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# Simulation studies of skin permeation

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Synopsis

Simulation studies were conducted using the multicompartmented membrane model to determine the effect on permeation of binding to the stratum corneum and washing of the skin surface. Under infinite dose conditions, binding lengthens the lag period but does not change the steady-state flux. Amounts penetrating at any arbitrary time are reduced. Under finite dose conditions, binding causes significant reductions in the amount reaching the sink at a given time. There is a 50-fold decrease in the amount penetrated at 12 hours, when binding changes from 70% to 90% bound. Washing of the skin surface reduces the amount penetrated, but significant quantities may still get through the skin. At very short wash times, skin and blood concentrations are nearly proportional to contact time. Peak blood concentrations occur hours after washing, reflecting continuing permeation from the stratum corneum. Following a 30-minute application, the amount excreted during four days is proportional to the amount found in the stratum corneum at 30 minutes, provided that the transport coefficient through the stratum corneum and the elimination rate constant are not too small. If partition coefficient is the only variable, both total amount excreted and peak blood concentration are proportional to the amount found in the stratum corneum at 30 minutes.

## INTRODUCTION

Simulation of percutaneous absorption can be used to predict penetration behavior and explore permeation mechanisms. Several models, diffusional and compartmental, have been used to describe the permeation of exogenous compounds into and through the skin. Approaches for estimating percutaneous absorption from physical-chemical data have been reviewed (1).

Hadgraft modeled permeation through skin as a diffusion process and included the uptake by capillaries (2). He showed that a high oil/water partition coefficient favored skin retention and therefore increased reservoir function. Specific binding to skin components was not considered.

Chandrasekaran *et al.* described the dual-sorption model of skin uptake, which divides permeant molecules into those that are "dissolved" in the stratum corneum, and thus free to diffuse, and those that are bound to membrane components (3). Binding was assumed to follow a Langmuir-type relationship. This model, applied to percutaneous absorption from an "infinite dose," accounted for the fact that diffusion coefficients based on the lag time differed in value from those calculated from the equation for

steady-state permeation. Experimental evidence suggested that the drug was bound to non-lipid components, perhaps proteins.

Decontamination of skin exposed to toxins to prevent absorption has been the subject of several reports (4). The amount absorbed depends on the time elapsed after exposure as well as the washing treatment utilized. In some cases, solvents intended to remove contaminants serve also to compromise the skin barrier and are therefore counterproductive. There are a number of experimental difficulties in conducting washing experiments. The importance of the simulation approach is that it eliminates experimental artifacts from consideration and describes the effect of cleaning the skin surface on skin permeation under ideal conditions.

A previous report described a simulation model (multicompartmented membrane model) in which the stratum corneum (SC) is sectioned into component lamina and the permeation process is treated as the sum of a series of first-order transfers (5). Briefly, the model consists of a donor, five sequential stratum corneum compartments, a single aqueous tissue compartment, and a sink. The model was used to illustrate the effect of changes in donor volume on skin distribution and uptake.

The multicompartmented membrane model has been extended to treat the questions of stratum corneum binding and skin washing (to remove an application from the skin surface after a fixed period of time). Intuitively, we would expect binding to the stratum corneum to affect absorption rate. However, the degree to which this occurs is not easily evaluated because it is difficult to design an experiment in which binding is the only variable. Simulated data provide a workable means for estimating the extent to which binding affects penetration.

For the binding studies, a series of "dead-end" compartments was added to the basic model to represent bound permeant. The idea is a variation of the dual-sorption model previously described (3). However, it is more versatile in that it is not limited to infinite dose simulation.

For the washing studies, the sink was replaced by a systemic central compartment (representing the body) from which excretion occurs by a single first-order process. With this variation in the model, it is possible to simulate blood concentration and urinary excretion if appropriate values of the elimination rate constant and volume of distribution are selected. Other, more complex pharmacokinetic designs may also be employed.

## MODEL PARAMETERS

Major model variables include the intercompartment transfer constant, K, which is analogous to a stratum corneum diffusion coefficient, and the ratio of rate constants describing transfer between donor and the first stratum corneum compartment, which represents a partition coefficient (PC). Permeant concentration and donor volume are also adjustable.

In the binding studies, it was assumed that the fraction bound was constant. This corresponds to the low-concentration region of a sorption isotherm. It is also possible to model the entire isotherm by specifying the saturation binding value and an affinity constant.

Several transfer coefficients in the models were kept constant. The transfer coefficients

between stratum corneum and aqueous compartment were 2 $h^{-1}$ in the binding simulations and 0.03 $min^{-1}$ in all washing simulations. The transfer coefficient from aqueous compartment to the sink in the binding simulations was 5 $h^{-1}$; it was 0.08 $min^{-1}$ from aqueous compartment to the blood in the washing simulations. The cross-sectional area was 1 $cm^2$ in all cases, and the stratum corneum thickness was assumed to be 10 μm. The values of the constants were arbitrary, as the simulations were intended to show trends rather than mimic a particular situation. The values were chosen so that transport control resided within the SC section of the model.

## RESULTS AND DISCUSSION

### BINDING STUDIES

The model, shown in Figure 1, was modified from the original version (5) to include stratum corneum compartments (labeled B) that are not part of the transfer pathway. These compartments represent binding sites. Permeant molecules that leave the main channel and enter the B compartments cannot diffuse to other sections of the membrane until they redistribute from these blind sections of the model. This situation is analogous to binding to structural proteins within the stratum corneum, which would reversibly immobilize a bound molecule. Note that transport kinetics are unaffected by the portion which is bound; only the "free" (unbound) permeant is available for diffusion.

A series of penetration curves under infinite dose conditions is shown in Figure 2. Some data from the same study appears in Table I. The only variable in these simulation experiments was the extent of binding within the SC; all other model parameters were kept fixed. Binding of the permeant results in an increase in its concentration within the skin. At early times the amount penetrated is reduced; the higher the extent of binding, the smaller the amounts reaching the sink at any given time. Inspection of Table I shows that this effect is highly significant. With a change from 70% bound to 90% bound,

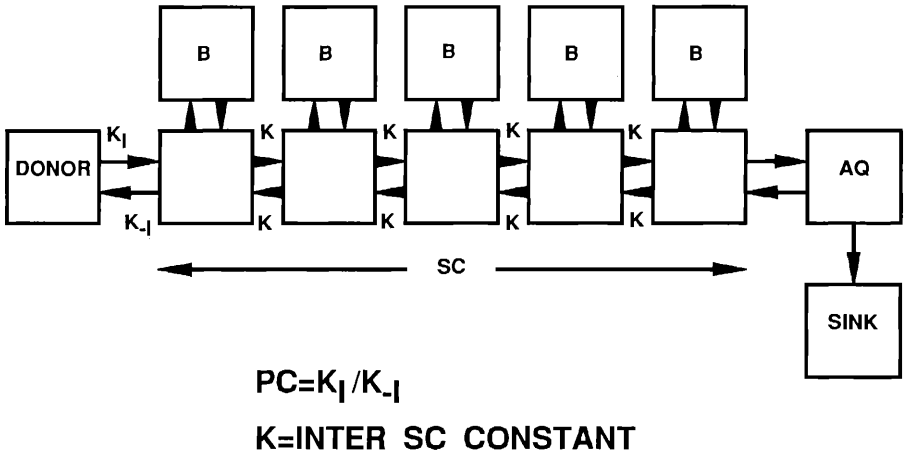


**Figure 1.** Model for binding studies. The stratum corneum consists of five compartments connected in sequential fashion. Transfer is described by K, the intercompartmental transfer constant. Stratum corneum compartments labeled B contain bound permeant. The AQ compartment represents the viable skin tissues.

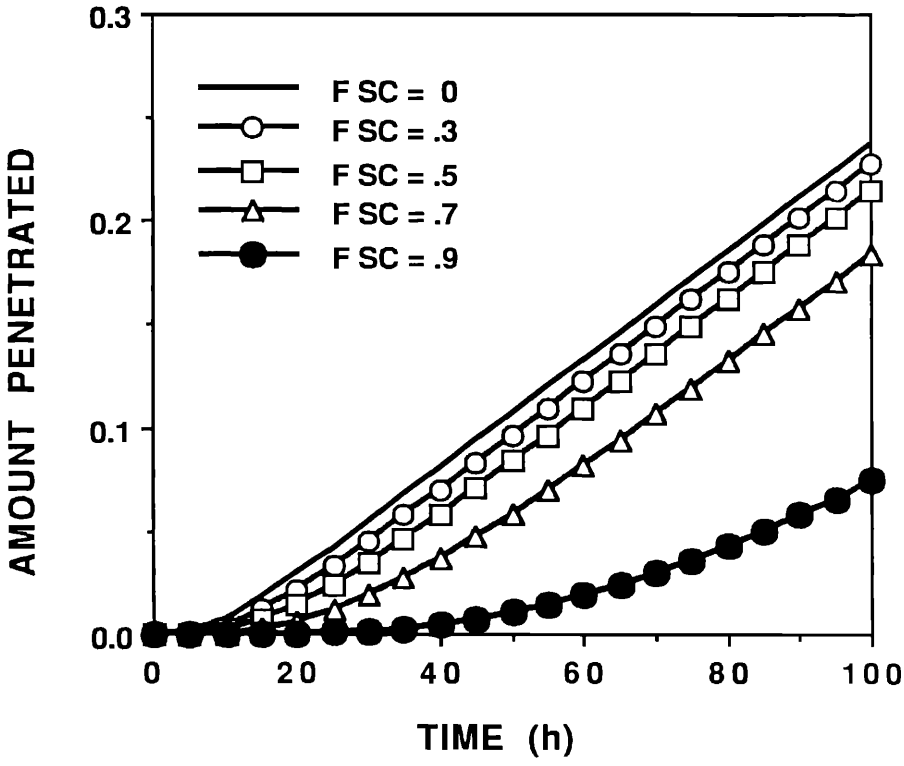


**Figure 2.** Amount reaching the sink with various degrees of stratum corneum binding, infinite dose conditions. F values shown in figure represent fraction bound. ($K = 0.4\ h^{-1}$; PC = 15; donor concentration = 10 mg/ml; donor volume = 1 ml).

the amount reaching the sink in 12 hours is reduced 50-fold. However, Figure 2 shows that if the permeation process is permitted to continue long enough, the same steady-state flux will eventually be established regardless of the fraction bound (although the time required for this might be impractically long in the case of highly bound substances). Thus an important effect of SC binding is delay in the establishment of a steady state. In terms of a simple diffusional model, we would say that the lag time has been increased.

**Table I**
Results From Simulation Studies of Stratum Corneum Binding Under Infinite Dose Conditions ($K = 0.4\ h^{-1}$; PC = 15; donor concentration = 10 mg/ml; donor volume = 1 ml)

| Fraction bound in SC | Amount in skin at 12 h (mg) | Amount penetrated at 12 h (mg) | Steady-state flux ($mg/cm^2/h$) |
|---|---|---|---|
| 0 | 0.065 | 0.011 | 0.00261 |
| 0.3 | 0.084 | 0.0067 | 0.00261 |
| 0.5 | 0.104 | 0.0036 | 0.00261 |
| 0.7 | 0.138 | 0.0010 | 0.00258 |
| 0.9 | 0.226 | 0.00002 | * |

* Steady-state not reached in 100 hours.

The situation is quite different when a small amount (finite dose) of material is applied to the skin surface. Results are plotted in Figure 3 and summarized in Table II. Steady state is not established under finite dose conditions; Table II lists the peak flux value in its place.

An increase in the degree of binding causes a rise in the amount in the skin at 12 hours, although the incremental increase in skin amount is small (Table II). The most dramatic change is in penetration. Binding causes significant reductions in the amount that reaches the sink at 12 hours. Again, there is a 50-fold difference in the amounts penetrated between a situation in which 70% is bound and one in which 90% is bound.

The peak flux value is also affected. An increase in the extent of binding causes a reduction in the maximum flux, particularly as the degree of binding approaches very large values. There is also a dramatic shift in the time at which the peak occurs. For example, in the absence of binding, the maximum flux is observed at about 12 hours; with 50% bound, the peak time is 21 hours; with 90% bound, peak time goes up to about 94 hours.

The results indicate that binding makes skin penetration more difficult. This would probably have been predicted in a qualitative sense. However, the simulations show that at high fractions bound, the effect is much greater than might have been anticipated. When the fraction bound reaches 0.9, the rate of penetration and amount penetrated at

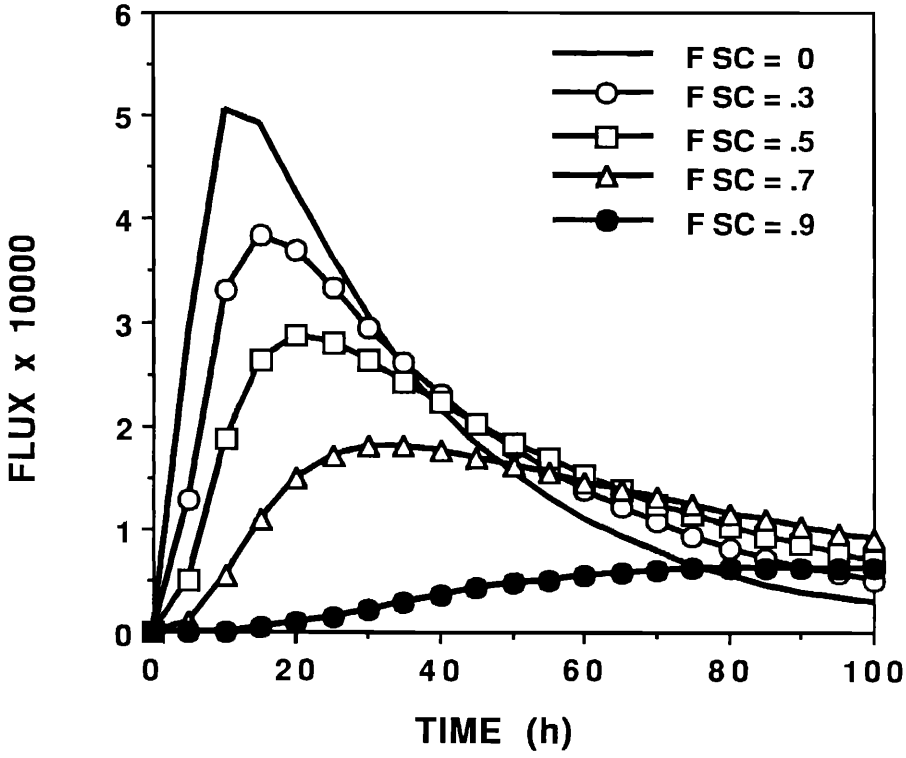


**Figure 3.** Penetration flux as a function of extent of stratum corneum binding under finite dose conditions. ($K = 0.4\ h^{-1}$; PC = 15; donor concentration = 10 mg/ml; donor volume = 2 μl).

Table II
Results From Simulation Studies of Stratum Corneum Binding Under Finite Dose Conditions (K = 0.4 $h^{-1}$; PC = 15; donor concentration = 10 mg/ml; donor volume = 2 μl)

| Fraction bound in SC | Amount in skin at 12 h (mg) | Amount penetrated at 12 h (mg) | Peak flux ($mg/cm^2/h$) |
|---|---|---|---|
| 0 | 0.013 | 0.0036 | 0.00051 |
| 0.3 | 0.015 | 0.0021 | 0.00038 |
| 0.5 | 0.017 | 0.0011 | 0.00029 |
| 0.7 | 0.018 | 0.00029 | 0.00018 |
| 0.9 | 0.019 | 0.000006 | 0.00006 |

early times are markedly reduced and the time for peak penetration shifts to a much larger value.

SKIN WASH STUDIES

A number of skin products are applied, allowed to remain on the skin for some period of time, and then washed off. The purpose of these simulations is to determine whether washing after a short period of time would limit skin uptake and penetration of product components.

The model (Figure 4) was somewhat different from that shown in Figure 1, in that binding was not considered. In addition, the model contained a blood compartment in place of the "sink," and there was provision for elimination from the blood by a first-order kinetic process.

Data from simulations were compiled to see the effect of wash time on blood concentration (Figure 5). The amount in the skin and blood concentration at 12 hours, as well

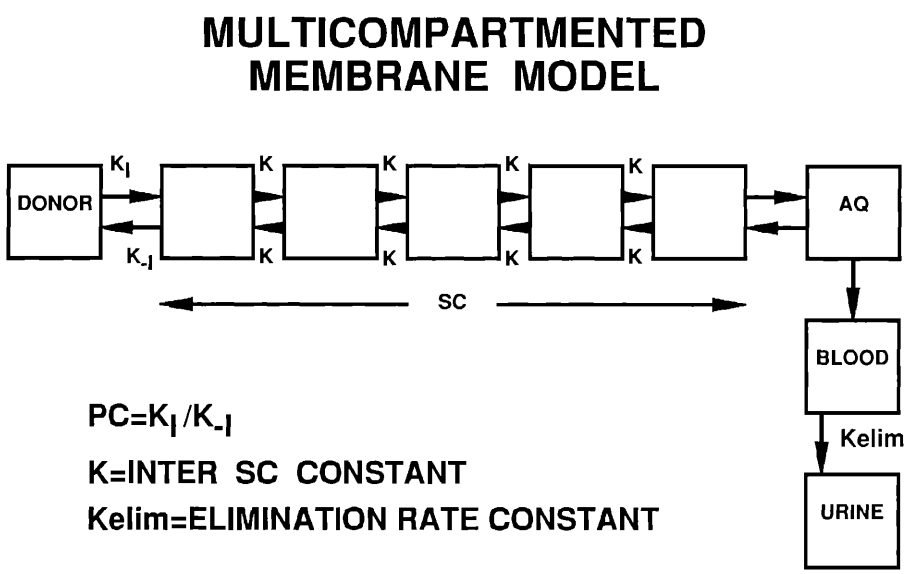


Figure 4. Model for washing studies.

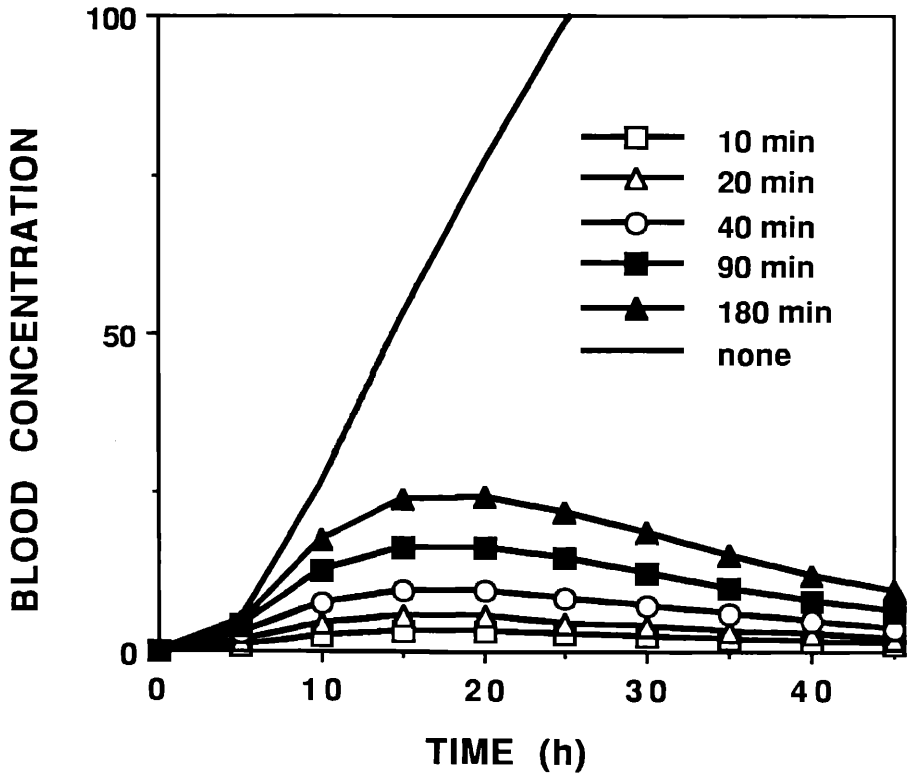


**Figure 5.** Effect of wash time (shown in figure) on blood concentration. (K = 0.01 $min^{-1}$; PC = 15; donor concentration = 10 mg/ml; donor volume = 1 ml; elimination rate constant = 0.00165 $min^{-1}$; volume of distribution = 5000 ml).

as the total amount excreted at 48 hours, are compiled in Table III. In one case the donor was not washed; this situation corresponds to the infinite dose type of application, which serves as a reference for the other results.

As expected, shortening the contact time reduced the amount absorbed into and through the skin. The blood concentrations from all of the treatments are quite low, as would be expected for most substances that are absorbed through the skin. However, it should

**Table III**
Results From Simulation Studies in Which the Donor Was Washed From the Skin at Various Times After Application (K = 0.01 $min^{-1}$; PC = 15; donor concentration = 10 mg/ml; donor volume = 1 ml; elimination rate constant = 0.00165 $min^{-1}$; volume of distribution = 5000 ml)

| Wash time (min) | Amount in skin at 12 h (mg) | Blood concentration at 12 h (mg/ml × $10^7$) | Amount in urine at 48 h (mg) |
|---|---|---|---|
| 10 | 0.0032 | 2.8 | 0.0047 |
| 20 | 0.0061 | 5.2 | 0.0086 |
| 40 | 0.0106 | 8.8 | 0.0147 |
| 90 | 0.0184 | 14.8 | 0.0250 |
| No wash | 0.0694 | 36.8 | 0.0826 |

be noted that even when the application is washed off, significant penetration into the circulation does occur.

At very short contact times, the amounts getting into the skin and then the circulation are approximately proportional to the exposure time (Figure 6). As the contact time is lengthened, this is no longer true. With an exposure time of one hour, the total amount absorbed is approximately 10% of that following extended contact. It should also be noted that blood concentrations continue to climb after washoff (Figure 5), with a peak blood level at about 15–20 hours.

These data illustrate the storage function of the stratum corneum. Even after the skin is washed, the substances that have gotten into the stratum corneum continue to diffuse, and a significant proportion may eventually reach the viable skin layers and then the circulation.

A series of simulations were run to determine the effect of changes in partitioning and transport parameters on skin uptake and penetration at 12 hours following a short (15-minute) exposure to the donor. The effect of changes in partition coefficient is simply stated: an increase in partition coefficient results in a proportional increase in both skin and blood levels (Figure 7). Alteration in transfer coefficient (K) is more complex, as shown in Figure 8. Blood concentrations increase as the value of K is made larger; however, skin levels decrease because the rate of loss from the stratum corneum to the compartments downstream occurs at a faster rate.

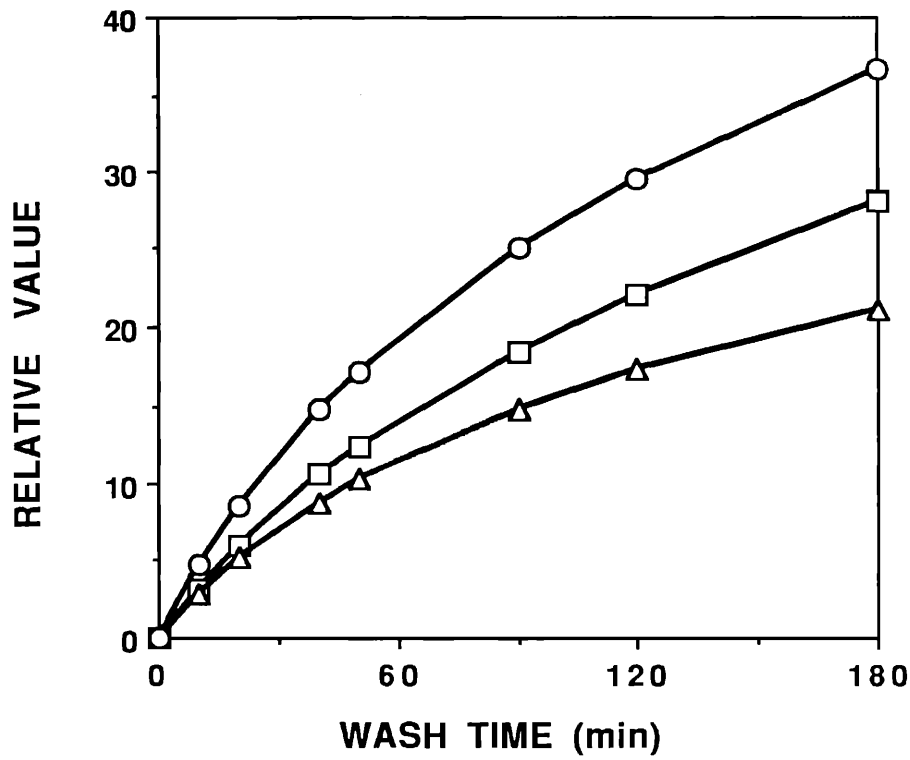


**Figure 6.** Relationship between wash time and relative amount in various locations. Parameter values are given in Figure 5. □, amount in skin at 12 hours; △, blood concentration at 12 hours; ○, amount in urine at 48 hours.

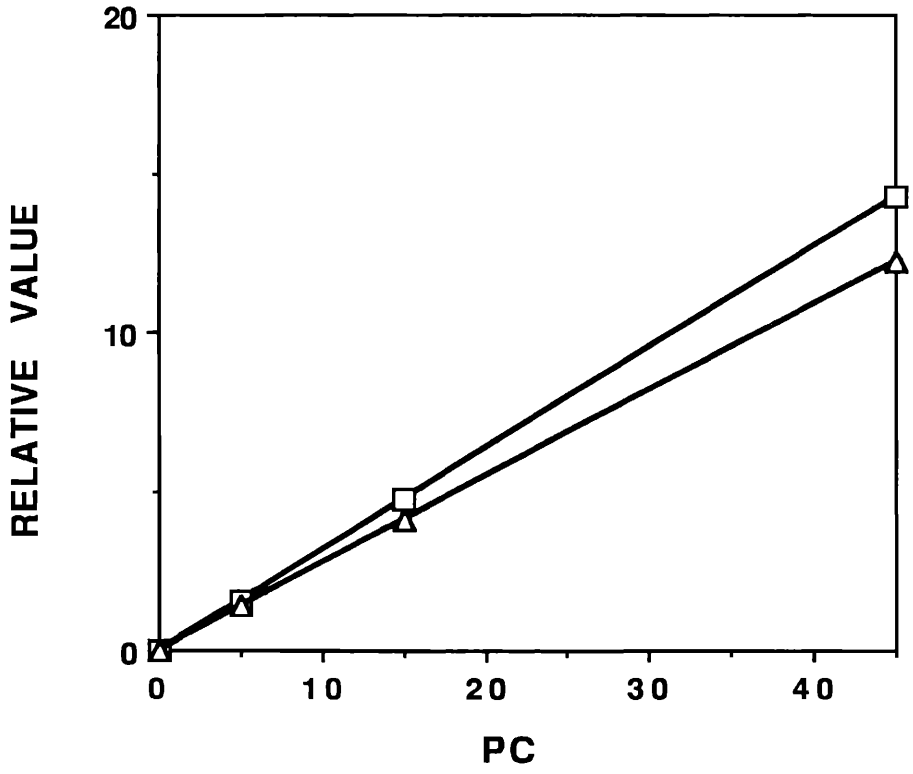


**Figure 7.** Effect of changes in partition coefficient on skin and blood values. Other parameters are same as in Figure 5. □, amount in skin at 12 hours; △, blood concentration at 12 hours.

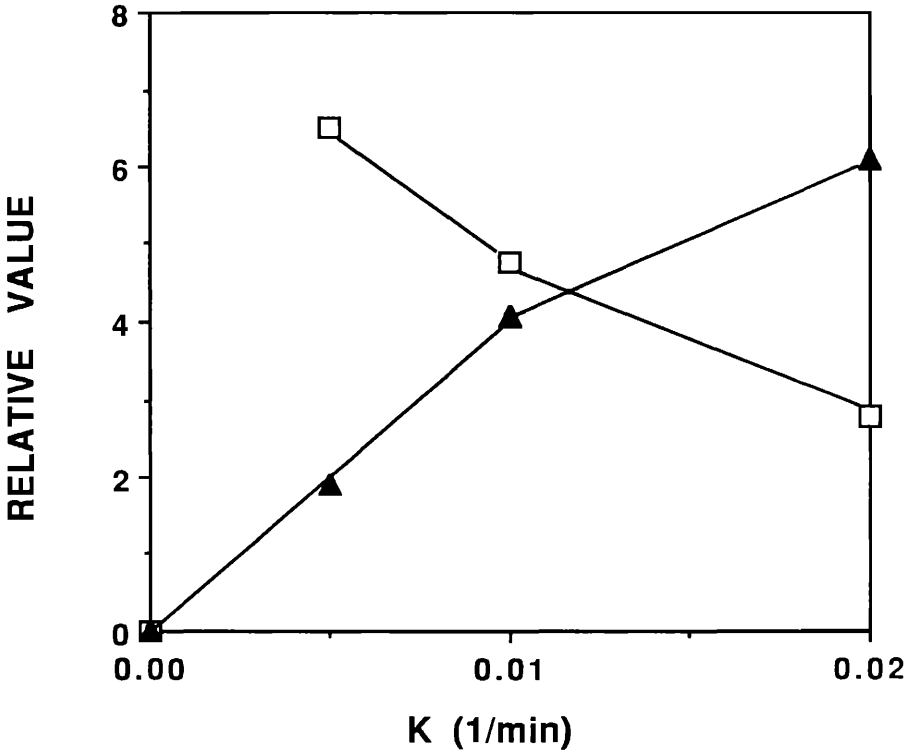


**Figure 8.** Effect of changes in intercompartmental transfer coefficient on skin and blood values. Other parameters are same as in Figure 5. □, amount in skin at 12 hours; ▲, blood concentration at 12 hours.

Recently Rougier and co-workers described studies they conducted on short-term application of drug solutions to human volunteers and animals (6). The amount of radiolabeled drug excreted over a four-day period after a 30-minute application was proportional to the amount obtained in skin strips following the same application time. This relationship held for several drugs at different applied concentrations, regardless of vehicle (6). Therefore, skin stripping experiments can be predictive of the total amount of a substance that will eventually be absorbed into the body.

We were interested in exploring the effect of several parameters on excretion and blood values, using the simulation model to mimic conditions used by Rougier and co-workers. Figure 9 shows the relation between excretion and amount in the stratum corneum under conditions such that the only variable was the SC/vehicle partition coefficient. This corresponds to the use of different drugs or possibly the same drug in several vehicles with the varying solubility. As was shown by Rougier *et al.* (6), the amount excreted after four days is proportional to the amount in the stratum corneum. Furthermore, so are the peak blood concentrations (Figure 10).

Figure 11 shows how differences in transport coefficient (K) affect 96-hour excretion values and peak blood levels. This amounts to comparing permeants that have different diffusion coefficients but the same partitioning behavior. The amount found in the stratum corneum was essentially the same in every case. Blood concentrations were

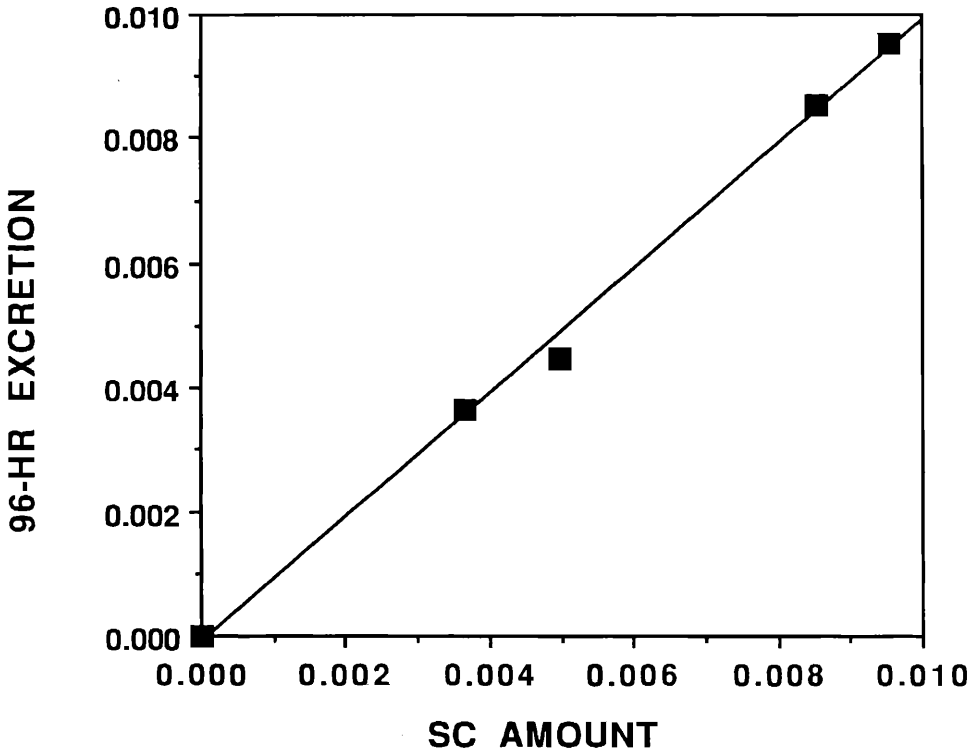


**Figure 9.** Amount excreted in urine at 96 hours versus amount in the stratum corneum at 30 minutes, both following 30-minute application, for various values of PC. (K = 0.02 $min^{-1}$; donor concentration = 10 mg/ml; donor volume = 5 μl; elimination rate constant = 0.0016 $min^{-1}$; volume of distribution = 5000 ml).

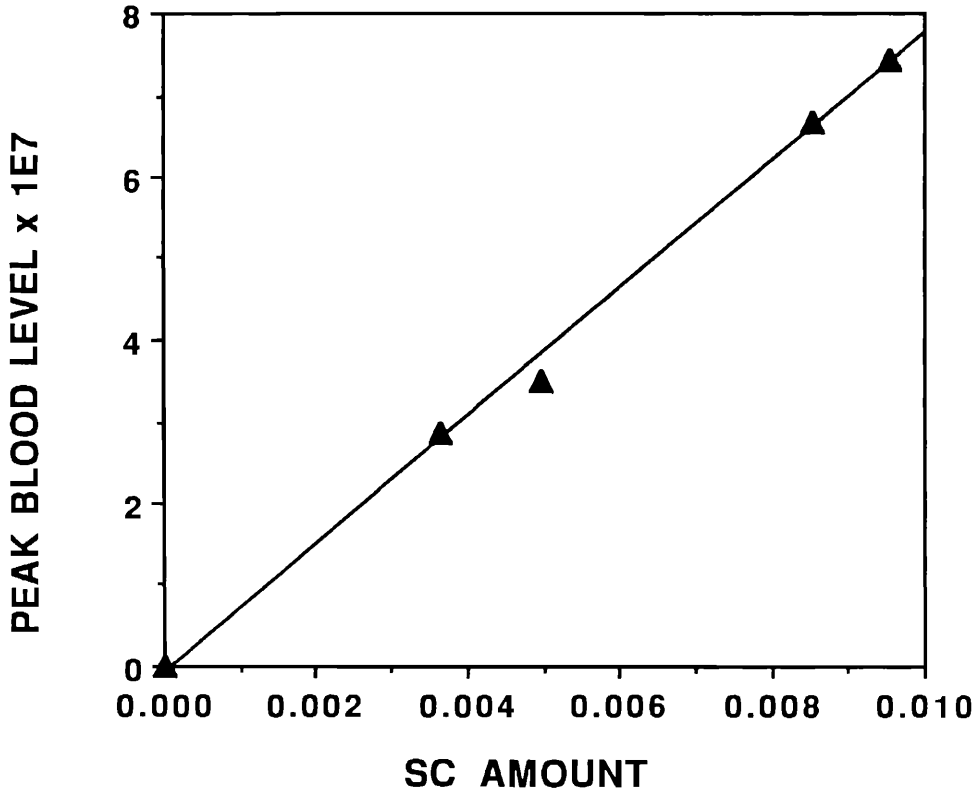


**Figure 10.** Peak blood levels versus amount in the stratum corneum at 30 minutes, both following 30-minute application, for various values of PC. Parameter values are same as in Figure 9.

inversely related to K. For three of the hypothetical permeants, the amounts excreted at four days were approximately the same, as would be expected. However, where the transport coefficient was very low (0.00125 or 0.0025 $min^{-1}$), the amount excreted was significantly less than from the other applications. This is explained by deviation from two assumptions made in designing the experiment. One is that four days is sufficient to allow essentially complete absorption of whatever has been sorbed by the stratum corneum; the second is that four days is long enough to allow essentially complete elimination of what has entered the blood. Either or both of these assumptions may be violated in situations in which the rate of transport across the stratum corneum is remarkably slow. A lack of correlation would also be expected if the elimination rate constant were extremely small.

## CONCLUSIONS

While it is risky at the present time to model skin permeation without conducting preliminary experiments, simulations of the type described in this paper are a useful adjunct to the empirical information obtained in the laboratory. Using this approach, we can anticipate the effects of changing permeation parameters and/or pharmacokinetic characteristics of substances applied to the skin. While the quantitative differences

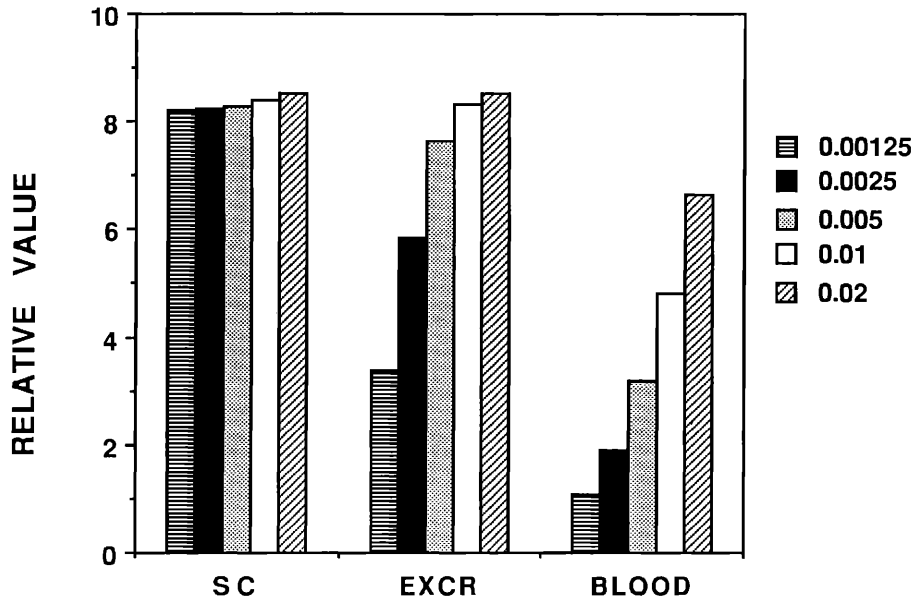


**Figure 11.** Effect of K on relative value of amount in stratum corneum at 30 minutes, amount excreted at 96 hours, and peak blood concentration. (PC = 10; other parameter values are same as in Figure 9.)

described above depend on the particular parameters employed in setting up the simulations, the trends are quite general. The type of data presented in this paper helps to identify factors significantly affecting skin transport.

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