($K \ll B$) at low initial amounts to 1 at high initial amounts, the exponent in Eq. 1 (the reciprocal of the time constant) will vary from M/V to $M/2V$ in those cases where $V_1 = V_2$. For the example considered, where the volumes are unity, the respective time constants are 1 and 0.05, and the respective half-lives are 0.693 and 0.693/2. At low initial amounts, C_P is ~0.5 C_E and 0.75 C_E at the times 0.693 and 0.693 × 2, respectively. The corresponding errors as previously defined would be 50 and 25%. At high initial amounts, C_P is ~0.75 C_E and 0.9375 C_E ($1 - 0.5^4$) C_E at the times 0.693 and 0.693 × 2, respectively. The corresponding errors are 25 and 6.25%.

A criterion for deciding whether Eq. 4 is applicable is easily established by using the equation with a few concentrations paired in time from the two experiments. Since the equilibrium concentration is time independent, the values calculated by concentrations obtained at different times should be in agreement within experimental error. Having established linearity, the free fraction α can be evaluated using Eq. 2.

Nonlinear kinetics should be suspected when a lack of consistency in the estimated equilibrium concentrations is manifested. In principle, the estimated equilibrium values calculated using Eq. 4 converge to the true equilibrium value when evaluated with concentrations obtained at later times (note how relative error changes as function of time in the nonlinear region in Fig. 1). Under such circumstances, Eq. 4 should not be employed.

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Influence of Protein Binding on the Accumulation and Depletion of Drug from the Skin

Keyphrases □ Protein binding--accumulation and depletion of drug from skin

To the Editor:

Recently the drug scopolamine has been shown to exhibit a nonlinear sorption isotherm with skin (1). The binding was deduced to be associated with the proteinaceous phase since the sorption isotherm was not significantly changed by removal of lipids (1). For drugs that bind in a saturable fashion to skin, the binding can have dramatic effects on the transport process as manifested by an increase in the diffusional lag time with a decrease in the upstream concentration (2). To elucidate the effect of reversible binding, describable by the law of mass action, on the accumulation and depletion of drug from the skin, a simple model will be considered. A fixed volume of skin will be considered to be well-stirred such that within the skin there are no gradients of free drug normal to the surface. The clearance per unit surface area of free drug from this volume is equivalent to the permeability of the drug through the skin. Sink conditions are assumed to exist, and the product of the free concentration and clearance represents the mass rate input into the body. Analysis of the simple model rather than the transport model characterized by a nonlinear diffusion equation suffices to bring forth the influence of the saturable, reversible binding on the accumulation and depletion of drug in the skin.

The dynamics of the accumulation and depletion of drug will individually be investigated as a function of the steady-state concentration in the skin. The dynamics will then be compared between the two modes at given steady-state concentrations. During the accumulation mode, steady-state concentrations will be envisioned to be established by constant fluxes applied to the skin. Upon removal of the input, the steady-state concentrations become the initial concentrations for the depletion mode. The use of the nonlinear binding to achieved prolonged delivery to the body in the depletion mode and methods to shorten accumulation rates relative to depletion rates are then discussed.

The nonlinear system will exhibit linear behavior when the binding isotherm is in the linear region or the fraction of bound drug becomes very small. Thus, a linear system serves as an extrapolative extreme for the nonlinear system. In the linear system the accumulation of drug within the skin is given by the following equation:

$$C = C_{ss}(1 - e^{-k_{el}t}) \qquad \text{(Eq. 1)}$$

$$C_{ss} = \frac{J \cdot A}{CL}$$

where C is the concentration in the skin during accumulation, C_{ss} is the steady-state concentration, J is the flux applied to the skin, A is the area to which the flux is applied, k_{el} is the elimination rate constant from the skin, CL is the clearance from the skin, and t is time. The depletion of drug from the skin once steady state has been achieved and the input removed is given by:

$$C = C_{ss}e^{-k_{el}t} \qquad \text{(Eq. 2)}$$

where C is the concentration during depletion. In Eq. 2 t is relative to the time depletion commences. The accumulation and depletion curves are symmetrical around $C = 0.5\ C_{ss}$. The symmetry of the curves is maintained regardless of the magnitude of the elimination rate constant. The time to reach 50% of the steady-state concentration in the accumulation mode and the time to fall to 50% of the steady-state concentration in the depletion mode are equal. The equality becomes apparent when the equations are rearranged to express time explicitly as a function of the ratio of the concentration at time t to the steady-state concentration. Equations 3 and 4 correspond to Eqs. 1 and 2, respectively.

$$t = (1/k_{el}) \ln \frac{1}{1 - C/C_{ss}} \qquad \text{(Eq. 3)}$$

and

$$t = (1/k_{el}) \ln \frac{C_{ss}}{C} \qquad \text{(Eq. 4)}$$

Thus, from either Eq. 3 or 4, the time at which $C/C_{ss} = 0.5$ (hereafter called t_{50}), is $(1/k_{el}) \ln 2$.

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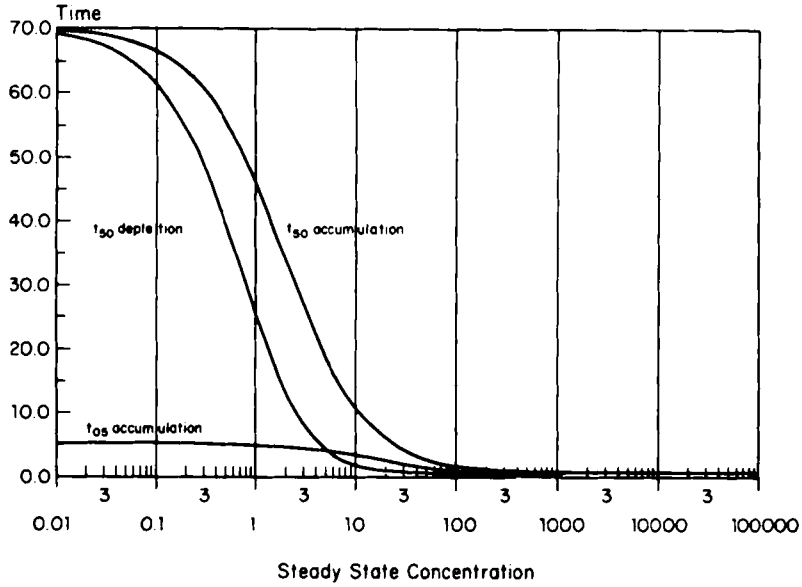

Figure 1—t_{50} *for accumulation and depletion, and* t_{05} *for accumulation,* versus, *the steady-state concentration or normalized flux* (k_{el} = *1*, B = *100*, K = *1*).

The equations representing the accumulation and depletion in the nonlinear system have been solved in closed form (3). The nonlinear differential equations for both modes are integrable and yield implicit solutions of the concentration as a function of time. The equation for the accumulation mode is:

$$\left[\frac{BK}{(K+C_{ss})^2}+1\right]\ln\frac{1}{1-C/C_{ss}} + \frac{BK}{(K+C_{ss})^2}\ln\frac{K+C}{K}+\frac{B}{K+C_{ss}}\cdot\frac{C}{K+C}=k_{el}t \quad \text{(Eq. 5)}$$

where C is the concentration of free drug in the skin at time t, C_{ss} is the steady-state concentration, K is the dissociation constant of the drug protein complex, B is the equivalent concentration of binding sites, and k_{el} is the elimination rate constant.

The equation for the depletion mode is:

$$\left(\frac{B}{K}+1\right)\ln\frac{C_{ss}}{C}+\frac{B}{K}\ln\frac{K+C}{K+C_{ss}}+\frac{B(C-C_{ss})}{(K+C_{ss})(K+C)}=k_{el}t \quad \text{(Eq. 6)}$$

The t_{50} of the steady-state concentration in both the accumulation and depletion modes was evaluated as a function of the steady-state concentration for a nonlinear system where $B = 100$, $K = 1$, and $k_{el} = 1$. The steady-state concentration can be achieved through a constant mass delivery to a defined area of skin. The results of the analysis are presented in Fig. 1. Since the elimination rate constant from the skin is unity, the abscissa for Fig. 1 can be viewed as the flux per unit thickness of skin. Considering the abscissa to represent a flux-like term will be particularly useful when discussing the accumulation mode.

Examination of Fig. 1 reveals that t_{50} for the accumulation mode is always greater than that for the depletion mode except at the extremes in steady-state concentration. At either extreme (high- or low-steady-state concentration) t_{50} for both the accumulation and depletion modes converge, and the common values become independent of the steady-state concentration. At low-steady-state concentrations the binding remains in the linear region throughout the accumulation to and depletion from these upper bounds (steady-state concentrations). At high steady-state concentrations the bound fraction becomes small relative to these steady-state concentrations and the system assumes a linear character. When the free concentrations are in the nonlinear region of protein binding for a significant period of time in either mode relative to the time used to characterize the system, *e.g.*, t_{50}, an asymmetry will be manifested in these times.

The independence of t_{50} from the steady-state concentration, exhibited at the extremes in Fig. 1, is a manifestation of linearity. Note that the time in either Eq. 3 or 4 is a function of C/C_{ss}. In contrast the nonlinear equations (Eqs. 5 and 6) cannot be rearranged to eliminate an explicit dependence of t_{50} on C_{ss}.

The larger value of t_{50} at the low concentration, linear limit compared with the high concentration, linear limit is a manifestation of an apparent volume increase due to the protein binding. Since the clearance from a fixed area of skin is constant, t_{50} will increase as the volume increases. The apparent volume of distribution at the low concentration linear limit relative to the volume at the high concentration linear limit is $(1 + B/K)$. Thus, the apparent 100-fold expansion in volume at the low concentration, linear limit becomes reflected in a corresponding increase in t_{50} at this limit relative to the high concentration, linear limit.

In the nonlinear region between the linear extremes, t_{50} increases monotonically as the steady-state concentration decreases for both the accumulation and depletion modes. The lower the initial concentration, the longer the free concentrations will remain above 50% of the initial concentration (steady-state concentration) in the depletion mode. The depletion of the drug in the skin as measured by the decline in the free concentrations is buffered by the drug–protein interaction. The buffering effect is greater with low concentrations, since under these conditions a larger fraction of the drug will be bound.

Since the steady-state free concentration is proportional to the flux, low initial concentrations can be achieved with low fluxes. To achieve the same mass rate input into the body at steady state, and the same amount of free drug in the skin at the initiation of the depletion mode, a reduction in the flux must be compensated for by an increase in the area. Thus, after removal of the input to the skin, the mass rate input to the body declines from a common value but more slowly with the lower

initial concentration. The extra mass required to prolong delivery to the body is provided for by the larger amount of bound drug in the skin in cases where low initial concentrations and appropriately adjusted areas are used to obtain the same initial amount of free drug.

On the other hand, t_{50} for the accumulation mode is always greater than or equal to that for the depletion mode. Thus, in achieving prolongation to the body by reducing the steady-state concentration a price is paid in terms of an increase in t_{50} for accumulation. The protraction in time required to reach steady state with the reduced flux can be circumvented by first delivering drug to the skin at a high flux for a short duration. After application of the pulse to promote the rapid attainment of the desired free concentration, the mass delivery rate to the body can easily be maintained. For the simple model, the system will be in steady-state instantly if the second flux (maintenance flux) is initiated at a concentration that is its steady-state concentration.

The effect of a pulse, which has a flux 10-fold higher than the maintenance flux, can be elucidated by comparing t_{05}, the time to reach 5% of the steady-state value for the pulse, with t_{50} for the maintenance flux. Since the higher flux establishes a proportionally higher steady state concentration, 50% of the steady-state concentration generated with a given flux and 5% of the steady-state concentration generated with a flux 10-fold higher are the same concentration. The curve representing the relationship between the t_{05} values and the steady-state concentration is presented in Fig. 1. In comparing the difference between t_{50} and t_{05} in Fig. 1, the comparison should be made with t_{05} values at steady-state concentrations 10-fold higher than those for corresponding t_{50} values. The difference increases as the steady-state concentration decreases, reaching the maximum value at the low flux, linear limit. Both t_{05} and t_{50} will become independent of the flux at the limit. The large apparent volume of distribution at this limit causes a magnification of the time constant, t_{50}, t_{05}, and the time differences.

A comparison of the t_{05} values for accumulation with the t_{50} values for depletion, where the flux is 10-fold higher for the former compared with the latter values, indicates the effect of the pulse on the dynamics of accumulation relative to depletion. The t_{05} values are generally less than the t_{50} values for depletion. The pulse reduces the accumulation time such that it is now less than the depletion time; without the pulse the accumulation time is always greater than or equal to the depletion time. Thus, with the use of a pulse followed by a reduced flux, the rapid attainment of steady state, low free concentrations, and prolonged delivery to the body after removal of the input are all achievable.

In principle there is maximum flux on the upper limit of the flux which the skin can accept, hereafter called the maximum flux. The maximum flux is achieved when the penetrant is at unit thermodynamic activity on the skin surface. Conceivably there are circumstances under which the maximum flux should be employed; for instance, if the minimum area of coverage and/or the most rapid termination is desired. The bend (region of nonlinearity) in the free concentration *versus* time curve for the simple nonlinear model occurs at concentrations in the vicinity of dissociation constant and is independent of the initial concentration (4). Therefore, a larger fraction of the drug can be removed from the skin in a given period of time the larger the initial concentration. In a linear system, the same fraction would be removed in a given period of time regardless of the initial concentration.

Using the maximum flux to achieve the highest steady-state concentration in the skin fixes the accumulation time t_{50}. The use of a two-pulse sequence where the flux of the first pulse exceeds the maximum flux is not possible. Although the accumulation time could be shortened by applying the maximum flux to a larger area of skin for a defined period and then reducing the flux, considerations of minimum coverage and/or rapid termination would be compromised.

In conclusion, transdermal input should be designed with a consideration of the influence of protein binding on the transport process. Because of the protein binding, the accumulation and depletion times, defined on the basis of the times to reach or decline to a given fraction of the steady-state concentration, respectively, are not independent of the steady-state concentration. Thus, the dynamics will vary for cases where different fluxes and corresponding changes in area are used to obtain the same total mass input rate. In addition, protein binding creates an inherent assymmetry in the dynamics of the accumulation and depletion modes.

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