Prediction of Drug Disposition Kinetics in Skin and Plasma Following Topical Administration

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Received February 28, 1983, from the **Departments of Pharmacy and Pharmaceutical Chemistry, School of Pharmacy, University of California-San Francisco, San Francisco, CA 94143* and the ‡*Department of Pharmacy, University of Nottingham, University Park, Nottingham, NG7 2RD, U.K.* Accepted for publication May 23, 1983.

Abstract □ The development of a physically based pharmacokinetic model for percutaneous absorption is described. The simulation includes four first-order rate constants assigned the following significance: (*a*) absorption across the stratum corneum; (*b*) diffusion through the viable tissue; (*c*) a retardation process which retains penetrant in the stratum corneum (and hence provides a means to mathematically produce a "reservoir" effect, for example); and (*d*) uptake from the skin into the systemic circulation and subsequent elimination from the body. The kinetic equations of the model are solved and expressions are obtained for the concentration of penetrant within the stratum corneum (and available to subsequently partition into the viable epidermis) and the plasma concentration of the administered substance, as a function of time. Using example values for the four rate parameters, disposition profiles for the penetrant in skin and plasma were derived. The cases considered cover slow and fast stratum corneum penetrants, substances which are excreted rapidly or slowly from the body, and absorbing molecules with a variety of relative stratum corneum-viable tissue affinities. The results suggest a framework for the prediction of pharmaceutically and clinically relevant information following the topical administration of therapeutic agents for local or systemic effect.

Keyphrases □ Percutaneous absorption—pharmacokinetics of skin penetration, plasma concentration prediction □ Plasma concentration prediction—pharmacokinetics, percutaneous absorption, topical administration □ Pharmacokinetics—percutaneous absorption, plasma concentration prediction, topical administration

Percutaneous absorption is a complex phenomenon which is currently attracting an increasing level of study. In addition to the fundamental goal of more completely understanding skin penetration, an important reason for this expanded effort is the somewhat recently realized potential for effective systemic drug delivery using the transdermal route (1-3). Equally pertinent, and now subject to some reexamination, is consideration of the efficaciousness of existing drugs and dosage regimens for the treatment of local dermatological disease.

The heightened interest in percutaneous absorption encompasses many aspects: (*a*) the development of new delivery systems (4-6), (*b*) the search for agents capable of enhancing penetration (7-11), and (*c*) the continuing effort to understand skin absorption rate and extent in terms of accepted biological facts and penetrant physicochemical properties (12-20). In the first group, one may cite the appearance of transdermal therapeutic systems containing nitroglycerin for the treatment of angina pectoris (21) and the surprising suggestion that topically applied liposomes are able to exert an influence on the local and systemic distribution of an encapsulated drug (22, 23). Of the agents offered as penetration enhancers, pyrrolidone, formamide, and sulfoxide derivatives are recent examples (7-11, 24). Another new compound, dodecylazacycloheptan-2-one (25, 26), appears to have enhancement potential, although its mechanism of promotion remains unclear.

It is the third category, however, to which this paper is directed. Specifically, the objectives are to present a physically based pharmacokinetic model for percutaneous absorption and to demonstrate its application to the prediction of drug disposition kinetics in skin and plasma following topical administration. The simulation is that recently described by Guy *et al.* (27). The approach is simplistic in concept, but sensitive to physicochemical changes in penetrant properties and to the manner in which the absorbing molecule may be expected to interact with the various strata of the skin. Four rate constants are specified in the model and are assigned specific physical significance. The previous work (27) showed that the urinary excretion rate data of three compounds (testosterone, benzoic acid, and hydrocortisone), obtained following topical application, can be successfully explained by the simulation and that rate constants, which are physicochemically consistent, can be derived. In this paper, the rate equations of the model are solved for (*a*) the concentration of penetrant within the stratum corneum and (*b*) the concentration of drug in plasma. Reasonable, representative values are assigned to the four kinetic parameters and drug disposition profiles are generated for a variety of example cases. The predictive capacity of the approach in clinically relevant situations is indicated and discussed.

THEORETICAL SECTION

Schematic and compartmental representations of the pharmacokinetic model are shown in Fig. 1 and are designed to indicate the putative physical significance on which this work is based. The simulation is linear and includes four first-order rate constants. The first (k_1) describes drug input across the stratum corneum and is a parameter that might be estimated, for example,

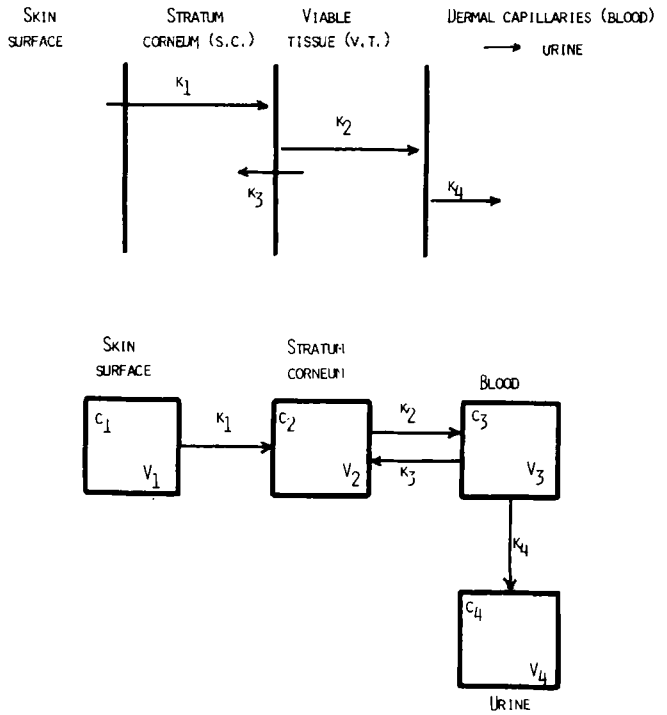

Figure 1—*Schematic and compartmental representations of the percutaneous absorption pharmacokinetic model.*

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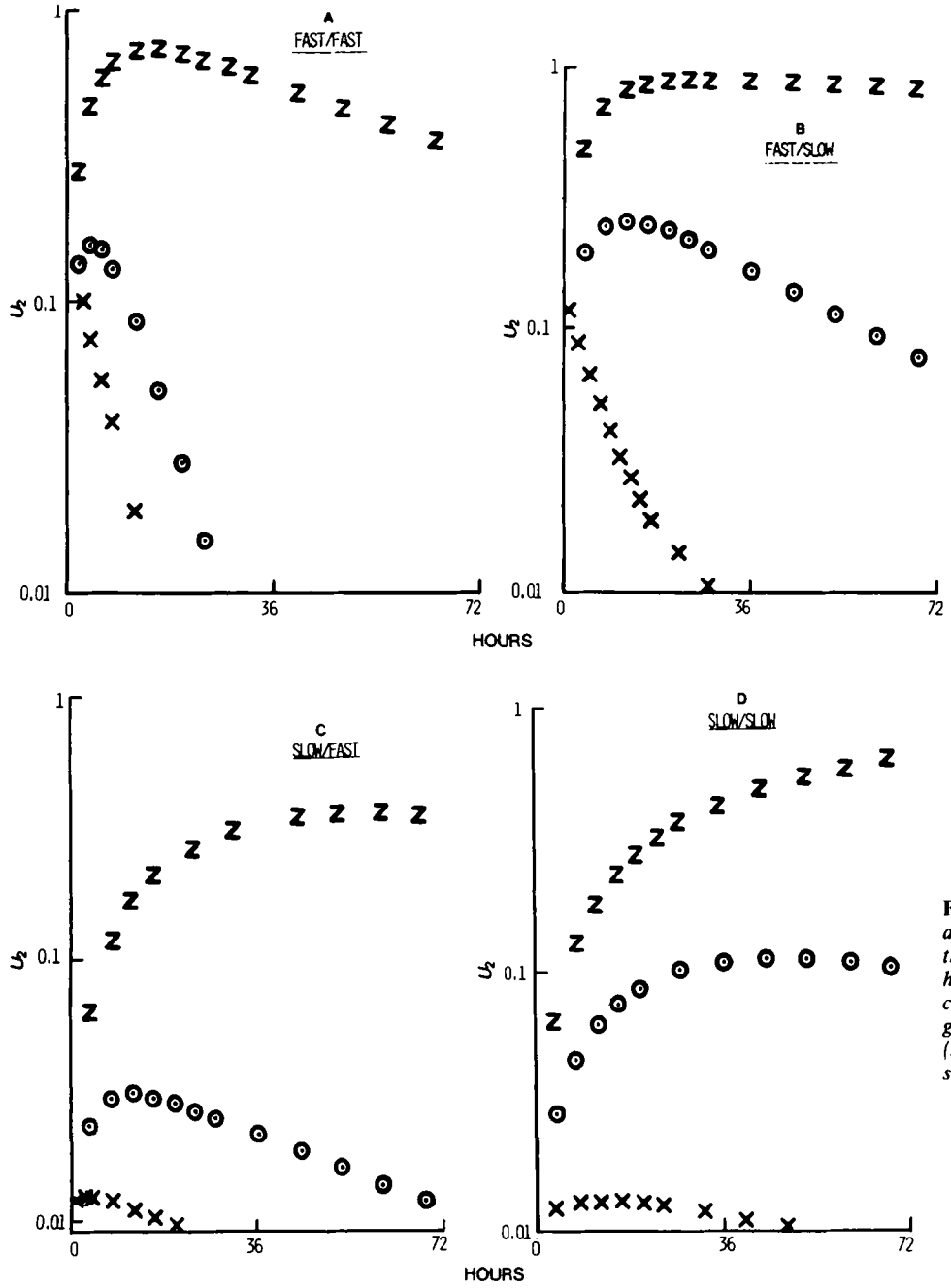

Figure 2—*Prediction of skin disposition kinetics as a plot of normalized concentration* u_2 versus *time. The curves correspond to penetrants with high (Z), medium (⊙), and low (X) stratum corneum affinities. Rate constants* k_1-k_4 *are given in Tables I and II. Key: (A) case fast/fast; (B) case fast/slow; (C) case slow/fast; (D) case slow/slow.*

by the disappearance of radioactivity from the skin surface following topical application of labeled compound (28, 29). The second, k_2, relates to drug penetration further into the skin, specifically movement across the aqueous viable tissue. The kinetic constant k_3 reflects the relative affinity of the penetrant for the stratum corneum compared with the viable tissue; in other words, k_3 will be large (relative to k_2) for substances that bind tightly to the stratum corneum or that exhibit a marked "reservoir" effect (30–33). Finally, k_4 describes drug elimination from the systemic circulation into the urine. The assignment of a first-order process for this step may, of course, be inadequate, in which case a more complex formulation will be necessary. In this instance, the theoretical treatment becomes more complicated but far from intractable. The previous description of this model indicates that it is particularly useful if the elimination of drug following parenteral administration is known (27, 29). Thus, ideally, application of the simulation includes independent assessment of the elimination process described by k_4 or a more sophisticated alternative.

Four concentrations are identified by the compartmentalization of the model. Surface concentration is C_1 and, in the following mathematical development, $C_1 = C_0$, the initial applied concentration, at time $t = 0$, *i.e.*, at the beginning of the experiment. Because of the assigned significance of k_2 and k_3, C_2 may be equated with the concentration of drug in the stratum corneum and available for subsequent partitioning into the viable tissue. Estimation of this parameter is useful, therefore, in terms of the dermatological application of the model. The concentration of drug in blood is represented by C_3. No attempt is made to differentiate between drug in the local cutaneous

Table I—Input (k_1) and Output (k_4) Rate Constants Selected for Application of the Model

Case	k_1, h^{-1}	k_4, h^{-1}
Fast/Fast	0.180	0.360
Fast/Slow	0.180	0.036
Slow/Fast	0.018	0.360
Slow/Slow	0.018	0.036

Table II—Rate Constants (k_2 and k_3) Chosen for Application of the Model

k_2, h^{-1}	k_3, h^{-1}	k_3/k_2	Relative Stratum Corneum Affinity
1.440	28.800	20.00	"High"
1.440	0.720	0.50	"Medium"
1.440	0.029	0.02	"Low"

Table III—Rate Constants (k_1–k_4), Previously Determined for Testosterone, Benzoic Acid, and Hydrocortisone, Used to Generate the Disposition Profiles[a]

Compound	k_1, h^{-1}	k_2, h^{-1}	k_3, h^{-1}	k_4, h^{-1}
Testosterone	0.058	1.44	2.70	0.104
Benzoic acid	0.184	2.88	0.014	0.592
Hydrocortisone	0.022	1.44	0.180	0.158

[a] See Figs. 3 and 5; the values were taken from Ref. 27.

microvasculature and drug systemically available. Because it is not possible to sample the dermal capillaries, such a refinement is not presently justified by experimental capabilities. Lastly, C_4 is the concentration of drug in the urine; it follows that attention is focused on the renal excretion of the drug and this may or may not be an appropriate decision. However, because of the stipulation suggested above that drug excretion following intravenous dosing be assessed as a matter of course, then suitable corrections can be applied to take into account the elimination of the drug by other routes (29).

Four rate equations describe the kinetics of the model in Fig. 1:

$$\frac{dC_1}{dt} = -k_1 C_1 \qquad \text{(Eq. 1)}$$

$$\frac{dC_2}{dt} = \frac{V_1}{V_2} k_1 C_1 - k_2 C_2 + \frac{V_3}{V_2} k_3 C_3 \qquad \text{(Eq. 2)}$$

$$\frac{dC_3}{dt} = \frac{V_2}{V_3} k_2 C_2 - (k_3 + k_4) C_3 \qquad \text{(Eq. 3)}$$

$$\frac{dC_4}{dt} = \frac{V_3}{V_4} k_4 C_3 \qquad \text{(Eq. 4)}$$

where V_1–V_4 correspond to the volumes of compartments 1–4, respectively. Manipulation of the equations to obtain an expression for the amount of drug appearing in the urine as a function of time has been presented previously (27). The reduction to achieve relationships pertaining to drug levels in skin (C_2) and plasma (C_3) follow parallel steps (see *Appendix*). The drug concentration in the stratum corneum available for partitioning into the viable epidermis is:

$$u_2 = \frac{V_1}{V_2} k_1 \left[\frac{(k_3 + k_4 - k_1) \cdot \exp(-k_1 t)}{(k_1 - \alpha)(k_1 - \beta)} + \frac{(k_3 + k_4 - \alpha) \cdot \exp(-\alpha t)}{(\alpha - \beta)(\alpha - k_1)} + \frac{(k_3 + k_4 - \beta) \cdot \exp(-\beta t)}{(\beta - k_1)(\beta - \alpha)} \right] \qquad \text{(Eq. 5)}$$

The drug concentration in blood is given by:

$$u_3 = \frac{V_1}{V_3} k_1 k_2 \left[\frac{\exp(-k_1 t)}{(k_1 - \alpha)(k_1 - \beta)} + \frac{\exp(-\alpha t)}{(\alpha - \beta)(\alpha - k_1)} + \frac{\exp(-\beta t)}{(\beta - k_1)(\beta - \alpha)} \right] \qquad \text{(Eq. 6)}$$

In Eqs. 5 and 6, u_2 and u_3 are normalized concentrations (with respect to the initial applied concentration, C_0), *i.e.*:

$$u_2 = C_2/C_0 \qquad \text{(Eq. 7)}$$

$$u_3 = C_3/C_0 \qquad \text{(Eq. 8)}$$

and α and β are the roots of a quadratic (see *Appendix*) such that:

$$\alpha\beta = k_2 k_4 \qquad \text{(Eq. 9)}$$

$$\alpha + \beta = k_2 + k_3 + k_4 \qquad \text{(Eq. 10)}$$

As discussed previously for drug in urine (27), Eqs. 5 and 6 may be multiplied by a factor F, which is the fraction of the applied topical dose and metabolites recovered (and corrected for nonrenal excretion) in compartment 4.

EXPERIMENTAL SECTION

Using Eqs. 5 and 6, it is now possible to predict drug disposition kinetics in skin and plasma for various combinations of the four rate constants k_1–k_4. To illustrate this ability, the following approach is adopted. The input (k_1) and output (k_4) processes are arbitrarily defined as "fast" and "slow," thereby allowing four possible combinations (fast/fast, fast/slow, slow/fast, and slow/slow). Then, for each of these combinations, u_2 and u_3 are calculated for "high," "medium," and "low" ratios of k_3/k_2, *i.e.*, for different relative stratum corneum–viable tissue affinities. The numerical values selected for the rate constants are given in Tables I and II. The choice of the k_1 and k_4 ranges reflects the span observed previously between benzoic acid, testosterone, and hydrocortisone (27, 29). The k_3/k_2 ratios are designed to illustrate the ramifications of varying the effective stratum corneum–viable tissue partition coefficient[1] of the penetrant over a range of three orders of magnitude. A value of $40 \times 10^{-5}\ s^{-1}$ ($1.44\ h^{-1}$) was assigned to k_2 throughout. Such a figure has been shown to correspond to an effective solute diffusion coefficient through the viable tissue of $\sim 10^{-7}\ cm^2/s$; this is in reasonable agreement with earlier independent assessments (34). The k_3 values employed again span, but also extend, the range identified for the three penetrants given above (27). Because it is unlikely that a penetrant with less reservoir-forming ability than benzoic acid will be identified, the k_3 range has been extended in the direction of increasing stratum corneum affinity. Finally, to evaluate u_2 and u_3, V_1 and V_2 have been estimated as essentially equal for typical topical applications (*i.e.*, $V_1/V_2 \simeq 1$) and V_1/V_3 has been set equal to 2×10^{-5}, based on an applied volume of 100 μL and a plasma volume of 5 L. Hence, with four combinations of k_1 and k_4 and three k_3/k_2 values, twelve assessments each of u_2 and u_3 can be made.

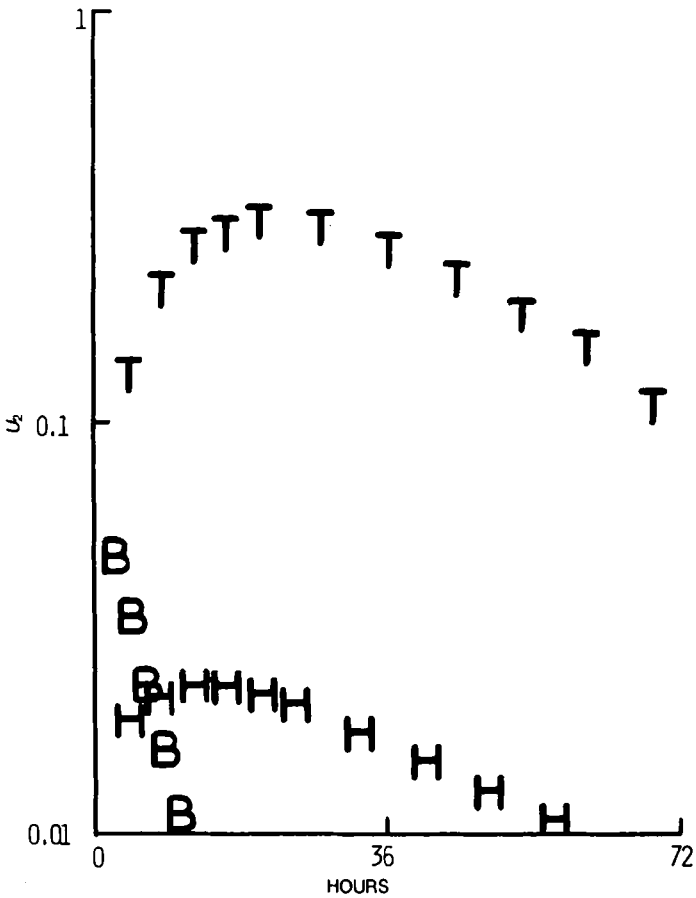

Figure 3—*Skin disposition profiles (u_2) as a function of time for testosterone (T), benzoic acid (B), and hydrocortisone (H). The curves were evaluated using the rate constants in Table III and Eq. 5.*

RESULTS AND DISCUSSION

Disposition Profiles in Skin—The graphs in Fig. 2 show a wide variety of behavior for the concentration–time course of a penetrant within the skin. There are marked differences between the curves in a quantitative sense of how much material can be found in the skin and for how long the substance is maintained within the cutaneous region. The curves clearly indicate combinations of rate constants which may not prove efficacious for the treatment of local (nonsurface) dermatological disease. For example, penetrants with low k_3/k_2 ratios fall into this category: either the drug is very rapidly eliminated from the skin (Fig. 2A–C) or it is present in relatively insignificant amounts (Fig. 2D). On the other hand, penetrants which are expected to ex-

[1] It is important to point out that the ratio of k_3/k_2 is not a true partition coefficient in the classical sense. However, because of the assigned significance of the rate processes which k_2 and k_3 describe, their ratio (a "pseudo-partition coefficient") will be related to the conventional, though not easily measurable, distribution constant of the drug between the stratum corneum and the viable tissue.

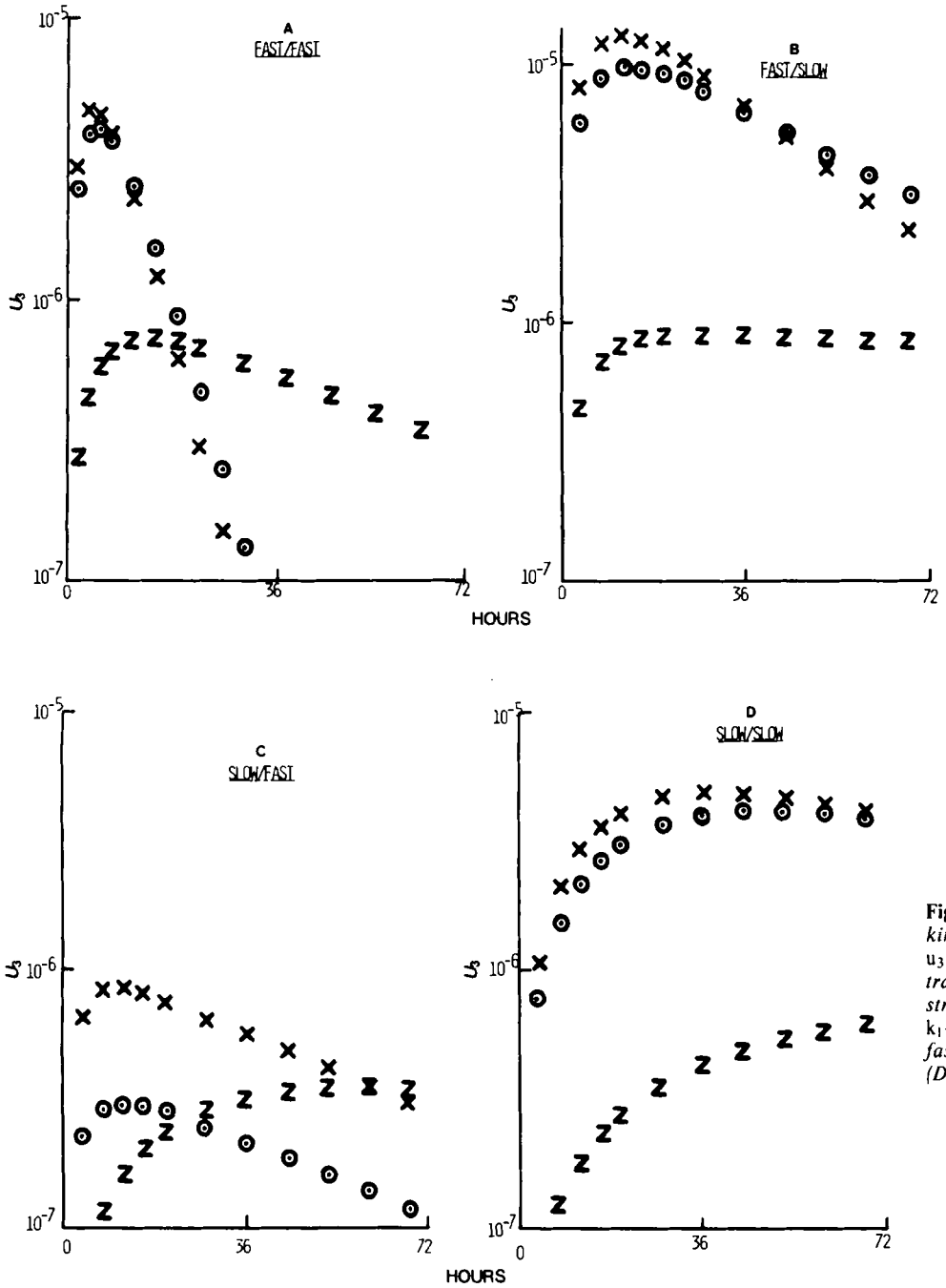

Figure 4—*Prediction of plasma disposition kinetics as a plot of normalized concentration* u_3 versus *time. The curves correspond to penetrants with high (Z), medium (⊙), and low (X) stratum corneum affinities. Rate constants* k_1-k_4 *are given in Tables I and II. Key: (A) case fast/fast; (B) case fast/slow, (C) case slow/fast; (D) case slow/slow.*

hibit substantial reservoir effects (30-33), *i.e.*, those with high k_3/k_2 values, achieve substantial and prolonged levels within the tissue. It may be noted that a fast/slow penetrant with $k_3/k_2 = 20$ (Fig. 2B, curve Z) produces potentially ideal local sustained-release characteristics over an extended time period. Of course, certain combinations of kinetic parameters may prove unlikely, *e.g.*, fast/fast with high k_3/k_2 and slow/slow with a low ratio. Furthermore, the model may not be able to distinguish between certain alternatives [the high k_3/k_2 curves in Fig. 2C (slow/fast) and D (slow/slow) provide such a case]. However, on the whole, the delineation between different permutations is good and the profiles, and their relative juxtaposition to one another, are consistent with the assigned physicochemical significance of the model.

In Figure 3, skin disposition curves are shown for testosterone, benzoic acid, and hydrocortisone. The profiles have been calculated using the rate constants quoted in the previous publication (27) of this kinetic model (see Table III). The distinction between the three compounds is striking—benzoic acid shows virtually no residence within the skin, merely a transient presence. The time course for the steroids is similar yet, quantitatively, testosterone achieves levels an order of magnitude greater than those of hydrocortisone. This observation is consistent with larger k_1 and k_3 values of testosterone and its consequently higher potential for stratum corneum reservoir formation.

Disposition Profiles in Plasma—Figure 4 shows the relative plasma disposition profiles for the various k_1-k_4 combinations considered. The curves provide a preliminary insight into the desirable transcutaneous properties required by a penetrant to be a candidate for systemic delivery *via* the topical route. Indication of sensible dosing intervals for such an objective is also available. Interestingly, the medium and low stratum corneum affinity penetrants are not distinguishable in terms of plasma level except for the slow/fast situation (Fig. 4C). Even then, the time course is identical; only the amounts are different. These observations are apparent despite a 25-fold difference between the k_3 values used in the medium and low cases. The reason for the apparent anomaly is straightforward. Only for slow/fast is the input (k_1) process substantially slower than the output (k_4) such that the differences in k_3 (medium *versus* low) can be reflected in the values of u_3.

In Figure 5, u_3 profiles for testosterone, benzoic acid, and hydrocortisone are plotted. The rate constants used for the calculations are given in Table III (27). Benzoic acid clearly falls into the fast/fast, low k_3/k_2 ratio, category. Testosterone and hydrocortisone climb to their maximum plasma levels more gradually and maintain appreciable concentrations over a prolonged period. The potential for sustained transdermal delivery of endogeneous corticosteroid hormones to treat clinical deficiencies would, therefore, appear attractive.

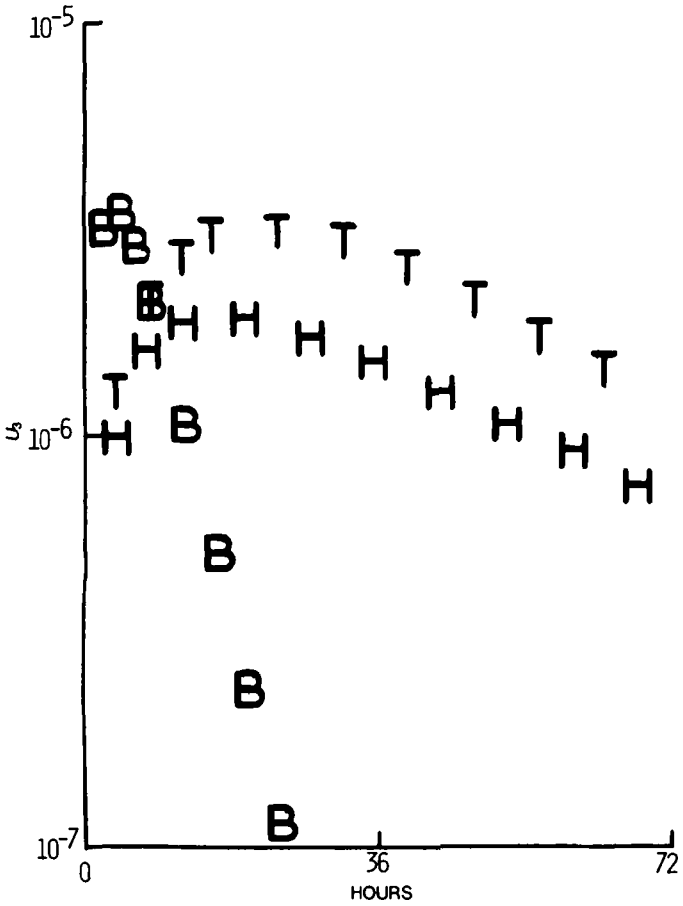

Figure 5—*Plasma disposition profiles (u_3) as a function of time for testosterone (T), benzoic acid (B), and hydrocortisone (H). The curves were evaluated using the rate constants in Table III and Eq. 6.*

APPENDIX

In this appendix, the derivation of Eqs. 5 and 6 is outlined. First, all concentrations are normalized with respect to C_0, the concentration in compartment 1 at $t = 0$:

$$u_i = C_i/C_0 \; (i = 1, 2, 3, 4) \qquad \text{(Eq. A1)}$$

Solutions for u_2 and u_3 are obtained using the technique of Laplace transformation. Substituting Eq. A1 into Eqs. 1-4 and transforming gives:

$$s\bar{u}_1 = 1 - k_1\bar{u}_1 \qquad \text{(Eq. A2)}$$

$$s\bar{u}_2 = \frac{V_1}{V_2}k_1\bar{u}_1 - k_2u_2 + \frac{V_3}{V_2}k_3\bar{u}_3 \qquad \text{(Eq. 3A)}$$

$$s\bar{u}_3 = \frac{V_2}{V_3}k_2\bar{u}_2 - (k_3 + k_4)\bar{u}_3 \qquad \text{(Eq. A4)}$$

$$s\bar{u}_4 = \frac{V_3}{V_4}k_4\bar{u}_3 \qquad \text{(Eq. A5)}$$

Equation A2 gives an expression for u_1, which may be substituted into Eq. A3. This latter equation and Eq. A4 then provide a pair of simultaneous equations which may be solved for u_2 and u_3. The algebra is trivial and the following results are obtained:

$$\bar{u}_2 = \frac{V_1}{V_2}\left[\frac{k_1(s + k_3 + k_4)}{(s + k_1)(s + \alpha)(s + \beta)}\right] \qquad \text{(Eq. A6)}$$

$$\bar{u}_3 = \frac{V_1}{V_3}\left[\frac{k_1k_2}{(s + k_1)(s + \alpha)(s + \beta)}\right] \qquad \text{(Eq. A7)}$$

where α and β are the roots of the quadratic:

$$s^2 + (k_2 + k_3 + k_4)s + k_2k_4 = 0 \qquad \text{(Eq. A8)}$$

Simple inversion of Eqs. A6 and A7 results in the expressions for u_2 and u_3 quoted in the text as Eqs. 5 and 6, respectively.

REFERENCES

(1) Y. W. Chien, "Novel Drug Delivery Systems," Dekker, New York, N.Y., 1982, pp. 149-217.

(2) S. K. Chandrasekaran and J. E. Shaw, in "Controlled Release of Bioactive Materials," R. Baker, Ed., Academic, New York, N.Y., 1980, pp 99-106.

(3) S. K. Chandrasekaran, H. Benson, and J. Urquhart, in "Sustained and Controlled Release Drug Delivery Systems," J. R. Robinson, Ed., Dekker, New York, N.Y., 1978, pp. 557-593.

(4) S. K. Chandrasekaran, A. S. Michaels, P. Campbell, and J. E. Shaw, *A.I.Ch.E.J.*, **22,** 828 (1976).

(5) J. E. Shaw, S. K. Chandrasekaran, A. S. Michaels, and L. Taskovich, in "Animal Models in Dermatology," H. I. Maibach, Ed., Churchill Livingstone, Edinburgh, U.K., 1975, pp. 138-146.

(6) S. K. Chandrasekaran, W. Bayne, and J. E. Shaw, *J. Pharm. Sci.*, **67,** 1370 (1978).

(7) S. A. Akhter, B. W. Barry, and M. C. Meyer, *J. Pharm. Pharmacol.*, **34,** 34P (1982).

(8) D. Southwell and B. W. Barry, *J. Pharm. Pharmacol.*, **33,** 1P (1981).

(9) D. Southwell and B. W. Barry, *J. Pharm. Pharmacol.*, **33,** 3P (1981).

(10) D. Southwell and B. W. Barry, "Abstracts," vol. 12(2), APhA Academy of Pharmaceutical Sciences, 1982, p. 129.

(11) S. A. Akhter, B. W. Barry, and M. C. Meyer, "Abstracts," vol. 12(2), APhA Academy of Pharmaceutical Sciences, 1982, p. 129.

(12) C. D. Yu, J. L. Fox, N. F. H. Ho, and W. I. Higuchi, *J. Pharm. Sci.*, **68,** 1341 (1979).

(13) C. D. Yu, J. L. Fox, N. F. H. Ho, and W. I. Higuchi, *J. Pharm. Sci.*, **68,** 1397 (1979).

(14) J. L. Fox, C. D. Yu, W. I. Higuchi, and N. F. H. Ho, *Int. J. Pharm.*, **2,** 41 (1979).

(15) W. J. Albery and J. Hadgraft, *J. Pharm. Pharmacol.*, **31,** 129 (1979).

(16) W. J. Albery and J. Hadgraft, *J. Pharm. Pharmacol.*, **31,** 140 (1979).

(17) J. Hadgraft, *Int. J. Pharm.*, **4,** 229 (1980).

(18) R. H. Guy and J. Hadgraft, *Int. J. Pharm.*, **11,** 187 (1982).

(19) J. Hadgraft, *Int. J. Pharm.*, **2,** 265 (1979).

(20) R. H. Guy and J. Hadgraft, *Int. J. Pharm.*, **6,** 321 (1980).

(21) P. Muller, P. R. Imhof, F. Burkart, L-C. Chu, and A. Gerardin, *Eur. J. Clin. Pharmacol.*, **22,** 473 (1982).

(22) M. Mezei and V. Gulasekharan, *Life Sci.*, **26,** 1473 (1980).

(23) M. Mezei and V. Gulasekharan, *J. Pharm. Pharmacol.*, **34,** 473 (1982).

(24) E. R. Copper, "Abstracts," vol. 12(2), APhA Academy of Pharmaceutical Sciences, 1982, p. 129.

(25) R. B. Stoughton, *Arch. Dermatol.*, **118,** 474 (1982).

(26) R. Vaidyanathan, G. L. Flynn, and W. I. Higuchi, "Abstracts," vol. 12(2), APhA Academy of Pharmaceutical Sciences, 1982, p. 126.

(27) R. H. Guy, J. Hadgraft, and H. I. Maibach, *Int. J. Pharm.*, **11,** 119 (1982).

(28) F. D. Malkinson, *J. Invest. Dermatol.*, **31,** 19 (1958).

(29) D. M. Anjo, R. J. Feldman, and H. I. Maibach, in "Percutaneous Penetration of Steroids," P. Mauvais-Jarvais, J. Wepierre, and C. F. H. Vickers, Eds., Academic, New York, N.Y., 1980, pp. 31-51.

(30) A. W. McKenzie and R. B. Stoughton, *Arch. Dermatol.*, **86,** 608 (1962).

(31) C. F. H. Vickers, *Arch. Dermatol.*, **88,** 20 (1963).

(32) R. B. Stoughton, *Arch. Dermatol.*, **91,** 657 (1965).

(33) R. K. Winkelman, *Br. J. Dermatol.*, **81** (Suppl. 4), 11 (1969).

(34) R. J. Scheuplein, *J. Invest. Dermatol.*, **48,** 79 (1967).

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