they tend to be of a minor nature and have resolved after cessation of transdermal delivery. It is generally observed that the skin reactions become apparent several days after application of the transdermal system; it has therefore been suggested that patients showing cutaneous sensitivity change or move their patches at intervals of three to five days rather than after a complete week of therapy.

2. Estradiol

A recent additional example of the membrane-moderated class of transdermal drug delivery system contains the hormone 17β-estradiol. The purpose of this device is to treat symptoms associated with the female menopause (e.g., high incidence of "hot" flashes). Plasma levels following transdermal application of three prototypal systems have been reported (Fig. 5) [23—25]. It has been demonstrated that, in females experiencing severe vasomotor symptoms, transdermal estradiol is efficacious at very low daily delivery rates (0.025 to 0.1 mg/day) [26—28].

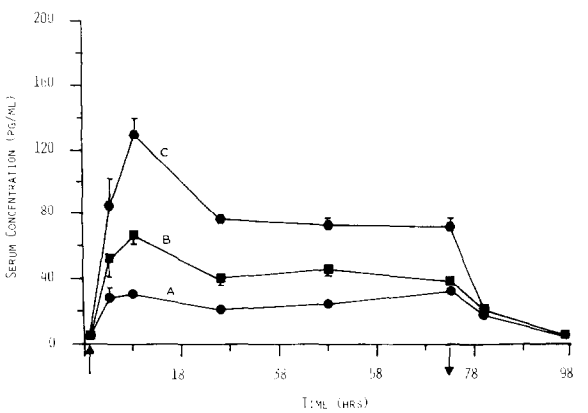

Fig. 5. Estradiol plasma concentrations (mean ± s.e., n = 14) following single three-day applications of 5-cm² (curve A), 10-cm² (curve B), and 20-cm² (curve C) transdermal delivery systems. (Adapted from Ref. [24].)

This administration produces an effect equivalent to a 20—40 fold greater oral dose of the hormone and does not increase the production of liver proteins [29]. An estradiol transdermal delivery system is currently marketed in Europe. A similar device has recently been approved by the U.S. Food and Drug Administration.

3. Nicotine

Only a limited number of studies have been conducted on the transdermal delivery of nicotine [30, 31]. In the experiments reported, nicotine base was administered in a 30% aqueous solution under a 5 cm × 5 cm polyethylene patch. The applied solution (26 μl) was equivalent to a 8-mg dose of nicotine. Plasma levels of nicotine were estimated by determining the amount of nicotine in the saliva of the subjects and were found to be 16 ± 12 ng/ml. The study suggested that transdermal nicotine could reduce craving for cigarettes and has the advantage that it does not produce the bad taste and gastrointestinal problems that are sometimes associated with nicotine chewing gum [32].

4. Nitroglycerin

The exponential growth of interest in transdermal drug delivery has been catalyzed by the development of systems containing the potent vasodilator nitroglycerin (GTN) for the treatment of angina pectoris. To date four transdermal delivery systems have been described [13, 33], in addition to more conventional ointment formulations of the drug. The devices include both matrix and membrane-moderated systems. Thus, for this compound, there is an entire spectrum of transcutaneous input vectors.

Delivery of GTN via the skin had already been established prior to the development of TDD *per se*. Simple formulations containing GTN (e.g., Nitrobid and Percutol 2% ointments) provide effective anti-anginal therapy for periods of up to about 8 hours, consider-

ably prolonging, therefore, the relief possible with conventional sublingual administration [34]. The very short half-life of GTN, coupled with its marked sensitivity to hepatic metabolism, makes it a suitable candidate for TDD. Four limitations characteristic of conventional topical vehicles may be identified, however:

1. The difficulty in obtaining reproducible dosage, both in terms of absolute amount of drug applied and with respect to the area of application.
2. Release of GTN from these ointments to the skin is rapid and the skin controls, therefore, the rate of drug input to the systemic circulation. Because of the variability in percutaneous absorption between individuals and between different skin sites on the same individual, the levels of GTN attained can fluctuate widely in any patient population.
3. Recent work has shown that micro-organisms on the skin surface can metabolize GTN [35, 36]. The effect of this degradation is possibly more pronounced when the drug is presented to the skin in these conventional formulations as compared with polymeric systems in which the GTN is physically protected within the device [3].
4. Elegance and, hence, patient compliance — the ointment must be spread as evenly as possible over a rather large surface area; it is then covered to minimize loss of drug, for example, to the patient's clothing. The dose interval for the ointments is 8-hourly as compared to the daily regimen provided by the newer delivery systems.

Nevertheless, it must be stated that the ointment formulations do have the advantage of low cost and easy conventional production. They do, furthermore, produce therapeutically effective and reasonably sustained levels of GTN as shown in Fig. 6 [37].

Three matrix devices containing GTN have been described (Fig. 7) [13, 33]. The significant features of each system are as follows:

(a) *Deponit-TTS*® : the device consists of a 350-μm thick adhesive film in which the GTN, adsorbed onto lactose, is dispersed [13]. The lactose is inhomogeneously incorporated into the adhesive such that the highest concentration is furthest from the skin. *In vitro*, the TTS releases GTN at a constant rate of approximately 10 $\mu g/cm^2 h$ following an initial burst phase which decays over the first three hours of release (Fig. 8). *In vivo*, appli-

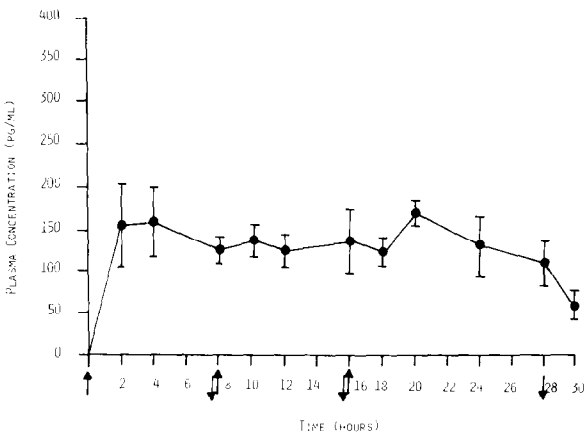

Fig. 6. Nitroglycerin plasma concentrations (mean ± s.e., n = 12) following application of 400 mg of 2% ointment over a skin area of 10 cm^2 at t = 0, t = 8 h and t = 16 h. (Adapted from Ref. [37].)

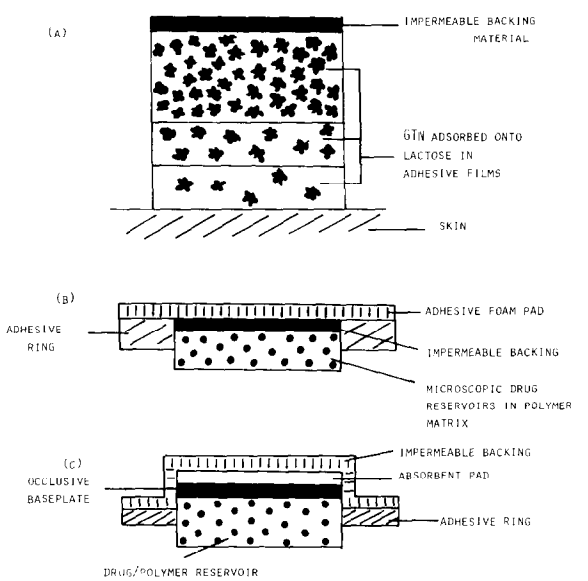

Fig. 7. Diagrams of matrix-type transdermal nitroglycerin delivery systems: (a) Deponit-TTS®, (b) Nitrodisc®, (c) Nitro-Dur®.

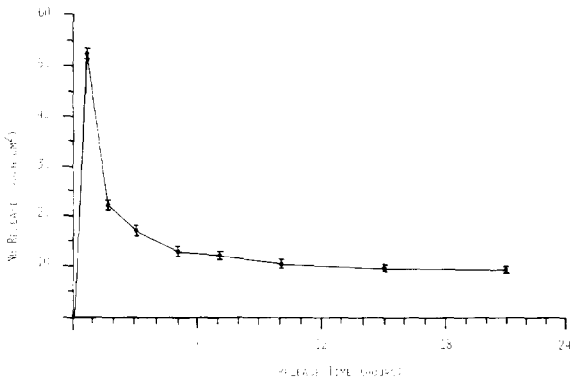

Fig. 8. Release rate (mean ± s.e., n = 4) of nitroglycerin from Deponit-TTS® *in vitro* at 34°C. (Adapted from Ref. [13].)

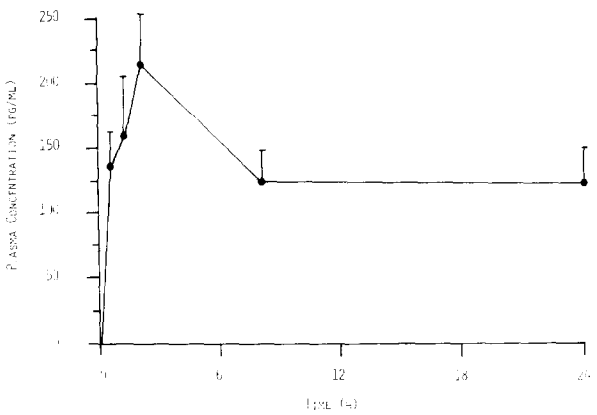

Fig. 9. Nitroglycerin plasma concentrations (mean ± s.e., n = 6) following a single 24-hour application of Deponit-TTS®. (Adapted from Ref. [13].)

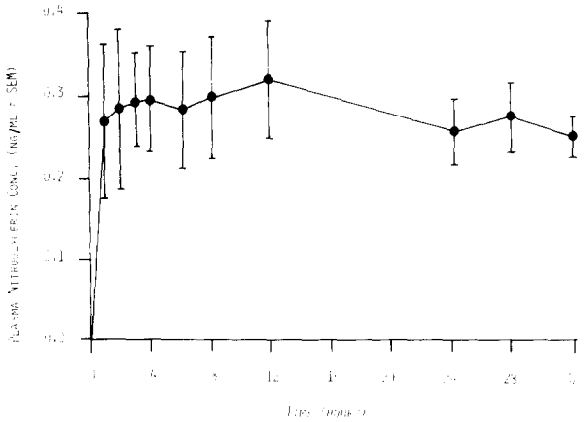

Fig. 10. Nitroglycerin plasma concentrations (mean ± s.e., n = 12) following a single application of Nitrodisc® (16 cm²). (Adapted from Ref. [11].)

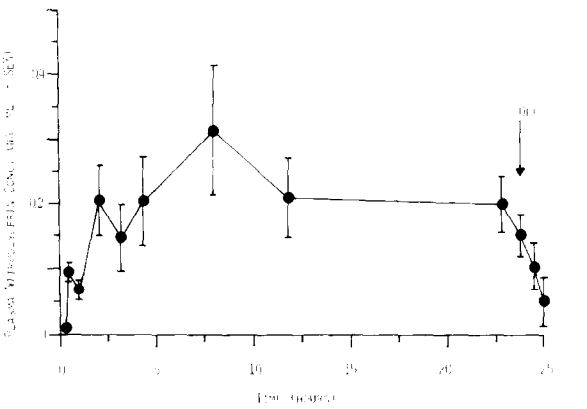

Fig. 11. Nitroglycerin plasma concentrations (mean ± s.e., n = 6) following a single application of a 20-cm² Nitro-Dur® system (removed at t = 24 h). (Adapted from Ref. [33].)

cation of patches 16 cm² in area to six individuals resulted in the mean plasma concentration versus time profile shown in Fig. 9.

(b) *Nitrodisc®* : GTN is dispersed throughout a silicone polymer in liquid microcompartments which act as very small drug reservoirs [11, 38]. The device is, therefore, sometimes referred to as the "microsealed drug delivery system." Unlike Deponit, the adhesive which holds this device to the skin is not involved in the control of drug release. An 8-cm² Nitrodisc containing 16 mg of GTN releases, *in vitro*, about 15 mg drug over 24 hours. It is pertinent to note that for this delivery system GTN is released *in vitro* as a linear function of the square root of time. When administered to humans, a larger version of the system (32 mg over 16 cm²) produces the plasma levels shown in Fig. 10.

(c) *Nitro-Dur®* : GTN is distributed homogeneously as a lactose triturate throughout a polymeric matrix containing polyvinylpyrrolidone and poly(vinyl alcohol) [12]. This system also releases GTN linearly with the square root of time: from a 10-cm² patch containing 51 mg of drug, 40—45 mg are released in a 24-hour period. *In vivo*, a 30-cm² system produces mean plasma concentrations

as a function of time as depicted in Fig. 11 [33]. Very recently, the FDA has approved Nitro-Dur II which contains GTN in acrylic-based polymer adhesives with a resinous cross-linking agent. The elegantly simple system is produced in a range of dosage strengths which deliver from 2.5 mg/24 h (5 cm^2) to 15 mg/24 h (30 cm^2).

The fourth transdermal GTN device (Transderm-Nitro®) is a membrane-moderated system essentially similar to that described above for clonidine [10]. Into an aqueous receptor phase *in vitro*, the patch releases GTN with zero-order kinetics (ca. 40 $\mu g/cm^2$ h) between 2 and 16 hours following an initial rapid burst effect. Application of a 10-cm^2 device to human subjects elicits the plasma concentration versus time profile shown in Fig. 12 [10, 37, 40].

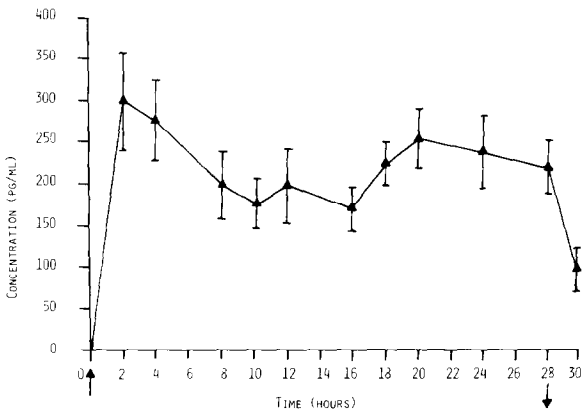

Fig. 12. Nitroglycerin plasma concentration (mean ± s.e., n = 12) following application of two 10-cm^2 Transderm-Nitro® devices from t = 0 to t = 28 h. (Adapted from Ref. [37].)

Despite the clear engineering differences between the systems described, Figs. 9—12 demonstrate that remarkably similar plasma levels are obtained *in vivo*. This is in part due to the physicochemical properties of GTN and the kinetic control provided by the stratum corneum. It is transport across the stratum corneum which dictates primarily the systemic concentrations observed. For some subjects, for whom the skin site of application is particularly permeable, the devices will control to a larger extent the input rate of GTN. In this way, potential overdosing and unpleasant side-effects can be miminized, especially if patients self-administer the device to a skin site which is damaged.

However, a significant question at this time is the desirability of continuous GTN dosing as provided by TDD. It is established that GTN is a drug to which tolerance may develop [41]. It is also apparent that drug efficacy following repeated transdermal administration may be compromised. A major multi-center clinical trial involving three U.S.-approved delivery systems is now underway, with particular attention focussing upon GTN pharmacological effect as opposed to simple pharmacokinetic behavior. Public discussion of the efficacy of transdermal GTN has been conducted in the letters and editorial sections of many medical and cardiology journals. Perhaps the only point of agreement is that the issue remains unresolved and warrants concern and physician care in the prescribing of these dosage forms [42]. Parenthetically, it should be added that the problem is not confined to GTN — a recent report, which considered the efficacy of transdermal isosorbide dinitrate, revealed similar tolerance behavior [43].

5. Scopolamine

The first drug to be delivered successfully across the skin was scopolamine, for the treatment of motion sickness. Again, the device is of the membrane-moderated configuration (see above) [1]. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. The *in vitro* release characteristics are illustrated in Fig. 13 [1]. There is an initial burst of drug, which is liberated from the adhesive, followed by zero-order release from the reservoir at 3.8 $\mu g/cm^2$ h. This steady release is maintained over a three-day period, the suggested lifetime of the device.

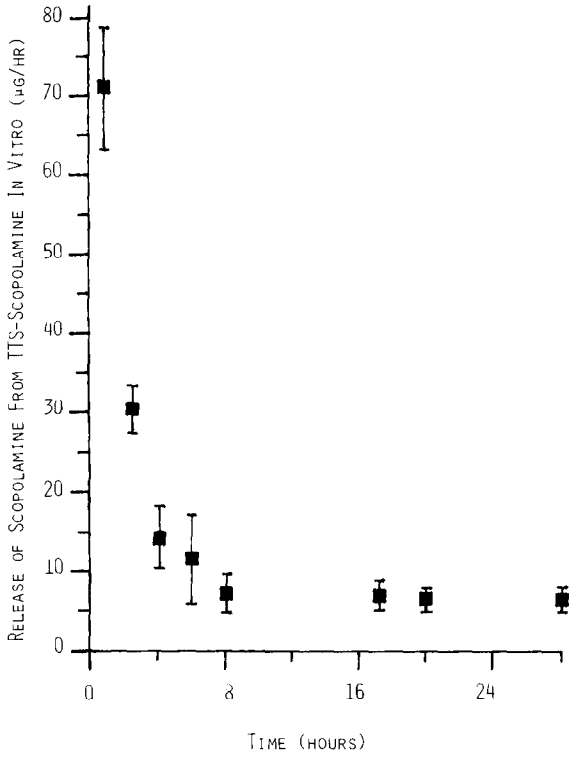

Fig. 13. Release rate of scopolamine from Scopolamine-TTS (Scopoderm®) *in vitro*. (Adapted from Ref. [1].)

In vivo, the ability of the scopolamine system to provide an analog of an intravenous infusion has been evaluated by monitoring drug urinary excretion rates during its delivery by the two modes of administration. The results are shown in Fig. 14 [44]. The transdermal excretion rate shows a peak value at 12—24 hours before settling to essentially the same rate as that seen following i.v. infusion. The difference at this early time is due to the rapid release of the loading drug dose in the contact adhesive of the patch. After removal of the patch, the urinary excretion rate falls to background levels more slowly than at the termination of i.v. infusion. This is because the skin contains a reservoir of scopolamine which is depleted at a rate less than the intrinsic clearance of the drug. In a brief study, plasma levels of scopolamine have also

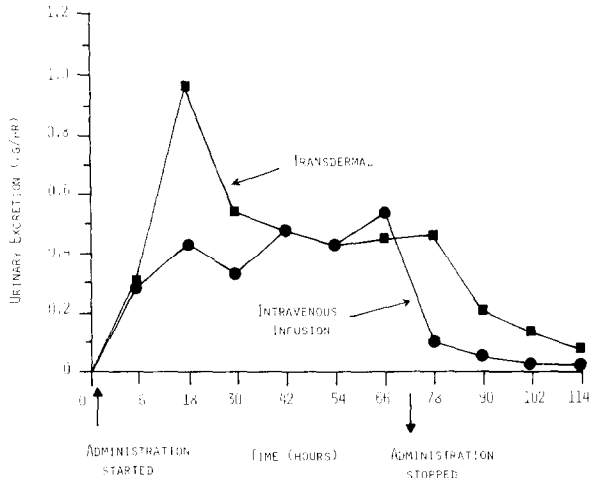

Fig. 14. Scopolamine urinary excretion rates (mean + s.e.) following transdermal (n = 7) and intravenous (n = 6, 3.7—6.0 µg/h) administration. Drug input was stopped at t = 72 h. (Adapted from Ref. [1].)

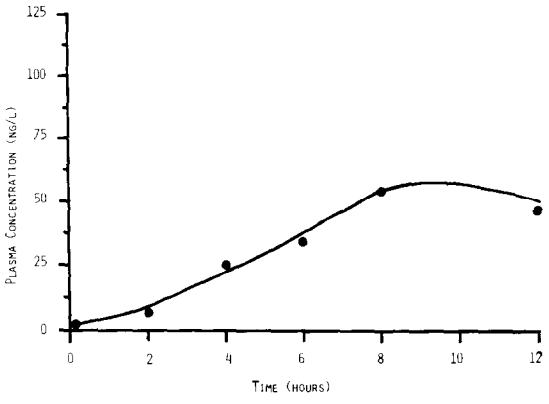

Fig. 15. Average (n = 4) scopolamine plasma concentrations following transdermal delivery. (Adapted from Ref. [45].)

been followed over a shorter period of time after TDD (Fig. 15) [45].

The relief of unwanted side-effects is a major advantage of the scopolamine transdermal system. The tachycardia and drowsiness associated with intramuscular scopolamine are minimized, although two-thirds of subjects tested experienced transient dry mouth. The efficacy of the system as compared with more conventional therapy has been thoroughly tested in a number of "real-

life" situations in which volunteers have been subjected to extreme oscillatory motions (e.g., seven days on heavy seas, various exposure times on a vertical oscillator) [46—52]. As with clonidine, it should be noted that a number of skin irritant responses have been observed; for example, two reports have cited an incidence of approximately 17% irritation. The reaction, however, did not increase in frequency after 72 hours of continuous patch use [52].

6. Timolol

A recent publication cited the transdermal delivery of the beta-blocking agent timolol [53]. This drug is subject to first-pass metabolism and TDD, therefore, would be an attractive route of administration. In the initial evaluation, the drug was administered in Plexigel 50 W (5% w/w polyethylene in mineral oil). The vehicle contained either 30 or 60 mg of timolol which was spread over a 25-cm^2 area of the skin. The formulation was applied to the chests of six volunteers. The application time was 30 hours and resulted in the plasma concentration—time profiles exemplified by Fig. 16. Timolol caused some skin irritation, although, in general, this was considered to be mild. Systolic blood pressure was reduced and post-exercise heart rate was suppressed in all subjects, thereby indicating significant beta-adrenergic blockade.

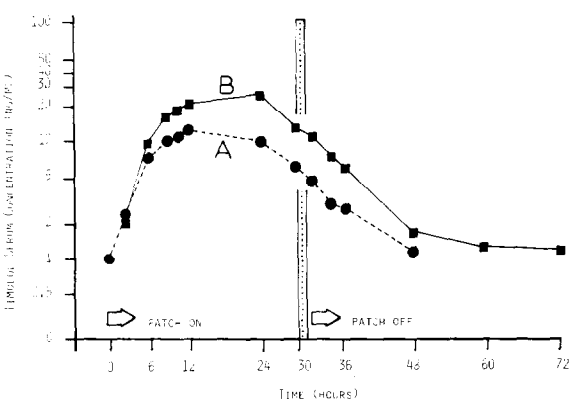

Fig. 16. Representative timolol serum concentration versus time profiles during transdermal delivery and following topical gel removal (at t = 30 h). Curve A obtained after a 30 mg application, curve B subsequent to a 60 mg topical dose. (Adapted from Ref. [53].)

KINETIC APPRAISAL OF TDD

Since transdermal delivery depends on the diffusion and partitioning of the active drug across the stratum corneum and viable tissue, it should be possible to predict the feasibility of TDD from the physicochemical properties of the drug. This has been achieved with some success using the linear kinetic model depicted schematically in Fig. 17 [54—57].

The kinetics of drug input from the system are described by k_{in}. This function may take many forms but has been considered either as the sum of zero-order and first-order processes or as a simple first-order event. The rate constant k_r relates to drug partitioning at the device/stratum corneum boundary and, for an ideal delivery system, this parameter will be very small. Drug diffusion across the stratum corneum and further transfer through

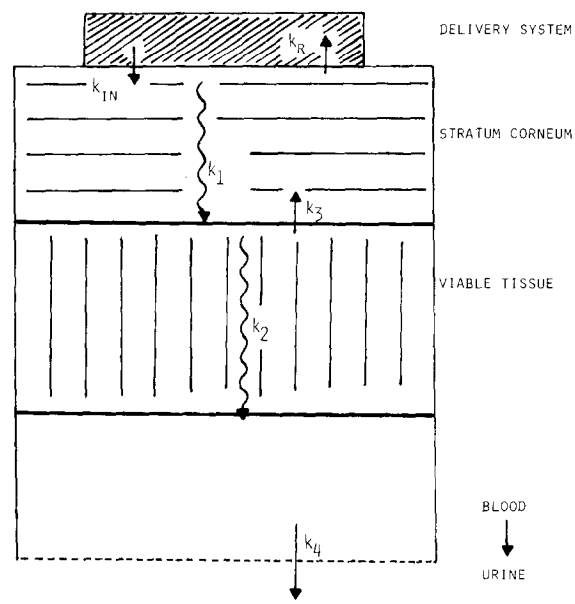

Fig. 17. Kinetic model for percutaneous absorption and transdermal drug delivery [54—57].

the viable epidermis are described, respectively, by k_1 and k_2. The values of these two rate constants are related to the molecular size and hence to the cube root of the molecular weight of the permeant [58]. There is a concentration discontinuity at the stratum corneum/viable tissue interface which results from the disparate environments of these two regions of the skin. The outer layer is lipophilic in nature whilst the inner is aqueous. The partitioning of the drug at the interface is described by the ratio k_3/k_2 and it has been shown empirically that this ratio can be described by $K/5$, where K is the octanol/aqueous pH 7.4 buffer partition coefficient [58]. Elimination kinetics of the drug from the blood are modelled by the rate constant k_4. For certain compounds a more complex excretion function may be necessary. This process cannot be predicted from the physicochemical properties of the drug. It is essential therefore that the clearance of the compound following i.v. administration be known in order that TDD feasibility can be evaluated. It should be stated that some drugs may be subject to metabolism as they pass through the epidermis and that this can also be modelled by the inclusion of appropriate rate constants [59].

Using the approach, transdermal delivery of GTN and clonidine has been modelled [55, 56]. Good agreement between *in vivo* plasma concentrations and the simulations has been obtained. Recent publications reporting pharmacokinetics of estradiol, scopolamine and timolol following TDD permit further validation of the model [60]. In Table 1, the appropriate transdermal rate constants, based on the physicochemical properties of these three latter compounds, are presented. To predict the plasma levels, the additional information in Table 2 is required. This table contains the following parameters:

1. k_{in} — For estradiol and scopolamine, k_{in} consists of two terms, k^0 and k_a. The first term, k^0, describes the zero-order rate of drug permeation across the rate-limiting membrane. This parameter is determined from an *in vitro* release experiment [24, 44]. The second term, k_a, is a first-order rate constant describing the release of the drug from the adhesive. The value of k_a has been assessed for the scopolamine patch [44] and this constant has been taken as being representative for other drugs delivered from similar membrane-moderated devices [55, 56, 60].

TABLE 1

Transdermal rate constants for estradiol, scopolamine and timolol [60]

	Estradiol[a]	Scopolamine[b]	Timolol[c]
k_1 (h^{-1})[d]	0.141	0.136	0.134
k_2 (h^{-1})[e]	2.22	2.14	2.11
k_3 (h^{-1})[f]	137	7.44	34.3

[a]Estradiol: molecular weight = 272.4 Da, log K = 2.49.
[b]Scopolamine: molecular weight = 303.4 Da, log K = 1.24.
[c]Timolol: molecular weight = 316.4 Da, log K = 1.91.
[d]Calculated from $k_1 = C_1 M^{-1/3}$, where C_1 is a known constant [58] and M = molecular weight.
[e]Calculated from $k_2 = C_2 M^{-1/3}$, where C_2 is a known constant [58] and M = molecular weight.
[f]Calculated from the equation $k_3/k_2 = K/5$ [58].

TABLE 2

Additional physicochemical and pharmacokinetic information for estradiol, scopolamine and timolol, used in the predictions of plasma concentration versus time profiles following transdermal delivery [60]

	Estradiol	Scopolamine	Timolol
k^0 ($\mu g/cm^2\,h$)	0.21	3.8	—
k_a (h^{-1})	1.3	1.3	1.3
k_r (h^{-1})	10^{-4}	10^{-4}	10^{-4}
k_4 (h^{-1})[a]	13.9	0.619	0.169
V (l)[b]	4.81	70	164
A (cm^2)	20	2.5	25
M (mg)	0.1	0.15	60

[a]$k_4 = \ln 2/t_{0.5}$ where $t_{0.5}$ is the drug half-life: for estradiol, 0.05 h [62]; for scopolamine, 1.12 h [44]; and for timolol, 4.1 h [61].
[b]V is evaluated for a 70-kg adult.

2. k_T — This rate constant has been set at 10^{-4} h^{-1} to reflect the fact that the topical systems have been efficiently formulated. The drugs have, therefore, a lower affinity for the vehicle than for the skin.
3. k_4 — The elimination rate constant as assessed by regular pharmacokinetic procedures and reported in the literature [61, 62].
4. V — The volume of distribution has been obtained from standard texts [61, 62] or (in the case of scopolamine) inferred from i.v. infusion data [44].
5. A — The area of application of the transdermal delivery system as reported in the recent investigations.
6. M — The amount of the drug incorporated into the adhesive, which acts as a loading dose, or (in the case of timolol) the amount of drug in the vehicle.

Agreement between the predictions of the kinetic model, based on the parameters in Tables 1 and 2, and the recently published *in vivo* data is shown in Figs. 18, 19 and 20 for estradiol, scopolamine and timolol, respectively. The results indicate that the simulation can predict very adequately the plasma-level time course of these drugs following TDD.

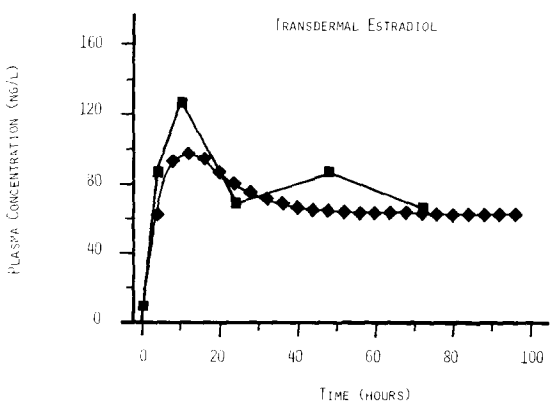

Fig. 18. Predicted [60] and *in vivo* [24] plasma concentration versus time profile for estradiol following transdermal delivery. The theoretical curve, which includes a baseline estradiol concentration of 8 pg/ml, was calculated from the parameters in Tables 1 and 2.

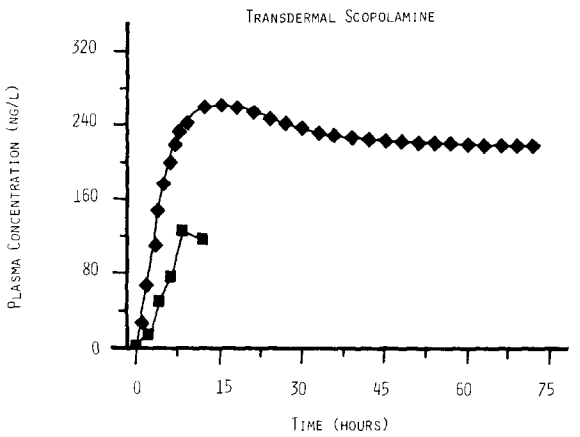

Fig. 19. Predicted [60] and *in vivo* [45] plasma concentration versus time profile for scopolamine following transdermal delivery. The theoretical curve was calculated from the parameters in Tables 1 and 2.

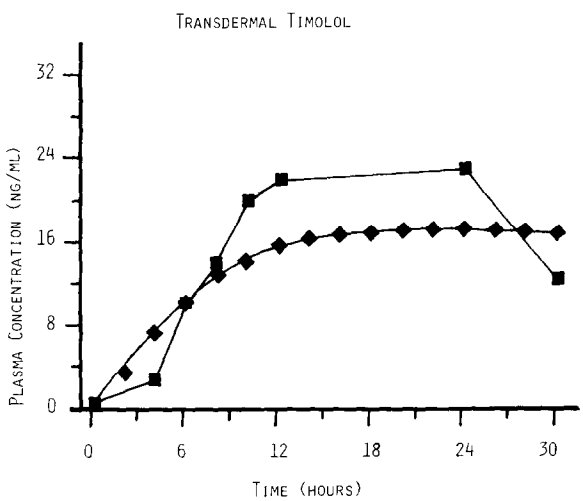

Fig. 20. Predicted [60] and *in vivo* [53] plasma concentration versus time profile for timolol following transdermal delivery. The theoretical curve was calculated from the parameters in Tables 1 and 2. The *in vivo* data are a representative set following a 60 mg topical dose in a gel vehicle.

COMMENT

The applicability of TDD is most limited at the present time by the necessity that the drug be extremely potent. It is possible that higher doses of drugs can be delivered through

the skin in the presence of penetration enhancers. A number of these agents have been identified and tested to various degrees, although none as yet are incorporated into marketed delivery systems. The estradiol patch contains a significant amount of ethanol [24] and it has been suggested that this solvent does in fact act as a promoter of hormone absorption through the skin. This hypothesis contradicts the stated purpose of the ethanol, namely to solubilize the estradiol within the patch reservoir. The simulation performed in the preceding section for estradiol assumes that the ethanol has no influence on skin permeability. The good agreement between prediction and experimental data supports the solvation, as opposed to a specific promotion, role of the alcohol.

There are potential problems associated with the incorporation of adjuvants into a transdermal formulation. Because an enhancer must act upon the skin in order for delivery to be improved, additional materials (e.g., the promoter itself or co-solvents) will gain access to the systemic circulation and to the local viable cutaneous tissue. There is an increased possibility, therefore, of irritant responses and other unwanted side-effects.

The degree of cutaneous metabolism which a transdermally delivered drug may experience is not well-defined. On a weight per weight basis, it has been calculated that the skin has an equivalent metabolizing capacity to that of the liver [4]. Of course, only a rather small fraction of skin surface area is in contact with a transdermal device at any particular moment and it is unlikely, therefore, that the "cutaneous first-pass effect" can approach that of the liver. For GTN, which is a drug very sensitive to metabolic degradation, skin metabolism in the rhesus monkey has been estimated to be about 16% [63].

Biotransformation by microflora on the skin surface has also been shown to be significant for GTN *in vitro* [35, 36]. With current experimental techniques, it is difficult to verify the exact site of topical drug metabolism. Advantageous use of the metabolizing capability of the cutaneous enzymes can also be identified. A number of examples of topical prodrugs have been prepared and delivered in model systems [5]. The majority of these examples are designed for the improvement of local action. Application of the approach to TDD has not yet been reported.

For any sustained delivery system, the desirability of maintaining a constant therapeutic drug level over a prolonged period of time can be questioned. Care must be taken to evaluate the drug for the occurrence of tachyphylaxis and/or tolerance following chronic and sustained administration. All devices manufactured to date provide essentially continuous drug input but it is not unreasonable to imagine the design of a TDD system which is programmed for pulsed delivery. In a similar context, the question of patient compliance should be considered. Generally, it would be advantageous to have a system which the patient has to replace either on a daily or weekly basis and this should be an important consideration in the engineering of new transdermal devices.

Two additional potential difficulties can be identified. Firstly, the site of application may influence the plasma levels obtained following TDD if the device releases drug at a rate which is comparable with the permeability of the skin. Differential availability may result, therefore, depending upon whether the application site is one of relatively high or relatively low permeability. The post-auricular position is one of high permeability and is recommended for the delivery of scopolamine from the marketed TDD system. Secondly, for membrane-moderated devices with a liquid reservoir, there is a possible risk of overdosing if the membrane becomes damaged. Since the skin is an excellent barrier to the ingress of molecules, the hazards involved are small except for drugs which are extremely potent and those agents for which the incidence of local reactions are high.

Finally, the growth of the biotechnology industry is leading to the production of many drugs which are peptides or their analogs.

These agents are highly potent and, at first sight, may be considered as ideal candidates for TDD. However, the nature of the barrier function of the skin is such that permeation of these molecules may be very low. Unless either (a) safe and reproducible means are found to reduce, in a controlled fashion, the stratum corneum resistance, or (b) the molecules can be engineered with favorable partitioning characteristics and reasonable oil and aqueous solubilities, then the transdermal delivery of these moieties will be difficult to achieve. TDD, therefore, is not a universal panacea for new drug input. The problems associated with topical administration are manifold and are not completely resolved at this time. In this review, we have attempted to highlight the progress which has been made and the challenges which remain. TDD is not a subject which can be approached simplistically without a thorough understanding of the physicochemical and biological parameters of percutaneous absorption. Researchers who attempt TDD without appreciating this fact do so at their peril.

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