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Review Article

Percutaneous absorption: possibilities and problems

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Introduction

Due to the synthesis and development of potent topical drugs, the absorption of drugs through the skin has been studied in considerable detail over the past two decades. Current interest in transdermal drug delivery systems has also lead to an increased interest in factors affecting skin permeability. However, the simple physical chemistry of percutaneous penetration has not been studied in a particularly systematic fashion. In order to optimize formulations it is beneficial to have a good understanding of the fundamental physical chemistry relating to the release and diffusion of drug molecules in the topical base and in the various layers of the skin. In this review some of the major factors which affect skin penetration will be discussed. Also their relevance to the rational design of formulations will be outlined.

Skin structure

The structure of the skin is of importance in determining the rate of diffusion of the drug to the lower layers of the epidermis and to the cutaneous vasculature. This will, of course, depend on the disease condition of the skin. In normal skin several routes of drug penetration are possible; these are shown schematically in Fig. 1. If we imagine a molecule on the skin surface and follow its passage downwards, the following layers will be encountered.

(1) The sebum which has little or no effect on the overall transfer rate of the drug (Higuchi, 1960)

(2) The stratum corneum. It is then possible for the drug to move by different routes.

(a) Transappendageal. The appendages which traverse the stratum corneum may provide a route for skin absorption. Eccrine glands are not thought to provide a significant mechanism for penetration since the drug would have to diffuse against

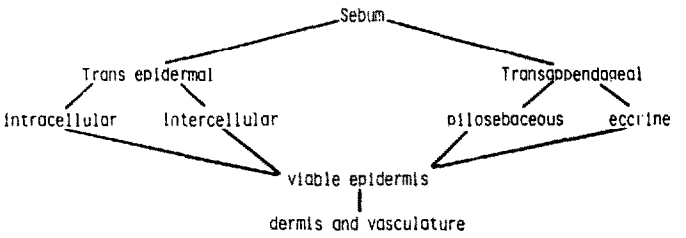

Fig. 1. Schematic representation of whole skin showing the different routes of penetration.

the current of fluid moving towards the skin surface which, in any event is of small surface area (Kligman, 1964; Scheuplein, 1967). Additionally there appears to be a valve mechanism at the opening of the gland which only opens during perspiration. In general, areas of the skin which have a large proportion of eccrine glands do not show an increased permeability (Barr, 1962). This route does not therefore seem to be particularly significant. A transfollicular route has been suggested in the past as being significant particularly in the early stages of penetration. It may be important for some large molecules and when large amounts of surfactants are present in the formulation. This shunt diffusion has therefore attracted some investigation (Scheuplein, 1967).

(b) Transepidermal. This is probably the most popular mechanism but, again, there are various alternative possibilities.

(i) Intracellular diffusion in which the active drug diffuses through the cornefied cells is one possibility which is the most favoured. The whole thickness of the stratum corneum contributes to the diffusional resistance, there being no single barrier layer within its structure. This may be seen by observing the gradual increase in the permeability of the stratum corneum as layers are removed by adhesive tape stripping (Tregear, 1966) or by the concentration distribution of the drug in the various strippings (Schaeffer et al., 1978a and b). The main arguments against this route are that the cornefied cells themselves are dense and offer a large diffusional resistance.

(ii) Intercellular. This route has attracted some interest recently. Although there is a small surface area, the diffusional resistance compared with the dead cells will be fairly low. There appears to be some evidence to suggest that certainly for small molecules this may be a major route (Albery et al., 1979c). However, it is difficult to obtain incontrovertible evidence to ascertain which is the most likely route of penetration. It is also very difficult to design definitive experiments to show the pathway.

(3) The viable epidermis may be regarded as being like an aqueous protein gel (Scheuplein, 1967). As such, small drug molecules will diffuse through this medium with diffusion coefficients of the order of 10^{-7} $cm^2 \cdot s^{-1}$. In most circumstances this layer will not provide much of a barrier. However, if the skin is damaged or if the drug is very lipophilic, the viable epidermis will act as a possible rate-limiting step. Once the permeating species has crossed this region it reaches the epidermal–dermal interface where the small blood vessels are situated. These remove the drug very

efficiently (Helde et al., 1954; Katz et al., 1971) and thus the drug concentration surrounding this region is considered to be very small. For the purposes of mathematical modelling it may be considered that sink conditions prevail.

Thus a detailed consideration of the skin's structure reveals a complex environment. In order to understand the basic physical chemistry of the diffusion of drugs through these regions, simplifications and approximations have to be made which are dependent on the methods used for studying the penetration rates. These assumptions will be discussed later as they are encountered.

Methods of studying percutaneous absorption

The methods of studying skin penetration may be separated into the following: in vitro, in vivo and mathematical.

In vitro techniques may be used to study the rates of release from topical formulations and also the rates of diffusion of drugs through excised skin and model skin. The rate of drug delivery from the topical preparation can be measured relatively simply from a cell as shown in Fig. 2 which is based on a design from Billups and Patel (1979). The amount of drug released will be proportional to the square-root of time (provided that the amount released is less than 60% of the total present) and the gradient of the amount vs square-root time plot will give a measure of the diffusion coefficient of the drug in the preparation (Higuchi, 1967; Hadgraft, 1979a). Fig. 3 shows a typical plot. It is important to make sure in this type of experiment that the membrane in the apparatus is in no way rate-limiting. Usually if the membrane does provide any resistance, the release profiles will not generate linear relationships between the amount released and the square-root of time. It is

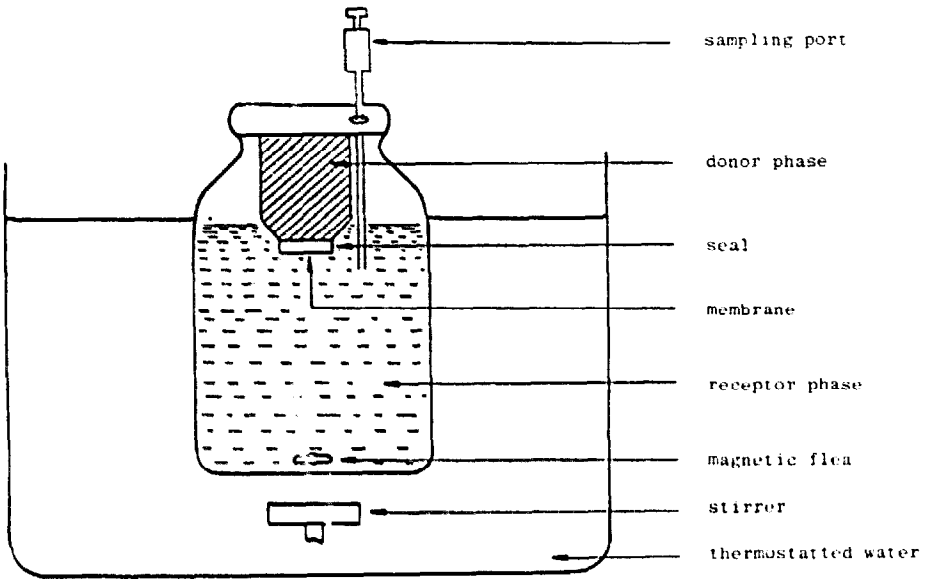

Fig. 2. In vitro diffusion cell for studying release rates of drugs from semi-solid formulations.

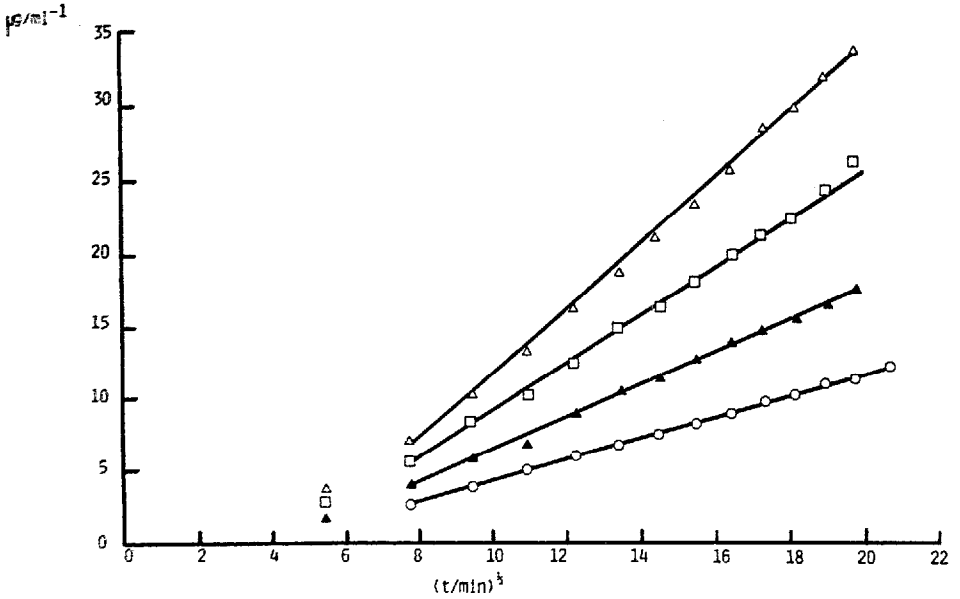

Fig. 3. Release of 10% w/w methyl salicylate from PEG systems at 30°C, △, PEG 600; □, PEG 350*; ▲, PEG 1500, ○, PEG 2000; (*, 20% PEG 200 plus 80% PEG 1000).

possible to design apparatus which do not require a membrane (Poulsen et al., 1968; Behme et al., 1982) but these will be of limited use in testing materials such as aqueous gels, etc., unless the receptor phase is lipid.

The major factors which influence the rate of release are the thermodynamic activity of the diffusant (Higuchi, 1960; Hadgraft et al., 1973; Woodford et al., 1982) and the micro-viscosity of the vehicle (Davis et al., 1981; Al-Khamis et al., 1982; di Colo et al., 1980). Both of these factors may be altered by formulation changes; however, it is often difficult to make modifications to one without the other. In some

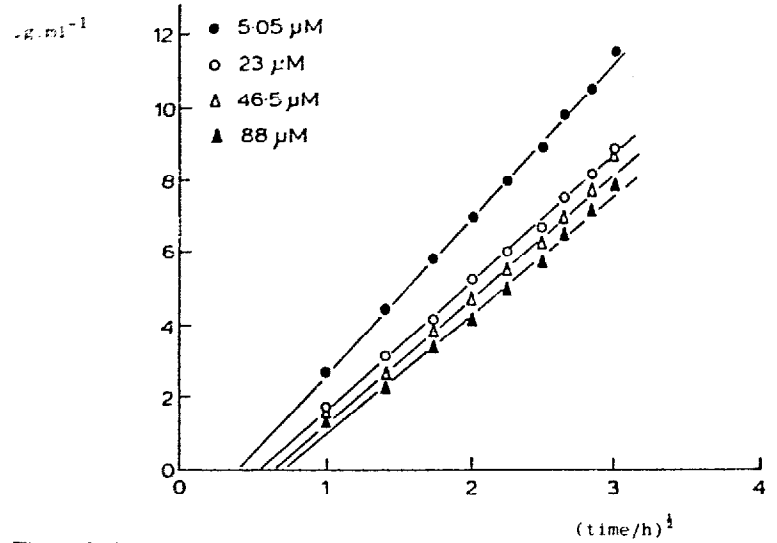

Fig. 4. Release of 10% w/w salicylic acid from Plastibase 50W at 37°C.

circumstances the drug is present in the base above its solubility limit. If this is the case then the rate of dissolution may be important. This may be seen by investigating the influence of particle size on release rate. Fig. 4 shows some in vitro data for the release of salicylic acid from Plastibase 50W. The results show that as the particle size of the salicylic acid decreases the release rate increases. This is in general agreement with in vivo findings which indicate an increased corticosteroid bioavailability with decreasing particle size (Barrett et al., 1965).

Most in vitro skin diffusion experiments are conducted using a Franz-type cell (Franz, 1975). The problems involved with this type of diffusion experiment are manifold. Firstly there is the choice of skin sample. It is important to use intact samples and a preliminary check of the skin's permeability with tritiated water will reveal any abnormalities. Different layers of the skin may be used in the cell including full thickness skin (Foreman et al., 1978). However, it is important to use a reproducible technique in the pretreatment of the sample and recent publications have indicated that the skin's permeability will be a function of its treatment and storage (Pitman et al., 1982).

The other difficulty often encountered is the analysis of the data produced by this type of experiment. A typical concentration time profile is given in Fig. 5. The diffusion coefficient (D) of the drug within the skin is often calculated from the lag time ($\tau = \ell^2/6D$). This procedure is subject to considerable error and it is better to use a computer simulation to fit the curve and thus estimate D by an iterative method (Foreman et al., 1976, 1977). Alternatively a permeability coefficient may be obtained from the steady-state region of the profile (Scheuplein, 1965). Absolute values for D cannot be measured by this approach since estimation of a correct vehicle–skin partition coefficient is almost impossible.

Other in vitro techniques include the use of model membranes to simulate skin (Busse et al., 1969; Albery et al., 1979a; Guy et al., 1979). Since skin is such a complex biological membrane, it is often easier to use model systems which are more homogeneous. If these are used it facilitates the estimation of those physicochemical

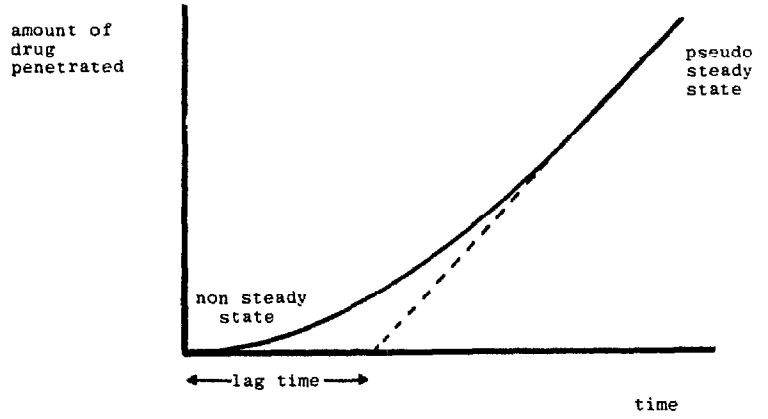

Fig. 5. Typical concentration–time profile for diffusion through epidermis.

parameters which are of significance in the different transport steps. The main problems in this approach are the choice of the model and then the justification of the relevance of the results to the real system.

In vivo measurements are also varied in nature and subject to difficulties in interpretation. Histological studies may reveal structural changes to the skin as the drug diffuses but these will only occur for a limited number of compounds, e.g. keratotolysis induced by salicylic acid (Strakosch, 1943). It is also difficult to estimate permeation rates and absolute amounts of drug absorbed from this type of analysis. Some histological work has been conducted to show the route of penetration but the results are often both conflicting and confusing.

The most common method for studying in vivo penetration is using radiolabelled tracers (e.g. Feldman et al., 1966; Wester et al., 1980; Anjo et al., 1980). The fate of a labelled drug applied topically may be studied in several ways. It is possible to measure the surface disappearance by placing a counter immediately above the application site. This will give some indication of the diffusional rate through the stratum corneum. However, the results are not unambiguously analyzable since it is difficult to estimate the quenching of the signal by the skin. It is also possible to analyze different 'tissue' compartments in the body. Urine and blood plasma analysis will give a measure of permeation rate but will not distinguish metabolites. Skin is a membrane which is metabolically active (Wester et al., 1980a), an important factor which is often ignored. It is also possible to biopsy the skin and obtain drug (plus metabolite) concentrations within the skin tissue itself. This information is useful in assessing the binding and reservoir capacity of skin.

The other way of measuring percutaneous absorption in vivo is to follow a physiological response after topical drug application. The blanching response from corticosteroids has been used to examine the effects of formulation changes on penetration rate (e.g. McKenzie et al., 1962; Sarkany et al., 1965; Barry et al., 1975). This is a useful technique but one that is difficult to quantitate. Qualitative differences between formulations are certainly observable but it is impossible to relate these to absolute quantities of steroid penetrating. It would be possible to get more information from the data if the amount of steroid required to trigger the response at the site of action was known accurately. These data are also difficult to analyze since the steroids form a reservoir in the stratum corneum (McKenzie et al., 1962; Vickers, 1963) and the response mechanism is subject to tachyphylaxis.

The nicotinates have also been used to study percutaneous penetration (Stoughton et al., 1960). These compounds penetrate the stratum corneum rapidly and dilate the blood vessels at the dermal–epidermal interface (Fulton et al., 1959). Formulations alter the time of onset of erythema (Fountain et al., 1969; Hadgraft et al., 1972; Lippold et al., 1982) and simple parameters such as thermodynamic activity can be studied by this means (Hadgraft et al., 1973). The results show that the thermodynamic activity of the drug in the formulation is an important factor in determining the penetration rate of the drug through the skin. Fig. 6 shows some data from Fountain et al. (1969) in which methyl nicotinate in polyethylene glycol 300 was applied to the skin. Agitation of fluid still on the surface of the skin after the initial response had subsided restored the erythema. This may be attributed to a

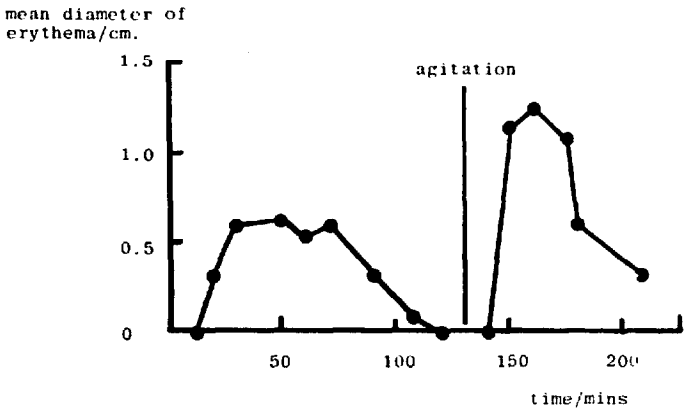

Fig. 6. The variation in diameter of erythema with time for a solution of methyl nicotinate in PEG 300.

viscosity effect in the vehicle in which the surface concentration of the nicotinate is depleted and diffusion through the vehicle is sufficiently slow that it becomes rate-limiting. Thus using this technique it is possible to study both processes within the skin and the vehicle. The response has also been studied in considerable detail using simple aqueous solutions and the results analyzed using a complex mathematical model (Albery et al., 1979c, 1983). The results show that for this type of compound the preferred route of absorption appears to be via the intercellular channels. More recent advances in this field have used photo pulse plethysmography and laser doppler velocimetry to follow the response–time curve in a more quantitative fashion (Tur et al., 1982). Using these techniques it is possible to use the nicotinates as marker compounds for assessing the efficiency of penetration enhancers. For example, the effect of urea on oily cream BP can be seen; hexyl nicotinate at 0.1% penetrates the skin to give a time of onset of erythema of 14.3 ± 0.6 min. Addition of 10% urea decreases this time to 11 ± 0.5 min ($n = 20$).

Mathematical modelling of percutaneous absorption has been used recently to assess the relevance of different physicochemical parameters in skin penetration (Nakagawa et al., 1976; Fox et al., 1979; Hadgraft 1979b, 1980). The problems involved with this approach are that the equations are complex and have no simple solutions. This is illustrated in Fig. 7. In most topical applications the time of skin contact is such that steady-state conditions are never established in the skin. This means that solutions to Fick's second law of diffusion in the base, stratum corneum, and viable epidermis are required with appropriate boundary conditions. The simple diffusion equations will be further complicated if the kinetics of metabolism are included. Solutions to this type of equation are possible either by computer simulation (Fox et al., 1979) or by the use of appropriate approximations to give simple analytical functions (Hadgraft, 1980; Guy et al., 1982). Even using the approximations generates equations which are not very easily understood. However, this approach does give the possibility of seeing how such factors as the partition coefficient affect the capacity of the drug to form a reservoir in the stratum corneum (Hadgraft, 1979b). Fig. 8 shows this effect. For a drug with a stratum corneum/water partition coefficient of 10, very little remains in the stratum corneum after a 10-day

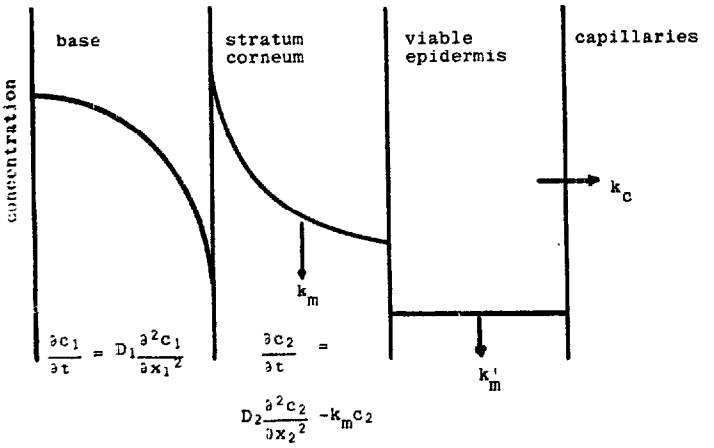

Fig. 7. Concentration profiles of a drug in the base, stratum corneum and viable epidermis and the associated diffusion equations.

period; if the partition coefficient is increased to 100, about 75% of the drug still resides in the outer layers of the skin after the same time period. This occurs as a result of the very low steroid solubility in the viable epidermis which then essentially holds back the drug in the stratum corneum.

It would be desirable to be able to predict drug levels in the skin, blood and urine following their topical application. The model could be used to predict formulation effects, drug structure effects and possible toxicological hazards. For this approach to be successful a relatively simple set of equations is required. The use of classical pharmacokinetics modelling has been made (Chandrasekaran et al., 1978; Riegelman, 1974; Wallace et al., 1978) and in a recent analysis the rate constants employed may be ascribed to some of the basic physicochemical parameters associated with percutaneous absorption (Guy et al., 1982b). A linear model has been used which is shown schematically in Fig. 9. In this scheme, k_1 reflects the diffusion of the drug

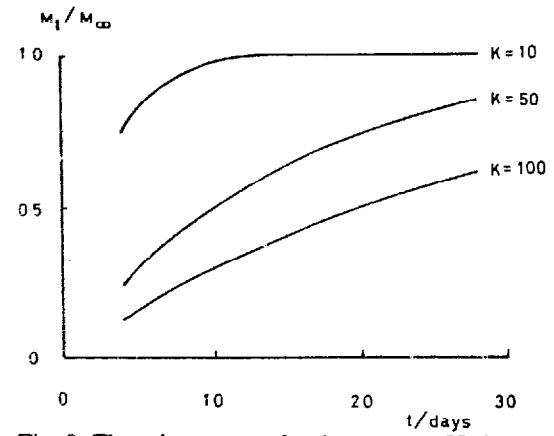

Fig. 8. The release rate of a drug over a 28-day period from the stratum corneum showing the effect of partition coefficient.

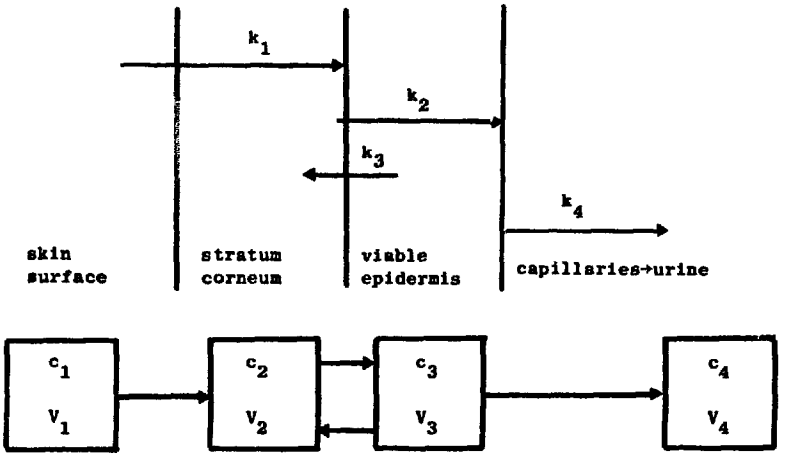

Fig. 9. Schematic representation of the pharmacokinetic model.

across the stratum corneum; it is thus a comparatively slow rate constant. k_1 should therefore be related to the molecular size of the drug. k_2 describes the diffusion of the drug across the viable epidermis and may thus be related to the transport of the diffusant in an aqueous gel. k_3 gives an indication of the relative affinity of the drug for the primarily lipophilic nature of the stratum corneum and the hydrophilic nature of the viable epidermis. The ratio k_2/k_3 may be understood by considering it to be a 'partition coefficient'. The faster the value of k_3 the longer the drug will be held up at the stratum corneum–viable epidermis interface. The last rate constant, k_4, is effectively the same as the elimination rate constant of the drug following intravenous administration. Using the scheme in Fig. 9 and solving the associated first-order differential equations gives an expression for the amount of drug that has reached the urine at time t compared to the amount in compartment 1 at time $t = 0$.

$$\phi_t = Fk_1k_2k_4\left\{1/k_1\alpha\beta - \frac{e^{-k_1t}}{k_1(k_1-\alpha)(k_1-\beta)} - \frac{e^{-\alpha t}}{\alpha(\alpha-\beta)(\alpha-k_1)} - \frac{e^{-\beta t}}{\beta(\beta-k_1)(\beta-\alpha)}\right\} \quad (1)$$

where α and β are the roots of the quadratic,

$$s^2 + (k_2 + k_3 + k_4)s + k_2k_4 = 0$$

and F is the fraction of the applied topical dose plus metabolites that is recovered in compartment 4. An example of this type of analysis is shown in Fig. 10. The theoretical curve for testosterone and the experimental data (Anjo et al., 1980) show good agreement.

The model may also be used to interpret data from multiple dosing. Fig. 11 shows the theoretical profile and the experimental data for the multiple application of hydrocortisone (Wester et al., 1980b). Again there is good agreement and the

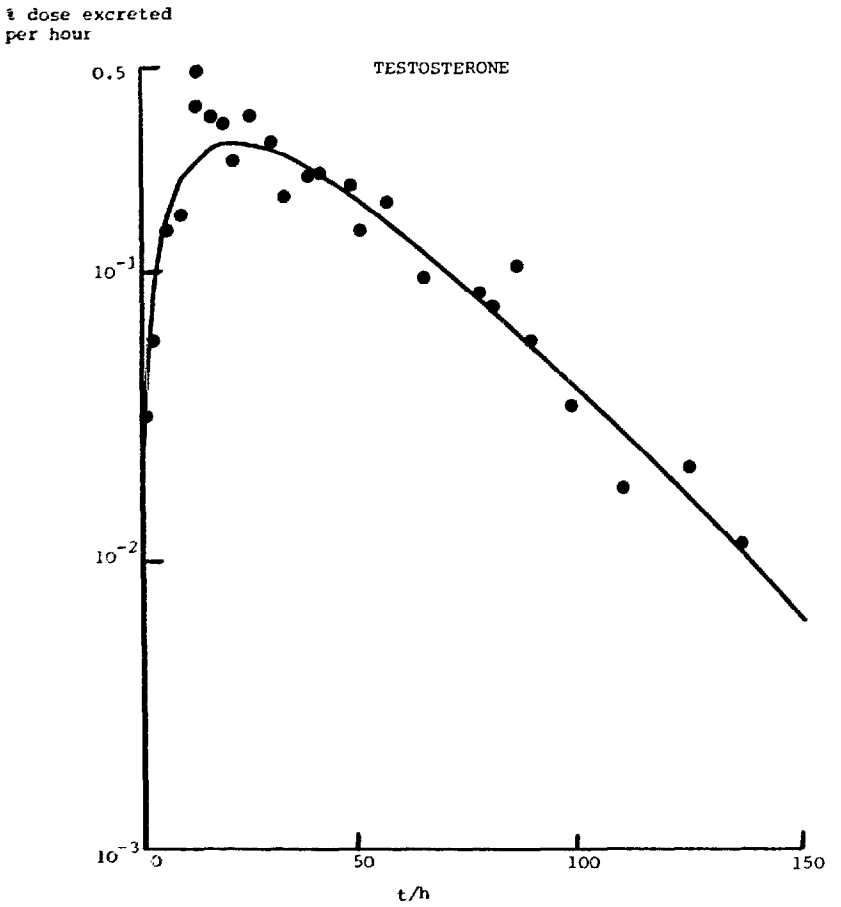

Fig. 10. Urine excretion data following topical application of testosterone predicted using Eq. 1 (solid line) and experimental data points, ●.

difference in excretion pattern between labelled drug applied on day 0 and on day 7 may be attributed to the physicochemical properties of hydrocortisone.

Novel administration techniques

There has been a recent trend towards using the transdermal route as a means of systemic drug delivery. Potent drugs may be delivered at a reproducible constant rate by this means provided, that the device which is applied to the skin acts as the rate-limiting step in the overall transport process (Shaw et al., 1976). Drugs such as hyoscine and nitroglycerin have been administered using this technique (Shaw et al., 1981; Noonan et al., 1980; Chien et al., 1976).

There are several advantages in the transdermal route provided the drug is absorbed in a sufficient quantity to have a systemic effect. It is possible to minimize the variation of absorption of drugs encountered in oral administration caused by pH changes, quantity of food intake and intestinal transit time. The drug is also

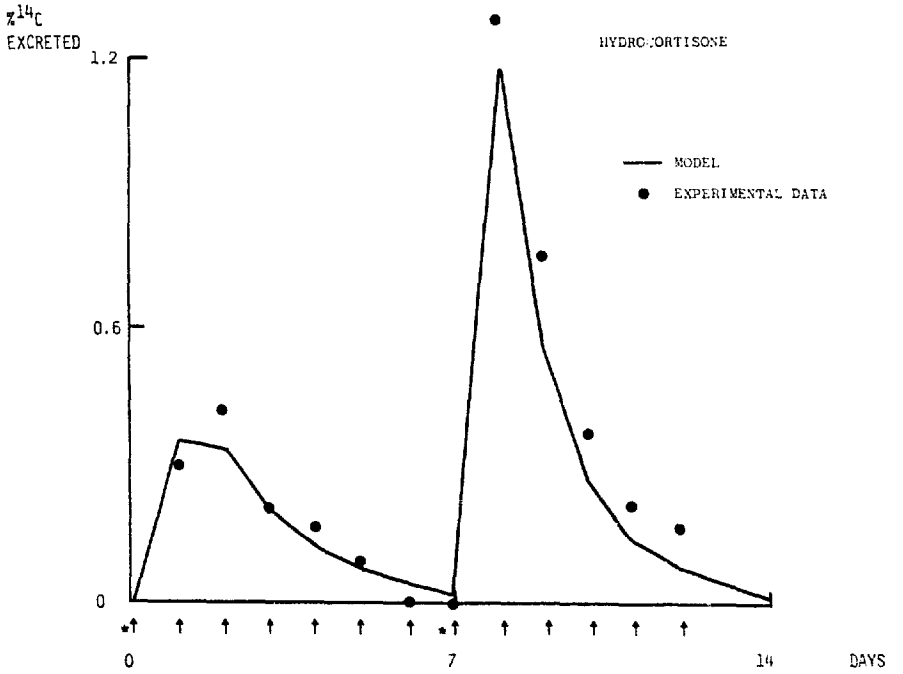

Fig. 11. Percutaneous absorption of [^{14}C]hydrocortisone. ↑ represents hydrocortisone application and *↑ represents [^{14}C]hydrocortisone application. ● represents experimental points and the solid line is the theoretical curve predicted by the pharmacokinetic model.

introduced directly into the systemic circulation, thus avoiding passage through the liver before distribution. This is important for drugs which undergo high first-pass metabolism. However, the transdermal route is only applicable to a relatively small number of drugs. They have to be active pharmacologically at low levels; they have to have the correct physicochemical characteristics to permeate the skin rapidly and they have to be relatively stable to the enzymes present in the epidermis.

Apart from the development of new polymeric systems there has also been considerable interest in simple modifications to conventional formulations. Liposomes have been used to deliver drugs to the skin and somewhat surprising results achieved (Mezei et al., 1979, 1980). Treatment with a liposomal gel formulation provided concentration of triamcinolone acetonide approximately 5 times higher in the epidermis than the control. In the future it may be possible to target drugs to specific regions of the skin using this type of strategy.

However, most effort in the modification of conventional designs has been in the development of ways to enhance the penetration of poorly absorbed materials. Penetration enhancers such as the sulphoxides (Sekura et al., 19. .), urea (Feldman et al., 1974), Azone (Stoughton, 1982) appear to improve temporarily the permeation characteristics of the skin to certain drug molecules. Their exact mechanism of action is unknown but with a detailed knowledge of their basic physical chemistry it should, in the future, be possible to design specific penetration enhancers.

Another concept has been the facilitated transfer of anionic drugs which, in general, are poorly absorbed (Barker et al., 1981). The technique utilizes the pH

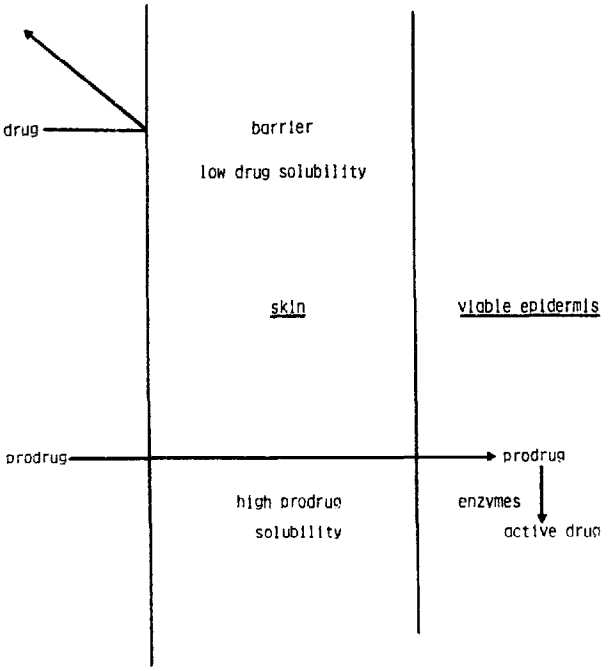

Fig. 12. Schematic representation of the prodrug approach to percutaneous absorption.

gradient that exists across the stratum corneum. At the outer surface of the skin, at pH 5, a carrier molecule becomes protonated and ion-pairs with the anion. The ion pair is sufficiently lipophilic that it partitions into the skin and diffuses to the stratum corneum–viable epidermis interface. It then experiences a region of pH 7.4 and the carrier is deprotonated, liberating the anion into the hydrophilic viable epidermis where it is relatively soluble. The deprotonated carrier is then free to diffuse back to the outer layers of the stratum corneum.

Prodrugs of poorly absorbed materials may also be synthesized to improve their transport characteristics (Bodor et al., 1980; Yu et al., 1979a and b). Their mechanism of action relies on metabolic processes within the skin transforming them to the active drug. This is shown schematically in Fig. 12. The initial drug structure has a very low solubility in the skin and will therefore not partition into it to any great extent. The partitioning behaviour is improved by simple chemical modification and the drug transports into the skin. Here it is metabolized back to the active drug. When a full understanding of the metabolizing enzymes in the skin is obtained, the use of prodrugs will be attractive. In order to ascertain the feasibility of this approach it is useful to model mathematically the processes of diffusion and metabolism (Hadgraft, 1980; Guy et al., 1982a).

One factor that is often ignored is that most studies are conducted on intact skin. For the purposes of systemic drug delivery and general toxicological investigations this is valid. However, most topical drugs are applied to diseased skin where the permeability will be markedly reduced. The permeability post-damage has been studied and the regeneration of the barrier function of the skin followed (Scott et al.,

1982). It is possible to model this situation although there will be difficulties in modelling the extent of damage and the regeneration process.

Conclusions

For the design of any topical drug delivery system, whether it is to deliver the drug locally or systemically, it is important to have an understanding of the underlying physicochemical principles of the total penetration process. The thermodynamic activity of the drug in the delivery system will influence the ability of the device to provide drug to the surface of the skin. Also the diffusion of the drug through the vehicle/device will be of importance. This is particularly true of transdermal delivery systems where it is desirable for the drug to be released with zero-order kinetics. This requires a knowledge of both diffusion theory and polymer chemistry. In order to appreciate the factors governing transport through the skin it is also necessary to understand the theory relating to non-steady-state diffusion. However, once these concepts are understood it is easier to understand the influences of both formulation and drug structure on the overall penetration rates of drug molecules. Further work needs to be conducted on in vitro–in vivo correlations and the fitting of mathematical models to in vivo data (Franz, 1975; Bronaugh et al., 1982).

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