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Transdermal drug delivery and cutaneous metabolism

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1. The delivery of drugs via the skin to achieve systemic therapeutic effect is currently under intense investigation.

2. The skin offers unique advantages and limitations for drug input into the body. For example, while hepatic first pass may be circumvented, the excellent barrier function of the stratum corneum (the thin outermost layer of skin) precludes, at present, all but the most potent drugs from this route of administration.

3. Examples of approved transdermally delivered drugs are scopolamine, nitroglycerin, clonidine and estradiol. The delivery systems which have been formulated for these agents have been designed to provide essentially zero-order input kinetics for between 1 and 7 days.

4. The impact of cutaneous metabolism on transdermal drug delivery has not yet been evaluated rigorously. Limited *in vivo* data for nitroglycerin suggest a cutaneous first pass effect of between 10 and 20%.

5. More work has been directed towards the use of topical prodrugs and the design of molecules better able to transport across the stratum corneum and then undergo local enzymatic activation.

6. Further research in this area will require a more specific quantitative understanding of the metabolic capabilities of human skin *in vivo*.

Introduction

The design of new drug delivery systems has become an area of major activity in the pharmaceutical industry. One of the most intensively studied routes of administration currently under consideration is the transdermal route (Guy and Hadgraft 1985 a). Although a key function of the skin is to provide a physical barrier to the ingress of chemicals into the body, it has been shown over the last 5 to 10 years that drug delivery across this tissue is possible (Arndts and Arndts 1984, Chandrasekaran 1983, Good 1983, Imhof *et al.* 1984, Karim 1983 a, b, Laufer *et al.* 1983, Lawson 1985, Muir and Metcalfe 1983, Price *et al.* 1981, Rose *et al.*, 1985, Schenkel *et al.* 1985, Vlasses *et al.* 1985, Wolff *et al.* 1985). Transdermal drug delivery can be used to achieve effective and sustained plasma concentrations in the systemic circulation and in the biophase at the site of action. It is the purpose of this paper to review and identify the potential and the difficulties which are associated with this means of drug delivery.

We first review the important structural and biochemical features of human skin and those characteristics which contribute to the barrier function are delineated. The interaction between the physical chemical properties of the drug with these biological criteria to control and limit the rate of drug access into the body via the skin is demonstrated. In turn, an appropriate model of the transdermal delivery process is established and tested. The question of cutaneous metabolism and its possible impact upon transdermal drug delivery is then addressed. The processes

which can cause inactivation of drug during its progress from a delivery system to the systemic circulation through the skin are identified. An attempt is made to establish the levels of metabolism which can be deemed significant with respect to this route of drug input. Also addressed briefly are questions relating to the design of suitable pro- or soft drugs for topical application such that advantageous use of the cutaneous metabolic apparatus can be obtained. Finally areas of research in this field which require further work at this time are specified.

Skin structure and function

Human skin consists of two important tissue layers, the epidermis and the dermis (figure 1) (Montagna 1974). The epidermis results from an active epithelial basal cell population and is approximately 150 μm thick. It is the outermost layer of skin, and the process of differentiation leads to the migration of cells from the basal layer towards the skin surface. As this process occurs the cells move away from the source of nutrient supply and undergo the process of keratinization. The end result of this process is the formation of a thin stratified and extremely resilient layer (the stratum corneum) at the skin surface. The statum corneum is, on average, approximately 20 μm in thickness, each cell layer occupying approximately 0·5–1·0 μm. The keratinocytes are hard flattened cellular components with reinforced cell membranes. The interior of the cells is filled with proteinaceous keratin. The intercellular space is occupied by a complicated lipid mixture which forms the 'mortar' holding the keratinized 'bricks' together (Elias 1983). The epidermis rests upon the much thicker (2000 μm) dermis. The dermis contains a dense capillary network and it is this microvasculature which resorbs penetrating drug molecules and makes them available in the systemic circulation. An important physical feature of the skin is its transition from an essentially lipophilic membrane, namely the stratum corneum, to a tissue much more aqueous in nature within the viable epidermis and dermis. We will show how this change in the physical properties of the skin can exert a significant effect on the rate of transport of materials across the tissue.

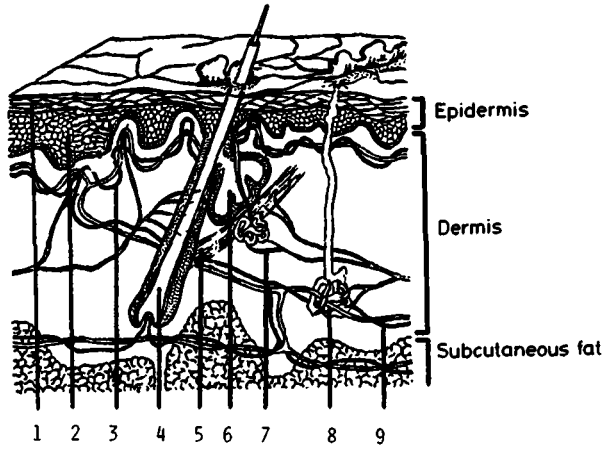

Figure 1. Anatomy of skin—schematic.

1. Stratum corneum; 2. Viable epidermis; 3. Capillary; 4. Hair follicle; 5. Smooth muscle; 6. Sebaceous gland; 7. Nerve fibre; 8. Eccrine gland; 9. Lymphatic.

The viable epidermis and the dermis are sites of high metabolic activity. The epidermis contains many enzyme systems because of its role in providing a replicating epithelial cell layer. The activity in the dermis is primarily associated with the sebaceous glands and the hair follicles in which considerable amounts of protein are synthesized on a continual basis. The number of enzymes present in the skin is extensive and the biotransformation reactions which the skin can carry out are also very broad (Bucks 1984). The extent of the skin's ability to perform chemical reactions is addressed in more detail below.

Transdermal drug delivery

The use of skin as a route of administration for drugs designed to elicit systemic effects is advantageous in a number of ways that will become apparent. A conventional topical dosage form, such as an ointment or a gel, however, may not be desirable for this purpose. The patient has to apply enough of the formulation to an area of skin sufficiently large to permit the flux of drug across the skin into the body to be such that the appropriate level within the biophase can be maintained. The use of a conventional dosage form requires that we pay attention to certain administration parameters such as the area of skin covered, the thickness of the applied phase, the extent to which the material should be massaged into the skin and whether the site should subsequently be occluded (i.e. covered) with a dressing. This rather arbitrary means of dosage application has, as a major consequence, variability in terms of the resulting pharmacological effect because the amount of drug administered is not well controlled and, as a result, the duration and extent of the therapeutic response is also subject to variability. The aim of a transdermal drug delivery system, therefore, is to deliver the active constituent into the systemic circulation through the skin at a predictable rate. The transdermal device should present the drug at a level which has been determined to be appropriate to elicit the desired pharmacological effect and the device should be of an area which will facilitate the attainment of this desired concentration within the biophase.

The advantages of transdermal drug delivery have been documented in previous publications (Barry 1983, Heilmann 1984) and can be summarized as follows.

1. The cutaneous route of drug input means that gastrointestinal and hepatic first pass metabolism are avoided. However, the route exposes the drug to the cutaneous metabolic apparatus and we will consider the possible ramifications of this fact later in the discussion.
2. If the system is well designed and delivers drug into the body at a rate which is system (as opposed to skin) controlled, then this means of drug administration will minimize both inter- and intra-patient variability.
3. The transdermal route of administration is ideal for the maintenance of a constant drug concentration within the biophase. This may not always be the desired result, in which case the judicious application and removal of transdermal patches may be necessary in order to produce the optimal sequence of pharmacologic effect.
4. The sustained nature of drug input available with transdermal delivery means that the duration of effect elicited by the drug may be extended.
5. Because of advantage 1, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary if, for example, the drug is given orally.

6. As a result of advantage 5, the frequency of drug dosing may be reduced and the possibility that the drug be over- or under-dosed is decreased.
7. In turn, the fact that drug needs to be given either in smaller quantities or on fewer occasions means that there is a good chance of improved patient compliance because of the simplified medication regimen.
8. Finally, because the medication is delivered into the system via an external device, drug input can be terminated at any point by the facile removal of the transdermal system. Of course material which has already partitioned out of the system and into the skin is less easily removed, but one is confident of the fact that only this material can enter the body once the patch is taken from the skin.

These advantages of transdermal drug delivery are of course counterbalanced by a number of limitations. The limitations principally relate to the fact that the stratum corneum of the skin forms an excellent barrier to the penetration of all materials into the body. Indeed, human skin evolved in order to provide an efficient and resilient container to keep the important materials (particularly water) of the human system within and to keep undesirable chemicals without (Flynn 1979). Thus, the first category of limitation that one can state for transdermal drug delivery is that the drug must be capable of skin penetration. What does this mean in terms of the physicochemical properties of the drug molecule? Firstly, the drug will probably have a molecular weight less than approximately 1000 daltons. There is nothing clear-cut about the number 1000, it merely reflects the fact that most simple drug molecules have molecular weights which fall below this figure. Chemicals which have molecular weights in excess of 1000 are typically complex—for example polymers, peptides and proteins. These materials are known to penetrate skin extremely poorly but the reason for this is probably not their size but is more likely related to their partitioning characteristics.

The partitioning behaviour, in fact, is particularly important. The skin is a multi-laminate membrane and changes from an avascular and lipophilic material (i.e. the outermost stratum corneum) to a much more aqueous internal structure, the viable epidermis and dermis, which are the sites of uptake of permeating drug into the systemic circulation. The successful permeability of a drug therefore requires that the molecules have solubility in the lipophilic environment of the stratum corneum and in the more aqueous environment of the viable epidermis and dermis. A drug cannot be exclusively soluble in just one phase, it must show solubility in both oil and aqueous phases.

A clear physiological limitation of transdermal drug delivery pertains to the effect which the drug itself elicits on the skin. The skin is a very sensitive organ of the body and displays insult in the form of irritation or allergic reaction. Thus, any drug molecule which causes such irritation or allergic reaction in a significant fraction of potential patients cannot be considered a viable candidate for transdermal delivery.

The excellent barrier function of the skin imposes a major limitation on the drug with respect to required dosage. At the present time successful transdermal candidates are potent drug molecules for which the daily dose is on the order of milligrams per day only. Thus, the resulting concentrations in the plasma are very small and are likely to be in the ng/ml range or less.

Other criteria which the drug will probably satisfy in order to be considered a viable transdermal candidate are the following: first, drug candidates will have short

biological half-lives. This is not a property inherent to transdermal drug delivery but is inherent to any form of sustained drug input; there is no need to control carefully the delivery of a drug with a very long biological half-life—the elimination kinetics themselves are capable of maintaining the desired, prolonged, duration of effect. Drugs, which are subject to extensive first pass metabolism, would of course be reasonably good transdermal candidates although given the topic of this paper we must pay attention to the potential for cutaneous metabolism and we must ask the question as to the magnitude of any potential cutaneous first pass effect. Drugs which do have short biological half-lives, and which are subject to extensive first pass metabolism, invariably require inconvenient conventional dosage regimens either orally or intravenously; this requirement, in turn, frequently produces side-effects and patient compliance difficulties. Drugs which do manifest these undesirable features may fall into the category of feasible transdermal candidates.

To illustrate these points, consider the drugs currently approved by the FDA as transdermal dosage forms in the US. Four compounds are immediately identifiable in this group. Scopolamine was the first approved transdermal device for the treatment of motion sickness. Nitroglycerin (GTN) then received FDA approval and triggered a huge interest in the transdermal route of drug administration. There are five GTN devices approved in the US and four are marketed in Europe. The third drug is clonidine, which recently received approval for the treatment of hypertension; this is a compound for which the irritation question has been debated carefully with respect to its long term potential as a transdermal drug (Weber *et al.* 1984). Estradiol for the treatment of female menopausal symptoms is the latest drug to receive approval; the data which have been released on this compound demonstrate persuasive pharmacokinetic and pharmacodynamic advantages for the cutaneous route of administration (Laufer *et al.* 1983, Schenkel *et al.* 1985).

Metabolic effects on transdermal drug delivery

To ascertain the effect of metabolism on the delivery of drugs through the skin requires: (*a*) careful consideration of the processes which control the passage of drug across the skin, and (*b*) knowledge of the magnitude of any biotransformation process which can act on the drug during its passage across the skin. However, the experimental evaluation of cutaneous metabolism as it pertains to drug delivery has not yet been achieved in any systematic or quantifiable fashion. What has been achieved at this time is:

1. An ability to understand transdermal drug delivery in terms of the physicochemical properties of the penetrant and the biological properties of the skin, and
2. A knowledge of the enzymatic richness of the epidermis and the types of biotransformation which may be encountered during a chemical's passage through the skin.

In this section, we describe a model for the transdermal movement of topically applied drugs and we assess how biotransformation can alter the ultimate plasma concentration versus time disposition profile of the administered compound. Quantitative answers for specific drugs utilizing this approach cannot, at this time, be made because the metabolic efficiency of the relatively small area of skin that a particular molecule might encounter following application has not yet been

determined. However, we can identify the extent to which metabolism could be significant (given that the transformation process operates with a certain efficiency) and these calculations permit assessment of the maximum possible metabolic degradation which might occur in transdermal drug delivery.

The process of percutaneous absorption is complicated and involves a large number of processes occurring either consecutively or simultaneously. To describe this myriad of events in a single and simple model is impossible. As a result, when an attempt is made to formulate a simulation for percutaneous absorption one has to incorporate the most significant events which have been experimentally identified and verified, and to concentrate attention on these specific events. If this approach is valid as a first approximation, re-evaluation of those processes for which less experimental verification and knowledge exists, and how these events can produce changes in the ultimate disposition of the drug in the biophase, can be considered.

Current understanding of transdermal drug delivery and percutaneous absorption permits identification of six key events which must occur in order for a drug to be released from a transdermal system and to appear in the systemic circulation (Guy and Hadgraft 1985 a):

1. Drug transports within the delivery system to the device–stratum corneum interface;
2. Drug partitions from the transdermal device into the stratum corneum;
3. Drug then diffuses through the layers of the stratum corneum.
4. Drug partitions from the stratum corneum into the much more aqueous in nature viable tissue;
5. Drug diffuses through the viable epidermal and dermal tissue;
6. Drug encounters the cutaneous microcirculation, enters a blood vessel and becomes systemically available.

One can envisage, therefore, the establishment of a concentration gradient of the drug from the device across the skin as shown in figure 2. The key words in the six basic steps identified above are diffusion or transport and partitioning. It is these processes, and the physical chemical properties of the drug that influence these events, which exert the most crucial control over the transcutaneous process. A comprehensive model of percutaneous absorption, therefore, would involve consideration of equations based on Fick's 2nd Law of Diffusion for the drug within the

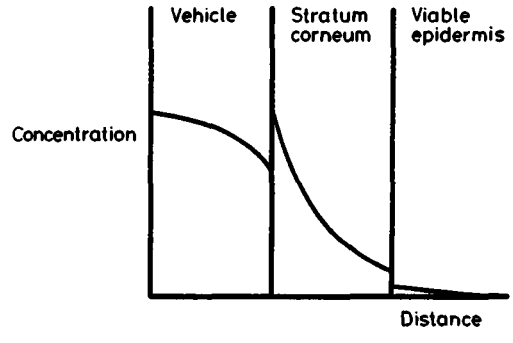

Figure 2. The concentration gradient of a topically delivered drug from the applied formulation and across the stratum corneum and viable epidermis.

device, the stratum corneum and the viable tissue, and the solution of these equations with appropriate boundary conditions. Such modelling is possible, and the equations can be solved with appropriate computer and mathematical techniques (Albery *et al.* 1983, Albery and Hadgraft 1979 a, 1979 b, Fox *et al*, 1979, Gienger *et al.* 1986, Guy and Hadgraft 1980, 1982, 1983, Hadgraft 1979, 1980, Michaels *et al.* 1975, Yu *et al.* 1979). However, when this approach is taken the correspondence between the model and the physiological system becomes less direct, and the interpretation of results more complex. To avoid this, we have developed a simple linear kinetic model (figure 3), which incorporates the basic features of the key events and does so in a way which is mathematically simple yet physiologically representative. The details of the kinetic model have been reported in a number of publications

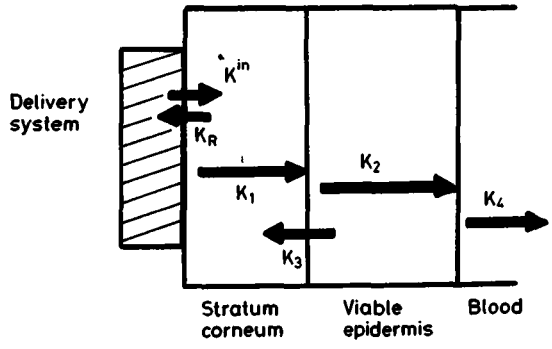

Figure 3. Linear kinetic model for percutaneous absorption and transdermal drug delivery (Guy and Hadgraft 1985 a, 1985 b, 1985 c, 1985 d).

(Guy and Hadgraft 1985 a, 1985 b, 1985 c, 1985 d). In brief the significance of the rate parameters can be summarized as follows:

K^{IN} describes the input function from the transdermal device and is discussed further below.

K_r reflects the fact that there will be competition for the drug between the device and the stratum corneum. An optimally designed transdermal device minimizes the value of K_r and optimizes the unidirectional transfer of drug from the device into the skin.

K_1 and K_2 describe, respectively, the diffusion of compound across the stratum corneum and viable tissue. It has been shown that these parameters can be evaluated simply from the molecular weight of the transporting drug (Guy *et al.* 1985).

K_3 accounts for the competition for the drug between the lipophilic stratum corneum and the much more aqueous in nature viable epidermal tissue. K_3/K_2 reflects an *effective* stratum corneum/viable tissue partition coefficient of the drug and may be predicted empirically from K/5 where K is the octanol-water partition coefficient (Guy *et al.* 1985). Thus, the more lipophilic a compound the greater the value of k_3, and the slower the partitioning process of the drug out of the stratum corneum into the viable tissue.

K_4 is evaluated from the biological half-life ($t_{1/2}$) of the compound ($K_4 = \ln 2/t_{1/2}$) and signifies the clearance of the drug from the systemic circulation.

The nature of the input function is dependent upon the design of the transdermal delivery system. The system which has been best characterized is the membrane-moderated device pioneered by Alza Research (Shaw and Chandrasekaran 1981). A schematic diagram of this device is shown in figure 4. The device consists of a reservoir of drug trapped behind a polymeric membrane. The device is attached to the skin surface through a pressure-sensitive adhesive which is part of the delivery system and through which the drug must diffuse in order to obtain access to the skin. This device is representative of the scopolamine (Price *et al.* 1981) and clonidine (Arndts and Arndts 1984) systems and of one of the nitroglycerin patches (Good 1983). The *in vitro* release characteristics of the scopolamine patch are shown in figure 5 (Chandrasekaran *et al.* 1978). The patch, it can be seen, releases drug in a bi-functional manner. There is an initial, rapid, first-order release superimposed upon the zero-order component. The first-order burst effect results from the rapid release of drug from the adhesive of the patch. The zero-order component originates from the diffusional control imposed by the polymeric membrane. Thus, the input kinetics of this type of device can be modelled by two concomitant processes, one first-order (k^1) and one zero-order (k^0) (Chandrasekaran *et al.* 1978). In conjunction

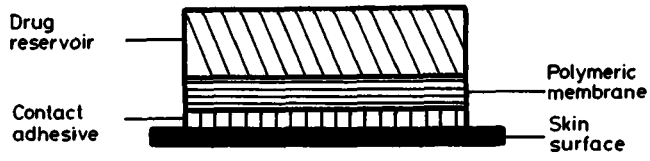

Figure 4. Diagram of a membrane-moderated transdermal drug delivery system (Good 1983, Shaw and Chandrasekaran 1981).

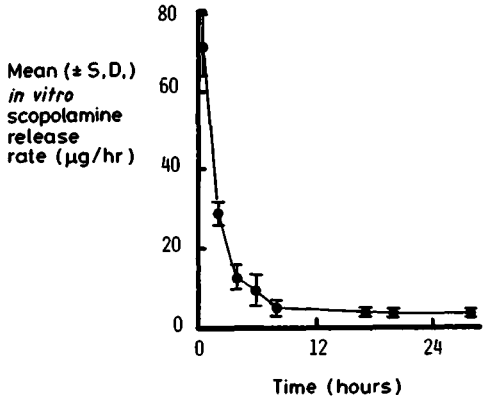

Figure 5. *In vitro* release rate profile of scopolamine from a membrane-moderated transdermal delivery system (Chandrasekaran *et al.* 1978). The drug release rate (R) as a function of time (t) is described by the empirical relationship: $R = k^0 + Fe^{-k^1 t}$, where $k^0 = 3{\cdot}8\,\mu g/cm^2/hr$, $F = 150\,\mu g/cm^2/hr$ and $k^1 = 1{\cdot}3\,h^{-1}$.

with the model shown in figure 3, we can now solve the differential equations to predict the resulting plasma concentration (C_p) as a function of time. The contributions to C_p from the first-order and zero-order input kinetics are given in the equations (1) and (2) below:

$$C_p\,(\text{first}) = \frac{Mk^1k_1k_2}{V}\left\{\frac{\exp(-\alpha t)}{(\beta-\alpha)(\alpha-\omega)(\alpha-\mu)} + \frac{\exp(-\beta t)}{(\alpha-\beta)(\beta-\omega)(\beta-\mu)} + \frac{\exp(-\omega t)}{(\alpha-\omega)(\omega-\beta)(\omega-\mu)} + \frac{\exp(-\mu t)}{(\alpha-\mu)(\mu-\beta)(\mu-\omega)}\right\} \quad (1)$$

$$C_p\,(\text{zero}) = \frac{Ak^0k_1k_2}{V}\left\{\frac{1}{\alpha\beta\varepsilon} - \frac{\exp(-\alpha t)}{\alpha(\alpha-\beta)(\alpha-\varepsilon)} - \frac{\exp(-\beta t)}{\beta(\beta-\alpha)(\beta-\varepsilon)} - \frac{\exp(-\varepsilon t)}{\varepsilon(\varepsilon-\alpha)(\varepsilon-\beta)}\right\} \quad (2)$$

where

V = volume of distribution of the drug
M = amount of drug in the 'priming' contact adhesive,
A = surface area of the device,
$\omega\mu = k^1k_1$; $(\omega+\mu) = k^1 + k_r + k_1$,
$\alpha\beta = k_2k_4$; $(\alpha+\beta) = k_2 + k_3 + k_4$,
$\varepsilon = k_1 + k_r$.

In recent publications, the model has been used to analyse C_p versus time data for nitroglycerin (Guy and Hadgraft 1985 c) and clonidine (Guy and Hadgraft, 1985 d) following transdermal delivery from membrane-moderated devices of the type described. The zero-order components of the release kinetics have been reported in the literature (Good 1983, Arndts and Arndts 1984). The first-order components are assumed to be identical to that of the scopolamine device and correspond to a release half-life of approximately 30 minutes (Chandrasekaran *et al.* 1978). We assume that the devices favour the unidirectional transfer of drug from the patch into the skin and assign k_r the small value of $10^{-4}\,hr^{-1}$. The transdermal kinetic parameters (k_1, k_2, k_3) are calculated as previously described. The volumes of distribution and the biological half-lives of these compounds have been reported in the literature (Benet and Sheiner 1985) and these parameters are also used in the calculations as shown in the equations given above. The amount of drug contained within the adhesive layer has also been reported. The areas of the devices are determined by the engineering of the patches. The entire collection of parameters necessary for the simulations is listed in table 1 for the two drugs. In figures 6 and 7, we show a comparison between the *in vivo* pharmacokinetic data following transdermal drug delivery and the predictions of the kinetic model (Guy and Hadgraft, 1985 c, 1985 d). There is good agreement between the theoretical, predicted, plasma concentrations and the experimental data. Also shown on these graphs are the first-order (F) and zero-order (Z) contributions to the total predicted curves (T). It can be seen that the loading dose, which is delivered to the skin with effective first-order kinetics, provides an important portion of the drug delivery and allows the target plasma concentration to be attained much more rapidly. More recent work has shown that the kinetic model, using the same approach as reported here, can successfully mimic the *in vivo* data obtained when estradiol, scopolamine and timolol are delivered transdermally from either devices of the type considered here or from simple topical vehicles (Guy and Hadgraft 1986). It appears, therefore, that the kinetic model,

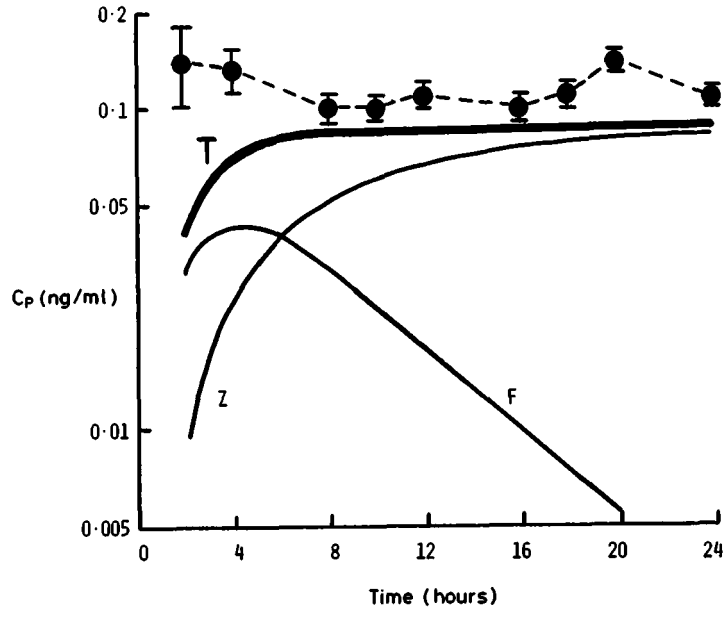

Figure 6. Comparison between theoretical prediction of the kinetic model (Figure 3) and the *in vivo* plasma concentration *vs* time profile for nitroglycerin (Good 1983). The parameters used to calculate the simulated curve are in table 1. ●——● *In vivo* data.

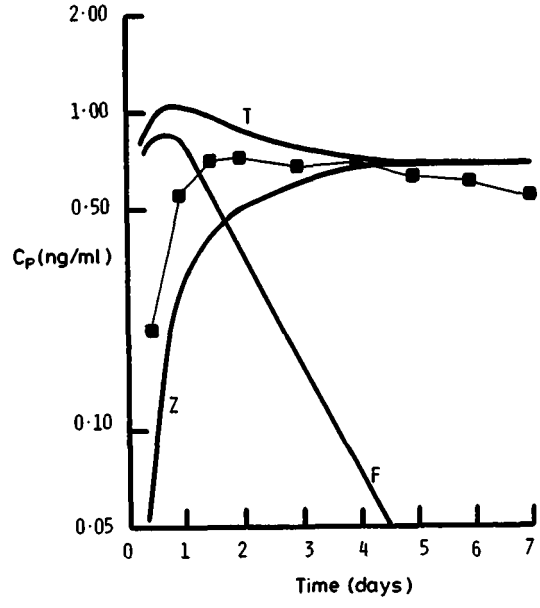

Figure 7. Comparison between theoretical prediction of the kinetic model (Figure 3) (Guy and Hadgraft, 1985 d) and the *in vivo* plasma concentration versus time profile for clonidine (Arndts and Arndts 1984). The parameters used to calculate the simulated curve are in table 1. ■——■ *In vitro* data.

although simple, does have considerable potential for the evaluation and feasibility estimation of potential transdermal drug delivery candidates. The model seems to be physicochemically and biologically reasonable and can successfully describe the percutaneous penetration and subsequent systemic disposition of those transdermally administered drugs so far considered.

In addition to the disappearance of drug from the device due to percutaneous absorption and systemic disposition, there are two potential metabolic events which may degrade a compound before its entrance into the general circulation. These are illustrated in figure 8. The drug may be degraded on the skin surface by the resident microflora which are commonly present, or, alternatively, the drug may be metabolized by the various enzymes present within the viable tissue of the skin. The potential biotransformation reactions which are known to occur within the skin are shown in table 2 (Tauber 1981). It can be seen that most classes of classic enzymatic reaction can take place. The significance of these biotransformations with respect to transdermal drug delivery has been described in some recent publications (Bucks 1984, Denyer *et al.* 1985, Noonan and Wester 1985). Of particular note are the calculated enzyme activity ratios within the skin as compared to those in the liver. These are presented in table 3 (Noonan and Wester 1985). It is clear that, as an organ, the skin does have significant metabolizing capacity. However, unlike the liver, in which the enzymes are concentrated within a defined region of tissue space, the cutaneous enzymes are distributed over the nearly $2\,m^2$ of skin surface area of a normal adult. Thus, when one considers drug delivery through a limited area of skin it is perhaps to be expected that metabolism cannot be of such a dramatic effect as that seen in the liver for certain drug moieties.

To evaluate the potential significance of cutaneous metabolism on transdermal drug delivery, a degree of insight may be obtained by extending the kinetic model to include the possibility of metabolism within the epidermis (Hadgraft 1980, Guy and Hadgraft, 1982). The extended model is shown in figure 9. The reason for adopting this approach is simply that experimental evaluation of cutaneous metabolism is extremely limited, at least with respect to the transdermal delivery of therapeutic

Table 1. Pharmacokinetic and physicochemical parameters used by the kinetic model (Guy and Hadgraft 1985 a, 1985 b, 1985 c, 1985 d) to calculate the predicted curves in Figures 6 and 7 for nitroglycerin[a] and clonidine[b], respectively.

	Nitroglycerin	Clonidine
Molecular weight (Da)	227·1	230·1
Log K	2·05	0·83
Half-life (h)	0·04	8·5
V (litres)	231	147
A (cm^2)	10	5
M (mg)	2	0·47
k^0 ($\mu g/cm^2/hr$)	36	1·6
k^1 (h^{-1})	1·3	1·3
k_r (h^{-1})	10^{-4}	10^{-4}
k_1 (h^{-1})	0·15	0·15
k_2 (h^{-1})	2·36	2·35
k_3 (h^{-1})	53	3·2
k_4 (h^{-1})	18·2	0·08

[a]Guy and Hadgraft 1985 c.
[b]Guy and Hadgraft 1985 d.

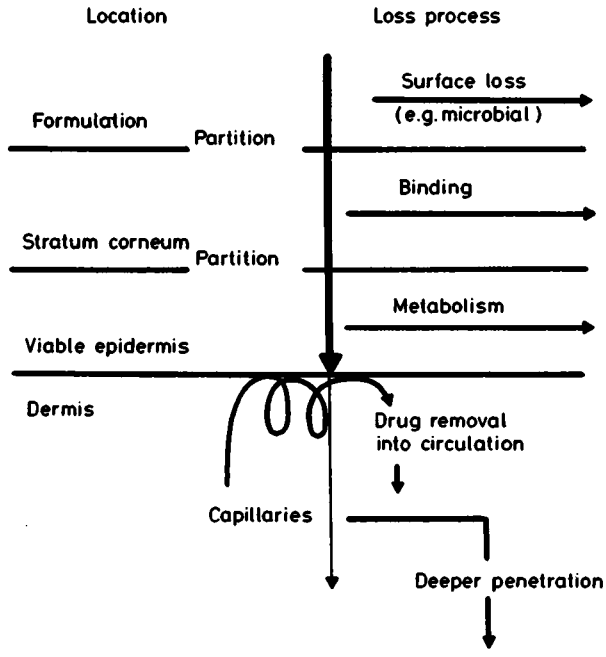

Figure 8. Diagrammatic representation of potential degradative pathways of a drug during transdermal absorption.

Table 2. Biotransformation reactions by skin (Tauber 1981).

Reaction	Enzyme(s) involved
Phase 1 oxidation reactions:	
aliphatic C-atoms	mixed function oxidases
alicyclic C-atoms	mixed function oxidases
aromatic rings	hydroxylases, mixed function oxidases
alcohols	dehydrogenases
deamination	monoamine oxidases
dealkylation	deethylases, demethylases
Phase 1 reduction reactions:	
carbonyl groups	ketoreductase
C=C double bonds	5(α) reductase
Phase 1 hydrolysis reactions:	
esters	esterases
epoxides	epoxide hydrases
Phase 2 conjugation reactions:	
glucoronidation	UDPG-transferases
sulphation	sulpho-transferases
methylation	catechol *O*-methyl transferases
glutathione	glutathion-*S*-transferases

agents. In figure 10 we show how changing the magnitude of the stratum corneum-viable epidermis partition coefficient of the drug and varying the magnitude of the metabolic rate constant k_M can effect the resulting amount of drug penetrating across the skin as a function of time. Increasing the partition coefficient increases the residence time of drug within the skin tissue and, hence, the metabolic effect

Table 3. Enzyme activity ratios, skin/liver (Noonan & Wester, 1985).

Enzyme	Activity ratio (skin/liver)	
	Whole skin	Epidermis[a]
Aromatic hydrocarbon hydroxylase	0·02	0·80
7-Ethoxycoumarin deethylase	0·02	0·80
Aniline hydroxylase	0·06	2·40
NADP-cytochrome C reductase	0·06	2·40

[a]Calculated assuming that the epidermis comprises 2·5% of whole skin.

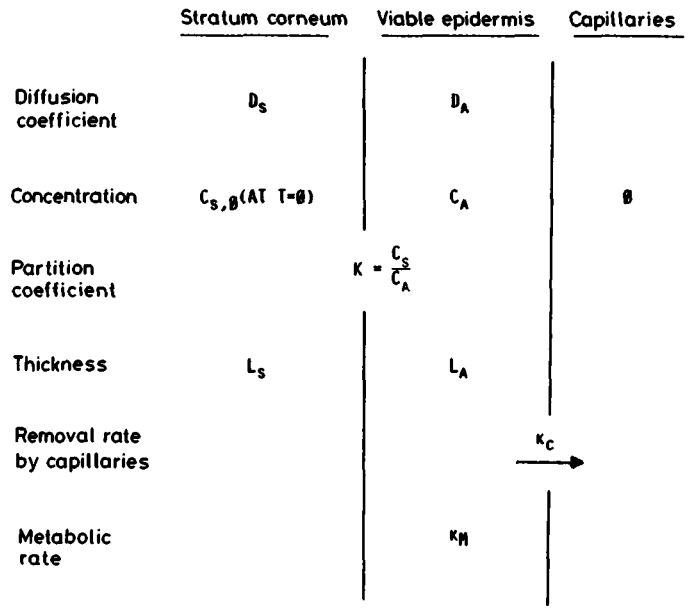

Figure 9. Extended model of skin absorption and transdermal delivery including cutaneous metabolism (Hadgraft 1980, Guy and Hadgraft 1982).

becomes progressively more significant. For a fixed partition coefficient, increasing the metabolic rate constant clearly leads to a decrease in the ultimate bioavailability of the penetrating molecule. There are no quantified values for the metabolic rate constant available at this time and hence interpretation of curves such as those shown in figure 9 must await further experimental work.

There have been attempts to quantify a 'cutaneous first pass' effect for nitroglycerin (Wester *et al.* 1983). It has been shown in rhesus monkeys that 15–20% of transdermally delivered nitroglycerin is metabolized during the drug's passage across the skin. This value has also been reported to be indicative of similar behaviour in man. The monkey data substantiating this claim are summarized in table 4. Nitroglycerin, of course, is an compound exquisitely sensitive to metabolism and it *may* be speculated that the degree of first pass effect within the skin observed for this material represents an upper limit on the potential of the skin to biotransform a transporting substrate.

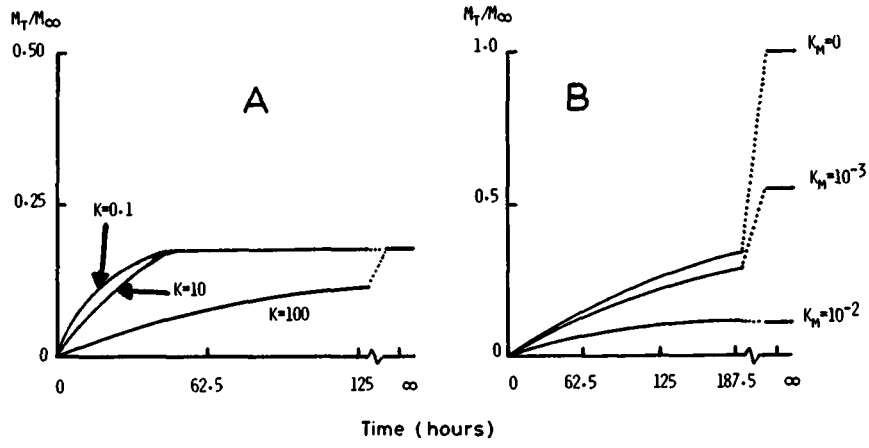

Figure 10. The effect of stratum corneum/viable tissue partition coefficient (K) and epidermal metabolism kinetics (K_M) on the fraction of the applied parent compound (M_t/M_∞) which reaches the cutaneous microcirculation (Hadgraft 1980). [A] Effect of varying K with a fixed $K_M = 0{\cdot}1$ (corresponding to $k_M = 44\ Ms^{-1}$). [B] Effect of varying K_M with a fixed $K = 100$.

Table 4. Bioavailability of topical nitroglycerin (GTN) in rhesus monkeys[a] and implied cutaneous 'first-pass' effect (Wester *et al.* 1983).

	Intravenous	Topical
Dose (mg)[b]	1·92 ± 0·01	19·0 ± 0·9
Plasma GTN *AUC* (ng·hr·ml^{-1})	19·1 ± 2·9	107·2 ± 18·3
Bioavailability (%)	—	56·6 ± 4·3
Plasma ^{14}C *AUC* (μg·hr·ml^{-1})	7·30 ± 0·80	55·5 ± 7·4
Bioavailability (%)	—	77·2 ± 11·7
Cutaneous first-pass effect (%)	—	20·6
Urinary ^{14}C (% dose excreted)	53·5 ± 6·8	38·8 ± 6·5
Bioavailability (%)	—	72·7 ± 10·1
Cutaneous first-pass effect (%)	—	16·1

[a]N = 3.
[b]The stated GTN doses were administered spiked with ^{14}C-labelled compound. GTN was assayed specifically in plasma and urine by h.p.l.c. Total radioactivity in plasma and urine was measured by liquid scintillation counting.

The metabolism of nitroglycerin by skin surface microflora has also been evaluated in culture and has been shown to be significant under certain circumstances (Denyer *et al.* 1984). Using half-lives for metabolism obtained from this *in vitro* work it has been possible to calculate (using an obvious extension of the pharmacokinetic model) the potential significance of surface degradation on the percutaneous absorption of the parent drug (Denyer *et al.* 1985). The results of these simulations are illustrated in figures 11 and 12. In figure 11 the first-order input of nitroglycerin is considered from a typical ointment preparation. It can be seen that, depending upon the degree of metabolism, a significant reduction in the plasma levels of the drug will result. For transdermal delivery, we expect the microflora to exert their maximal effect on the drug which is initially presented in contact with the stratum corneum, i.e. that contained within the adhesive. The metabolism of this material results in a prolongation of the time needed to achieve the target plasma

concentration (figure 12). This degradative process can be circumvented by increasing the amount of drug initially contained within the adhesive (Denyer *et al.* 1985).

It should be emphasized that these simulations remain theoretical; metabolic rate constants, either of the cutaneous microflora or of the epidermal enzyme systems have not yet been quantified. More work is required in order to determine the significance of possible cutaneous metabolism on transdermal drug delivery. These experiments are not easy to perform and their unambiguous interpretation is also difficult. Nevertheless it is important, particularly for those drugs for which the transdermal route is attractive because of their significant hepatic metabolism, that this biological event be characterized experimentally.

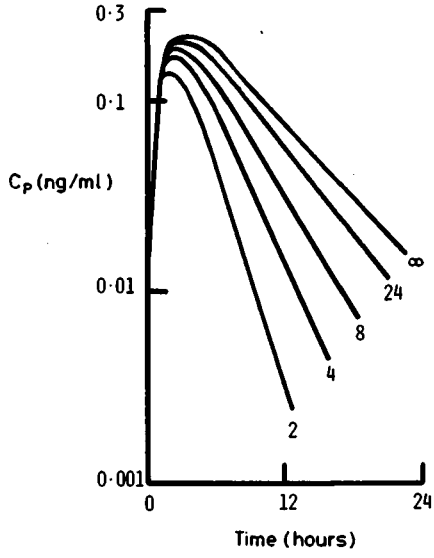

Figure 11. Simulated plasma concentration versus time profiles for nitroglycerin applied topically as an ointment (Denyer *et al.* 1985). The effect of surface microflora metabolism is shown: the numbers against the curves represent the half-life (h) of microbial biotransformation.

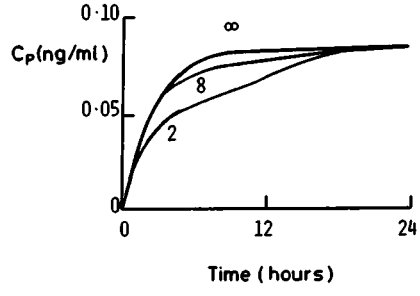

Figure 12. Transdermal delivery of nitroglycerin from a membrane-moderated system containing a 2 mg priming dose in the contact adhesive (Denyer *et al.* 1985). Effect of microbial degradation on the plasma concentration versus time profile is shown for different half-lives of metabolism (indicated, in hours, against the curves).

Cutaneous metabolism: possible beneficial effects

A recent review has addressed the question of the possible utility of cutaneous metabolism in eliciting desirable activation of transdermally absorbed materials (Bucks 1984). A number of prodrug and soft drug topical therapeutic agents have been synthesized and tested. The principal goal of this approach is to produce compounds whose permeation characteristics across the stratum corneum are enhanced by derivatization but which contain linkages that are labile to, for example, cutaneous esterases, resulting in the rapid and efficient liberation of the active compound once the stratum corneum barrier has been breached. In the context of this paper, it is inappropriate to review this material in depth but a few illustrative examples of this type of application may be presented.

A prodrug is defined as an inactive agent that is enzymatically activated to active drug in a predictable and controlled manner. Two examples of topical prodrugs are the theophylline (Sloan and Bodor 1982) and 5-fluorouracil (Mollgaard *et al.* 1982) derivatives shown in figure 13. The theophylline analogue was designed as an anti-proliferative agent and has been shown to produce the desired pharmacological effect *in vivo* in animal skin. The fluorouracil derivative penetrates the skin much more effectively than the highly polar parent compound. The ester group is cleaved efficiently following penetration of the stratum corneum and results in considerably enhanced topical delivery of the 5-FU parent material.

The other class of agent investigated are called soft drugs. A soft drug has been defined as a biologically active compound which is characterized by a predictive *in vivo* destruction (to inactive products) once it has achieved its therapeutic role. An

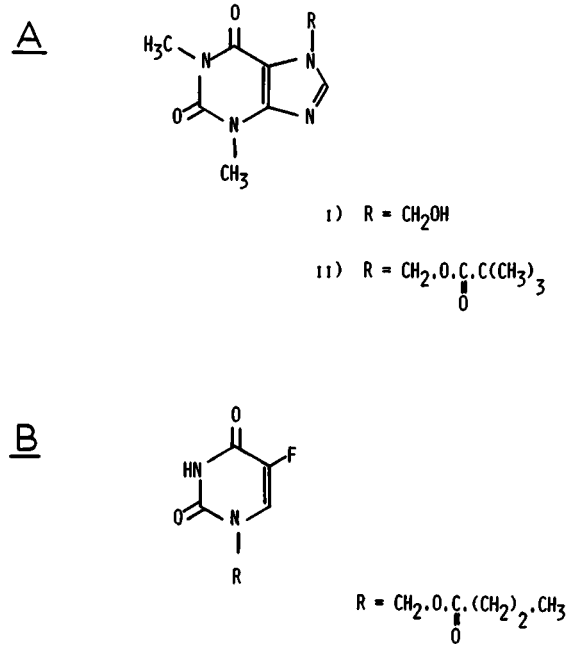

Figure 13. Structures of (A) theophylline (Sloan and Bodor 1982) and (B) 5-fluorouracil (Mollgaard *et al.* 1982) prodrugs.

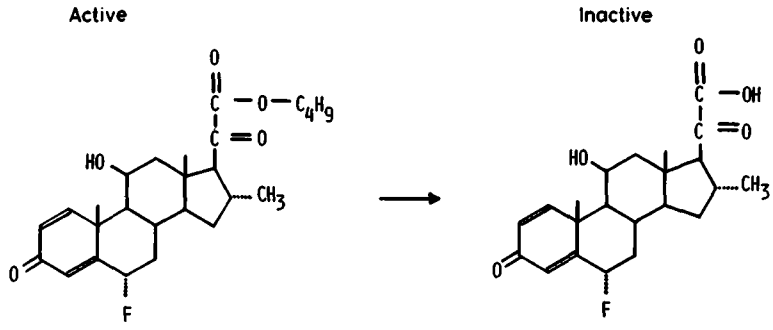

Figure 14. Biotransformation of the soft drug, fluorocortin-butyl ester, in man (Kapp *et al.* 1977).

example of a topical soft drug is a new type of topical steroid, fluorocortin-butyl ester (Kapp *et al.* 1977). This compound is active but is converted to an inactive metabolite (see figure 14) within the skin; it does not therefore elicit undesirable systemic side effects on subsequent uptake into the general circulation.

Thus, skin metabolism may prove a useful tool in the design of new cutaneous therapy. It may also have some applicability with respect to transdermal drug delivery of materials which show very poor percutaneous penetration. However, the significant disadvantage with the prodrug approach is that one administers a compound whose biological transformation is necessary in order to elicit the desired pharmacological systemic effect. The demonstration, therefore, of efficacy, safety and the absence of toxicity becomes a much more complicated problem.

Conclusions

Transdermal drug delivery has arrived on the pharmaceutical science stage. The success of the nitroglycerin devices assures that this mode of drug administration will attract considerable attention in forthcoming years. The role of metabolism by the skin, on the other hand, has not yet been significantly addressed and little is known about the potential detrimental effects (or possible utility) of cutaneous biotransformation reactions. It is important that the latter situation be rectified soon and that experimental techniques be developed to allow this important process to be probed in considerably more detail.

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