DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(4), 561-577 (1983)

# FUNDAMENTALS OF TRANSDERMAL CONTROLLED DRUG ADMINISTRATION: PHYSICOCHEMICAL CONSIDERATIONS

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In this brief overview I will touch upon a couple of the important environmental factors in perautaneous absorption and then consider some ways in which absorption through skin can be affected by formulation. The skin plus the applied dosage form comprise a laminate structure. As with any situation in which transport takes place across layers in series, the rate of the overall process depends critically on the rate of the slowest step. We can name at least three regions that may become rate limiting under various conditions. One region is the vehicle (in the case of a traditional dosage form) or device (in the case of a transdermal system). A transdermal device may contain its own rate limiting barrier or the diffusional characteristics may simply be such that transport through the vehicle or device is slower than through skin.





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A second possible location for the rate limiting step is the stratum corneum, the principal barrier layer of the skin for most compounds. The stratum corneum consists of dense, highly compressed, partially desiccated cells. This layer has regions rich in protein separated by a lipoidal framework. The living portion of the epidermis and the dermis are usually lumped together as both of these are essentially aqueous in nature. These skin layers represent, collectively, the third major region of permeation control. Highly hydrophobic, poorly water soluble drugs are the ones most likely to encounter significant resistance here.

Several mathematical expressions have been used to describe penetration through skin. Equation 1 describes membrane limited transport under steady state conditions. The flux, J, represents the amount of drug passing through the membrane system per unit area per unit time. In Equation 1, D is the diffusion coefficient within the membrane, h is membrane thickness and K is the membrane/vehicle partition coefficient. The quantity D K/h is referred to as the permeability constant, Kp.

$$J = \frac{D\,K}{h}\,C \qquad \text{(Eq. 1)}$$

It is assumed that the vehicle concentration, C, remains constant during the course of the experiment and that the drug permeates into a perfect sink. In most cases, the stratum corneum functions or the rate limiting barrier so that the parameters in Equation 1 refer to this skin layer. Under conditions such that the assumptions made in deriving Equation 1 are reasonable. The equation allows us to identify

the factors that may be manipulated so as to control persutaneous absorption rate. The membrane thickness remains essentially constant, but the other factors can be affected sometimes to a great extent, by differences in formulation. Figure 1 contains replicates of penetration experiments that show the pattern expected for membrane limited permeation. (1) The steady state flux is calculated from the straight line portion of each curve.

Where release from the vehicle is rate limiting, Equation 1 does not apply. Instead of reaching a steady state, flux is inversely proportional to the square root of time. Most of the situations described in this paper involve situations in which stratum corneum transport is rate limiting, so that Equation 1 will be useful in explaining the results.

## Hydration

The amount of moisture held by the stratum corneum is a function of the environmental relative humidity. Penetration

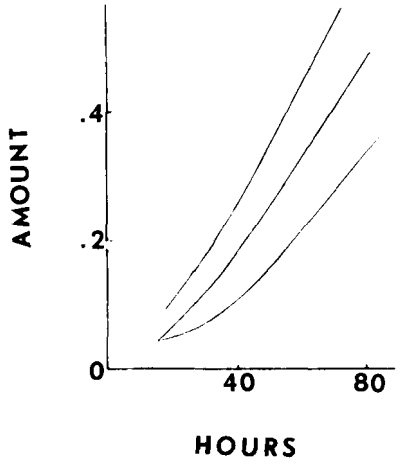


Fig. 1. Hydrocortisove penetration (in mg) through mouse skin from a 0.2% solution in 40% (v/v) 2-propanol and water. Each curve represents skin from a different animal. (Reproduced from Ref. 1 with permission of the copyright owner).

of salicylate esters was enhanced considerably when stratum corneum hydration was increased. (2) Many other studies have shown similar results, although the degree of penetration enhancement due to hydration of the skin varies from one drug to another.

Temperature

Raising skin temperature results in an increase in the rate of skin permeation. The effect is again a general one. With most published data, a plot of the log of permeability constant against the reciprocal of temperature is linear.

We are now in a position to compare some differences between open and closed systems. An open system is one in which the drug preparation is applied to the skin and then permitted to come to equilibrium with its surroundings. No occlusive wrap is used. This is the usual situation with typical dermatological and cosmetic products such as ointments, lotions and creams. A closed system is one in which the skin is occluded by plastic wrap or, in the case of a device, by an occlusive membrane in the device. Occlusion increases skin hydration and skin temperature. Both changes cause a rise in drug permeation rate through skin.

Drug

Some of the factors influencing skin penetration as a function of drug chemistry may be deduced from Equation 1. We would expect that larger molecules would have a smaller diffusion coefficient and therefore penetrate more slowly. While this is true, the diffusion coefficient is inversely

proportional to the square root or cube root of molecular weight so that, as long as molecular weight is not too large, the effect of molecular weight on the permeability constant is relatively unimportant. Changes in the skin/vehicle partition coefficient tend to be much more significant. For a series of related compounds permeating through the same membrane from the same solvent, a quantitative correlation between permeability constant and partition coefficient would be anticipated. Linear relationships were indeed found for the logarithm of the permeability constant as a function of the logarithm of partition coefficient for penetration of alkanols and steroids through human stratum corneum from aqueous solution.(3) However, there are limits to how far the permeability coefficient can be increased because, at some point, we would expect a shift in the rate limiting step to the aqueous tissues below the stratum corneum.

In considering the relationship between skin penetration and partitioning for a series of compounds, we must not lose sight of the importance of the drug solvent utilized. Some results with alkanol penentration through human stratum corneum are instructive.(4) With water as a solvent, an increase in hydrocarbon length results in an increase in the permeability coefficient. When a nonpolar substance ispropyl polmitate, was the solvent, the permeability coefficient became smaller as hydrocarbon length was made longer. The longer chain length alkanols have a smaller affinity for water than do the more polar members of the series. The tendency to partition into the skin is thus greater for the higher alkanols. The reverse is true for

solutions in a nonpolar solvent. In that case, the shorter alkanols have the higher partitioning tendencies and thus the higher permeability coefficient values.

Drug Concentration

The effect of concentration depends on the particular drug state and the characteristics of the dosage form. Assuming membrane limited transport, increasing the concentration of dissolved drug causes a proportional increase in flux. This continues until the saturation concentration (solubility limit) is reached, at which point there is no further change in flux. The expected pattern is shown in Figure 2. At concentrations higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug concentration for a prolonged period of time.

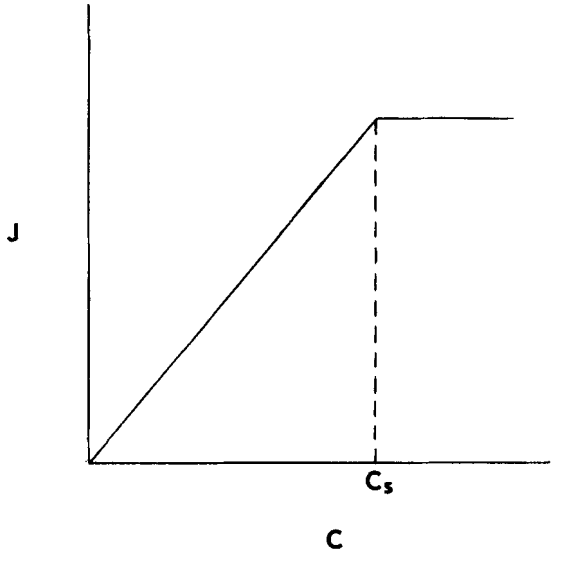


Fig. 2. Theoretical plot of steady state flux as a function of drug concentration. $C_s$ represents the solubility limit in the vehicle.

Drug Binding

Sorption measurements are often utilized to get some idea of the partitioning characteristics of a drug. Figure 3 is a sorption isotherm for hydrocortisove showing uptake by mouse stratum corneum from aqueous solutions containing 20% propylene glycol. (5) This particular isotherm is linear, as were others for the same drug in different solvents. However, nonlinear isotherms have also been observed.

A dual sorption model was applied to explain the sorption data for scopolamine. (6) A portion of the drug is dissolved in the membrane and free to diffuse. The remainder is held by binding sites, and though binding is reversible, bound drug molecules are not available to diffuse through the membrane. Binding of this type prolongs the time required to reach steady state penetration. There is thus a delay in the absorption of substantial quantities.

Figure 4 shows the penetration of benzocaine through hairless mouse skin. (7) which is believed to be similar

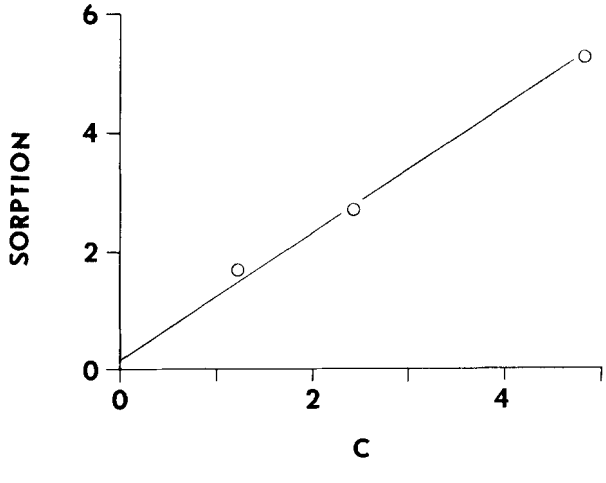


Fig. 3. Sorption of hydrocortisove by mouse stratum corneum from aqueous solution containing 20% propylene glycol Sorption is in µg/g and solubility in µg/ml.

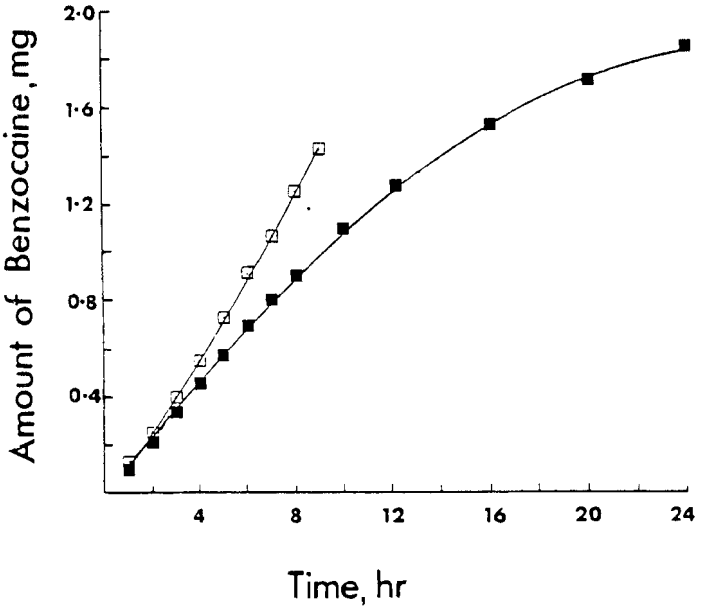


Fig. 4. Penetration of benzocaine through hairless mouse skin.
saturated solution (filtered)
saturated solution with 1 mg/ml excess drug
(Reproduced form Ref. 7 with permission of the copyright owner).

to human skin in terms of resistance to permeation. One curve is for penetration from a filtered saturated aqueous solution. The other is for penetration from a saturated solution containg excess drug. With the usual assumptions, we would expect both curves to be identical because the concentration of dissolved benzocaine is the same in both cases. As shown in Figure 5, the reason for the apparently anomalous behavior is extensive skin uptake of benzocaine. The loss of benzocaine from the donor (vehicle) due to penetration and skin uptake resulted in a substantial decrease in the transmembrane gradient and, consequently, a reduction in the penetration rate. In this particular example, skin binding was responsible for a decrease in flux only in the system which did not contain excess drug.

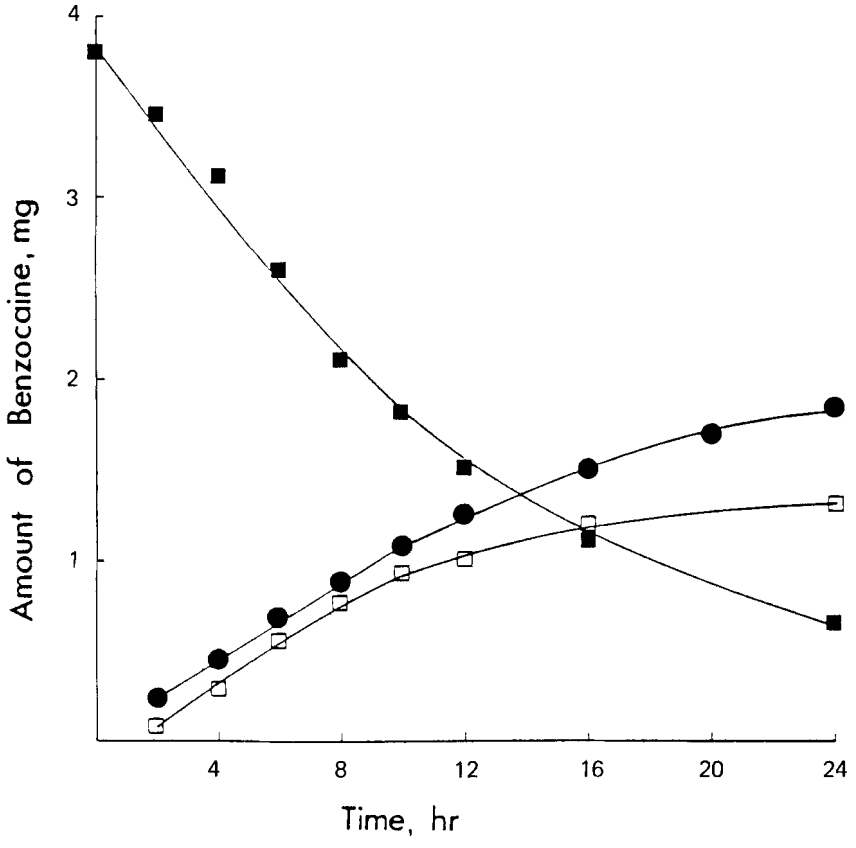


Fig. 5. Skin penetration of benozcaine from saturated aqueous solution
Donor
Receptor
Skin
(Reproduced form Ref. 7 with permission of the copyright owner).

With excess solid present, benzocaine lost from the donor to skin binding sites was replaced so that the initial drug concentration was maintained during the experiment.

pH

Application of solutions whose pH values are very high or very low can be destructive to the skin. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged

species. Many investigations have shown that the unchanged form has better penetration characteristics. However, for a number of drugs, there may also be significant skin absorption at pH values at which the ionized form is predominant.

## Solvents

Solvents can influence drug penetration through skin in several ways. Table I lists four possibilities. Affinity of solvent for the drug, often expressed in terms of solubility, is a factor that must always be taken into account. A high affinity for the drug effectively lowers the skin/vehicle partition coefficient, so that flux of drug through skin tends to be small. Reduction of affinity raises the partitioning tendency and flux is increased. Because no change in any skin property is involved, this type of solvent effect is completely noninteractive. The other factors in Table I all involve a skin interaction of one kind or another. Significant absorption of solvent may alter the character of the skin barrier and change drug partitioning behavior. Osmotic effects may result in hydration changes that can influence penetration by changing the diffusion coefficient of the drug in the barrier. Extraction of membrane components opens additional penetration pathways and increases penetration flux.

One way to evaluate different solvents in terms of the relative contributions of noninteractive and interactive influences on skin penetration is to compare the solvents under conditions of equal solvent affinity. Differences are then due to interactive changes in the membrane. An

TABLE I

Summary of Solvent Effects

| Effect | Parameter Influenced |
|---|---|
| 1. Affinity for drug | Skin/vehicle partition coefficient |
| 2. Solvent permeation | Skin/vehicle partition coefficient |
| 3. Osomotic properties | Diffusion coefficient |
| 4. Extraction of skin components | Diffusion coefficient |

example of such an analysis, applied to in vitro penetration studies of benzocaine from three solvents through two membranes, is shown in Table II (8). Flux data at several benzocaine concentrations was used to compute permeability constants. The value for hairless mouse skin from aqueous solution was calculated from penetration data for a saturated solution containing excess drug. Using results for aqueous systems as reference theoretical permeability constants were calculated for the other solvents on the assumption that no interactions with skin took place. A ratio of experimental to calculated permeability constant of about unity indicates that the assumption of noninteraction was correct. For the polypropylene membrane, which is essentially inert, ratios slightly higher than unity were found (see Table II). These are probably due to water influx into the vehicle in the diffusion cell. Examination of the results for hairless mouse skin shows that propylene glycol had little interactive effect but that polyethylene glycol 400 caused a significant decrease in skin penetration.

Figure 6 shows the effect of variations in cosolvent concentration on in vitro penetration of hydrocortisove through mouse skin. The linearity of the plot of flux against the ratio of drug concentration to solubility for the systems containing propylene glycol is in accord with the notion that interactions with skin are not significant. However, several differences are evident for the results from mixtures of 2-propanol and water. The maximum flux is significantly higher than for the other solvent system and there is no apparent dependence of flux on the concentration:

TABLE II

Estimation of Membrane Interaction

| SOLVENT | SOLUBILITY at 30° (mg/ml) | RATIO OF EXPERIMENTAL TO CALCULATED PERMEABILITY CONSTANT | |
|---|---|---|---|
| | | Polypropylene Membrane | Hairless Mouse Skin |
| WATER | 1.26 | —— | —— |
| PROPYLENE GLYCOL | 146.0 | 1.8 | 0.9 |
| POLYETHYLENE GLYCOL 400 | 435.0 | 1.5 | 0.1 |

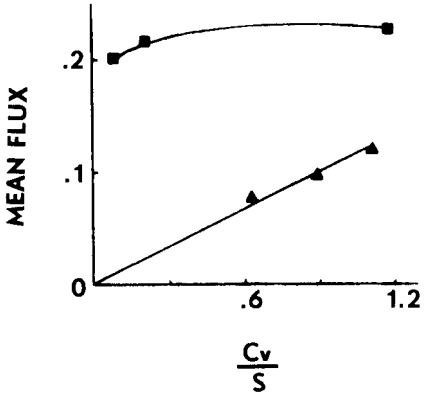


Fig. 6. Mean steady state flux of hydrocortisove (μg $hr^{-1}$ $cm^{-2}$) as a function of the ratio of concentration to solubility in the vehicle
2-propanol-water vehicle
propylene glycol-water vehicle
(Reproduced from Ref. 1 with permission of the copyright owner).

solubility ratio. Both differences are indicative of interactive effects between 2-propanol and the skin barrier.

Surfactants

Although used primarily for their ability to improve the physical characteristics of dosage forms, surfactants can also influence percutaneous absorption. Various anionic surfactants interact with proteins in the skin to produce local irritation. In some cases, extraction of water-holding components within the skin has been demonstrated.

Nonionic surfactants are often preferred in pharmaceutical products, because skin irritation is usually not a problem with these materials.

In a study of benzocaine penetration through hairless mouse skin, in vitro, it was found that nonionic surfactants could influence flux under certain conditions. (9). A series

of polyoxyethylene monylphenols were utilized in these experiments. Water was the solvent. At a fixed benzocaine concentration, the addition of surfactant caused a reduction in flux. The decreased in flux was greater when a higher surfactant concentration was utilized. Also, flux was reduced to a greater extent as the hydrophilic portion of surfactants in the series was made longer (Fig. 7). These results suggested that solubilization caused a reduction in the concentration of diffusible (free) drug. Effectively, the concentration gradient across the membrane was reduced.

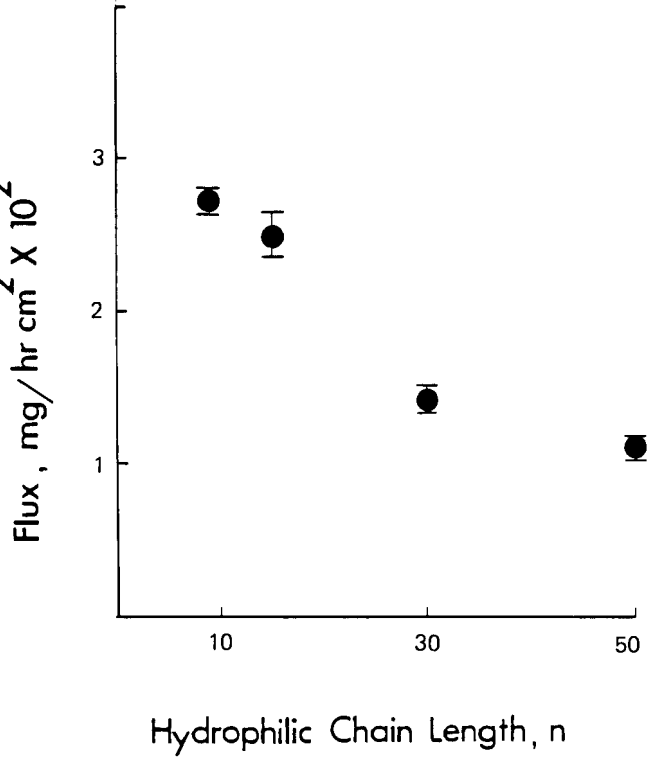


Fig. 7. Effect of hydrophilic chain length of nonionic surfactants, 0.0227 M, on skin penetration of benzocaine from aqueous solutions, 1.262 mg/ml. (Reproduced from Ref. 9 with permission of the copyright owner).

From solubilization studies, the fraction of drug available for diffusion was calculated; a linear relation between flux and the free concentration was found (Fig. 8).

When saturated solutions or suspensions of benzocaine were studied, no difference in flux was found regardless of differences in polyoxyethylene chain length or surfactant concentration. In these systems, the free benzocaine concentration was the same. The conclusion was that these nonionic surfactants had caused no significant change in skin properties.

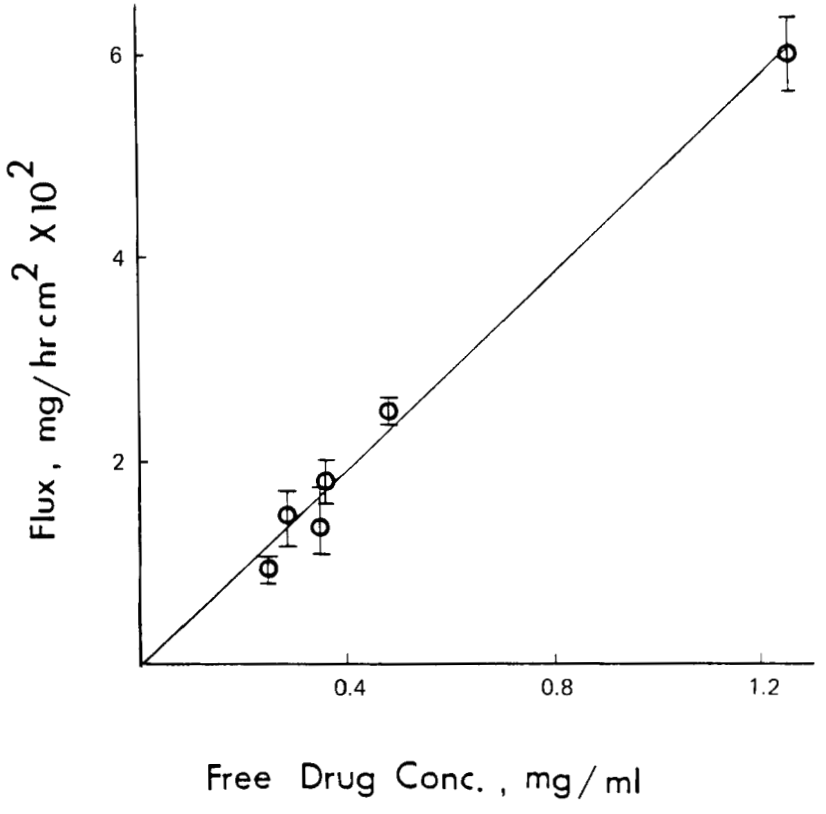


Fig. 8. Effect of free drug concentration skin penetration of benzocaine from aqueous solutions, 1.262 mg/ml. (Reproduced from Ref. 9 with permission of the copyright owner).

Acknowledgement

I wish to thank former graduate students (currently productive industrial scientists) who contributed so much to the studies conducted in our laboratory that were briefly described in this paper.

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