Quantitative Interpretation of *In Vivo* Buccal Absorption of *n*-Alkanoic Acids by the Physical Model Approach

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Abstract □ The human studies of Beckett and Moffat on the buccal absorption of *n*-alkanoic acids were quantitatively and mechanistically interpreted by the theoretical physical model approach. It is believed that a determination of the incremental partition coefficient for the methylene group in the relevant biophase has been achieved. Exceptionally good agreement of the absorption rate–buffer pH profiles between the experimental results and theory was found. The greater rates of absorption of the higher molecular weight acids in the homologous series at constant buffer pH of the drug solution are attributed entirely to the higher partition coefficients for these acids because their pKa values are essentially identical. However, the rightward shifts of the profiles of the homologous series relative to the dissociation curve are due not only to the increasing lipid solubility but also to the presence of an aqueous diffusion layer on the mucosal side of a biphasic aqueous–lipid barrier. A self-consistent, biophysically meaningful factor of 2.33 for the buccal lipoidal membrane–aqueous incremental partition constant for a methylene group was found. Significantly, this evaluative study probably represents the first example of the rigorous application of the physical model approach to the quantitative and mechanistic interpretation of the *in vivo* absorption of drugs.

Keyphrases □ Buccal absorption, *n*-alkanoic acids—quantitative interpretation □ *n*-Alkanoic acids, absorption—theoretical consideration □ Absorption rates, buccal—*n*-alkanoic acids

Recently, models based upon simultaneous chemical equilibria and diffusional mass transfer of acidic, basic, neutral, and amphoteric drugs through homogeneous and nonhomogeneous multicompartment barriers were studied and reported in detail (1, 2). This physical model approach to the understanding of drug transport was applied to various *in situ* drug absorption situations involving the intestinal, gastric, and rectal tracts with generally satisfactory results. It was also shown that the pH-partition theory is a limiting case of the more general approach presented.

In recent years, Beckett and his coinvestigators utilized the buccal absorption of drugs as an *in vivo* model for the study of drug transfer across physiological membranes (3–8). Employing a wide variety of organic drugs from acids to bases, they showed that the passive transfer of nonionic species across the lipid membrane of the buccal cavity was the primary transport mechanism.

In one particular paper, Beckett and Moffat (5) reported the influence of alkyl substitution on three groups of acids on buccal absorption, *i.e.*, those with the same pKa value and different solubilities, those with different pKa values and the same lipid solubility, and those with different pKa values and different lipid solubilities. The comparative absorption–pH profiles of the acids reflected the differences in their pKa values and/or their lipid–water partition characteristics. Indirectly, they attempted to correlate the buccal absorption data with partition coefficients of the acids in *n*-heptane–aqueous systems and with pharmacokinetic models (7, 8). Interestingly, the present authors noted that their physical models (1, 2) are explicitly related to the buccal absorption situation. Thus, the purpose of this paper is to examine quantitatively the absorption of the *n*-alkanoic acids with the physical model approach.

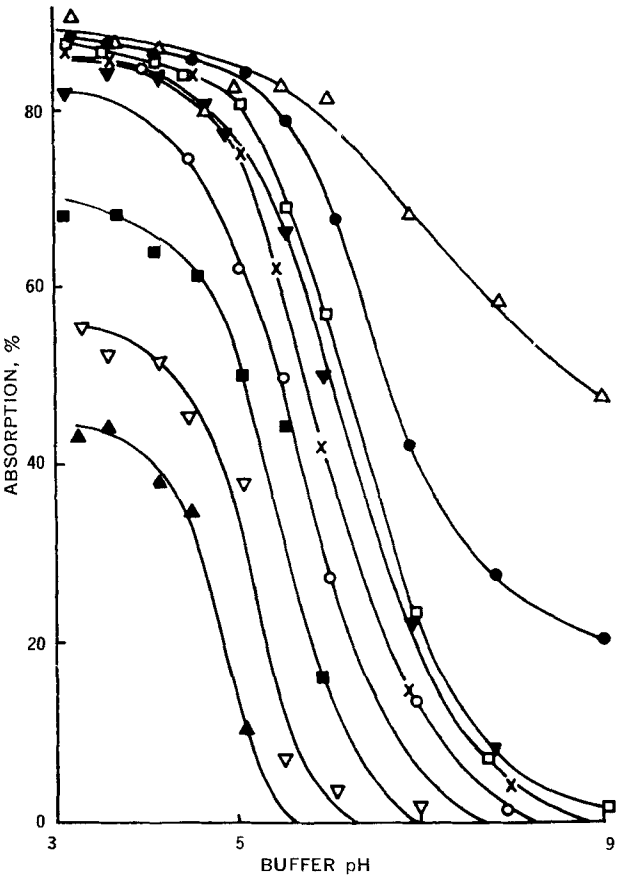

Figure 1—*Buccal absorption of* n-*alkanoic acid in man [redrawn from Beckett and Moffat (5)]. Key:* ▲, *butyric;* ▽, *valeric;* ■, *hexanoic;* ○, *heptanoic;* ×, *octanoic;* ▼, *nonanoic;* □, *decanoic;* ●, *undecanoic; and* △, *dodecanoic.*

THEORETICAL CONSIDERATIONS

The buccal absorption–pH curves of *n*-alkanoic acids ranging from butyric to dodecanoic acids (5) are shown in Fig. 1. The percent absorbed at any buffer pH is the fraction of drug absorbed after 5 min. of contact time in the buccal cavity. Beckett and Moffat (5) concluded that the measured absorption is a true passive transfer into the lipid membrane of the mouth. Since the pKa values for the acids are the same (pKa ~4.82–4.85 at 25°), it was also concluded that the differences in the relative absorption rates are related to the differences in the lipid–aqueous partition coefficients of the available nonionized species at any one buffer pH. Beckett and Moffat (5)

Table I—Buccal Absorption Data Treated in Accordance with the Physical Model[a]

n-Alkanoic Acid	Buffer pH	$f_{abs.}$ in 5 min.	Experimental K_u, sec.$^{-1}$ × 10^{-3}	$f(T)_{expt.}$	$T_{expt.}$
C_4	3	0.44	1.933	0.279	2.547
	4	0.41	1.759	0.254	2.563
	4.5	0.325	1.31	0.189	2.935
	5	0.15	0.542	0.078	4.789
	5.7	0.0	0.0	0.0	—
				Average	3.208
C_5	3	0.55	2.662	0.384	1.581
	4	0.52	2.447	0.353	1.599
	4.5	0.47	2.116	0.305	1.559
	5	0.35	1.436	0.207	1.556
	6	0.04	0.136	0.020	3.202
	6.4	0.0	0.0	0.0	—
				Average	1.9
C_6	3	0.70	4.013	0.579	0.7166
	4	0.67	3.696	0.533	0.7644
	4.5	0.625	3.269	0.472	0.7652
	5	0.525	2.481	0.358	0.7284
	6	0.16	0.581	0.084	0.7000
	7	0.0	0.0	0.0	—
				Average	0.735
C_7	3	0.82	5.720	0.825	0.2091
	4	0.79	5.202	0.751	0.2892
	4.5	0.74	4.490	0.648	0.3715
	5	0.665	3.645	0.526	0.3660
	6	0.30	1.189	0.172	0.3185
	7	0.05	0.171	0.025	0.2682
	7.8	0.0	0.0	0.0	—
				Average	0.3109
C_8	3	0.85	6.324	0.912	0.0946
	4	0.84	6.109	0.881	0.1178
	4.5	0.81	5.536	0.799	0.1723
	5	0.765	4.827	0.696	0.1774
	5.5	0.635	3.360	0.485	0.1891
	6	0.425	1.845	0.266	0.1765
	6.5	0.245	0.937	0.135	0.1354
	7	0.12	0.426	0.062	0.1037
	8.3	0.0	0.0	0.0	—
				Average	0.1459

[a] K_u, $f(T)_{expt.}$, and $T_{expt.}$ were calculated using Eqs. 3, 10, and 12, respectively.

stated that the absorption of the C_{11} and C_{12} acids are complicated by their increased lipid solubility of the ionized forms and surface-active properties.

One principal difficulty in relating the absorption data (Fig. 1) to a physical model is the lack of certain other kinetic information on which the model is based. However, as will be seen, reasonable assumptions can be made from the physical-chemical standpoint.

Initially the assumption is made that there are three homogeneous compartments, of which the first and third compartments are aqueous and separated by a lipid one[1]. The first compartment (mucosal side) consists of the bulk aqueous drug solution phase and a diffusion layer of thickness L_1. The second compartment is a lipid phase of thickness L_2, and the third compartment (serosal side) consists of the aqueous diffusion layer of thickness L_3 at pH 7.4. After the third compartment, there is assumed to be a perfect sink. The pH of each of the aqueous phases is assumed to be constant everywhere. This would be reasonable when the buffer capacity is high and no significant net transport of acids or bases is involved. Only nonionized drug species are assumed to transfer across the lipid membrane.

If the steady-state rate of buccal absorption may be approximated by a first-order process, then, as before (1, 2),

$$\ln \frac{Y_{w,1}}{Y_{w,1}(0)} = -K_u t \qquad \text{(Eq. 1)}$$

where $Y_{w,1}$ is the total aqueous concentration of alkanoic acid species on the mucosal side at any time t, and K_u is the rate constant.

[1] This corresponds to Model II-a in *Reference 2.*

In terms of the data given in Fig. 1, the fraction of drug absorbed[2] is

$$f_{abs.} = \frac{Y_{w,1}(0) - Y_{w,1}(t)}{Y_{w,1}(0)} \qquad \text{(Eq. 2)}$$

Consequently, with Eq. 1, the experimental rate constant at any buffer pH can be calculated by

$$K_u = -\frac{1}{t} \ln (1 - f_{abs.}) \qquad \text{(Eq. 3)}$$

From the theory (1, 2), the expression for the rate constant takes the general form

$$K_u = B_1 f(T) \qquad \text{(Eq. 4)}$$

where, in this three-compartment model,

$$K_u = B_1 \cdot \frac{1}{1 + (B_2/KX_1) + (B_3X_3/X_1)} \qquad \text{(Eq. 5)}$$

with

$$B_1 = \frac{AD_{w,1}}{VL_1} \qquad B_2 = \frac{L_2D_{w,1}}{L_1D_0R_2} \qquad B_3 = \frac{L_3D_{w,1}}{L_1D_{w,3}R_3} \qquad \text{(Eq. 6)}$$

Here, the $f(T)$ is a dimensionless constant with the limits $0 < f(T) \leq 1$; A and V are the geometrical surface area and volume of the drug solution, respectively; $D_{w,1}$ and $D_{w,3}$ are the diffusion coefficients in the aqueous diffusion layers in the first and third compartments, respectively; and D_0 is the lipid diffusion coefficient. The D_w of all ionized and nonionized species in a compartment are assumed equal. The lipid–aqueous partition coefficient[3] is K. R_2 and R_3 are the ratios of the true interfacial area to the geometrical area at the first and second compartments and at the second and third compartments, respectively.

The pH dependency on the absorption rate is given by the parameters X_1 and X_3, the fractions of nonionized species in the first and third aqueous compartments, which in the general case of alkanoic acids is

$$X = \frac{(H^+)}{(H^+) + K_a} \qquad \text{(Eq. 7)}$$

where (H^+) is the hydrogen-ion concentration and K_a is the dissociation constant.

The argument can now be presented that, particularly for the lower molecular weight alkanoic acids, B_3X_3/X_1 might easily be negligible compared to $1 + (B_2/KX_1)$ when the pH in the mucosal compartment is less than 7. First, L_3 is smaller than L_1, since L_1 can be easily the order of 50 μ and L_3 is probably the order of cell dimensions. Secondly, the two diffusion coefficients, $D_{w,1}$ and $D_{w,3}$, should be of the same order of magnitude. When the mucosal pH is less than around 6.0 or, at higher pH, if the absorption rate is small compared to the maximum rates (see Fig. 1), it follows that B_3X_3/X_1 should be negligible. This condition should apply to most of the data from butyric to octanoic acids. Thus, for the C_4 to C_8 acids, Eq. 5 for the absorption rate constant of acidic drugs reduces to a more simple expression[4] of an aqueous–lipid phase model:

$$K_u = B_1 \cdot \frac{1}{\left[1 + \frac{K_a}{(H^+)_1}\right]T + 1} \qquad (pH_1 \leq 7) \qquad \text{(Eq. 8)}$$

where

$$T = \frac{D_{w,1}L_2}{L_1KD_0} = \frac{P_{w,1}}{P_{0,2}R_2} \qquad \text{(Eq. 9)}$$

where T is the diffusion efficiency coefficient and is the ratio of the

[2] Unfortunately, the data (5) are single-point (in time) determinations. Therefore, a nonsteady-state (partitioning of binding) component is present in these data. It is believed, however, that the steady-state approximation is reasonable, as the mouth-rinse experiments indicated relatively little membrane partitioning of the solutes and binding.

[3] In *References 1* and *2*, the notation P was used for the partition coefficient.

[4] This corresponds to Model I in *Reference 2* or the model in *Reference 1.*

aqueous diffusion layer permeability ($P_{w,1}$) and lipoidal membrane permeability ($P_{0,2}$).

The two-phase model is probably a poor approximation of the three-phase model in the case of the buccal absorption of amines. The aqueous barrier on the serosal side may generally not be negligible in the case of amines (9, 10).

In Fig. 1 the percent absorption in 5 min. at pH $\leq$ 3 reaches approximately 87.5% maximum absorption with higher acids. By means of Eq. 3, one obtains $B_{1,expt.} = 6.931 \times 10^{-3}$ sec.$^{-1}$, where $B_{1,expt.}$ is the K_u value when $f(T) = 1$. Therefore, the experimental $f(T)$ for any alkanoic acid at any pH may be calculated by the relationship

$$f(T)_{expt.} = \frac{K_{u,expt.}}{B_{1,expt.}} \qquad \text{(Eq. 10)}$$

whereupon from the theory, *i.e.*, Eqs. 4 and 8, the experimental diffusion efficiency coefficient, T, is calculable. Thus,

$$f(T)_{expt.} = \frac{1}{\left[1 + \frac{K_a}{(H^+)_1}\right] T_{expt.} + 1} \qquad \text{(Eq. 11)}$$

or

$$T_{expt.} = \frac{1 - f(T)_{expt.}}{\left[1 + \frac{K_a}{(H^+)_1}\right] f(T)_{expt.}} \qquad \text{(Eq. 12)}$$

where $T_{expt.}$ is independent of buffer pH of the drug solution but is a characteristic property of the particular acid.

Since the pKa's of the acids are essentially equal, the theory predicts that the relative rates of absorption at constant pH among the alkanoic acids in the homologous series will be a reflection of their partition coefficients *via* T through Eq. 11. Referring to Eq. 9, one observes that T is inversely proportional to the partition coefficient. It follows then that T is small when K is large, and $f(T)$ approaches unity to give a maximum rate constant for absorption, B_1. Thus, $T_{expt.}$ has great significance in the evaluation of the data given in Fig. 1.

If it is reasonable to assume that the diffusion coefficients in the lipid membrane and in the aqueous phases change little with molecular weight, one may write

$$\frac{T_i}{T_{i+1}} = \frac{P_{0,2,i+1}}{P_{0,2,i}} = \frac{K_{i+1}}{K_i} \qquad \text{(Eq. 13)}$$

(i = number of C atoms in the *n*-alkanoic acid series) which relates the change in T or the permeability of the lipid membrane to the change in the partition coefficient. When a methylene group is added to the molecule, the increase in the partition coefficient within the homologous series may be expressed by

$$K_{i+1} = nK_i \qquad \text{(Eq. 14)}$$

where n is the incremental coefficient for a methylene group. Therefore, Eq. 13 becomes

$$\frac{T_i}{T_{i+1}} = n \qquad \text{(Eq. 15)}$$

Although n is not a true constant (11), it would be expected to show relatively little change from the C_4 to the C_8 acids in most organic solvents that do not allow appreciable dimerization.

RESULTS AND DISCUSSION

The results of the treatment of the absorption data (Fig. 1) with the aqueous diffusion layer–lipid membrane physical model are summarized in Table I. The rate constant K_u and the function $f(T)_{expt.}$ decrease with increasing buffer pH of the drug solution. It is significant that, as theoretically expected, the $T_{expt.}$ values of each alkanoic acid at various pH are essentially constant, with the exception of C_4 and C_5 acids at the high pH where the fraction of drug absorbed is fairly small. Since the scatter of $T_{expt.}$ for C_6 acid is small, the average $T_{expt.}$ (=0.735) was taken as the reference value for the subsequent analysis of the data and is, henceforth, referred to as T_6.

Table II—Comparison of $f(T)_{expt.}$ with Theoretical $f(T)$ Using Average $T_{expt.}$ Values and T Values with Incremental Partition Constants for a Methylene Group in the Homologous Series of *n*-Alkanoic Acids[a]

n-Alkanoic Acid	Buffer pH	$f(T)_{expt.}$	$f(T)$ with Average $T_{expt.}$	$f(T)$ with T_6 and $n = 3.15$	$f(T)$ with T_6 and $n = 2.3$
C_4	3	0.279	0.235	0.119	0.202
	4	0.254	0.214	0.107	0.183
	4.5	0.189	0.176	0.086	0.150
	5	0.078	0.112	0.053	0.095
	5.7	0.0	—	—	—
			($T = 3.208$)	($T = 7.293$)	($T = 3.888$)
C_5	3	0.384	0.342	0.299	0.368
	4	0.353	0.315	0.274	0.340
	4.5	0.305	0.265	0.228	0.288
	5	0.207	0.176	0.149	0.194
	6	0.020	0.033	0.027	0.037
	6.4	0.0	—	—	—
			($T = 1.9$)	($T = 2.315$)	($T = 1.691$)
C_6	3	0.579	0.573	0.573	0.573
	4	0.533	0.543	0.543	0.543
	4.5	0.472	0.482	0.482	0.482
	5	0.358	0.356	0.356	0.356
	6	0.084	0.080	0.080	0.080
	7	0.0	—	—	—
			($T_6 = 0.735$)	($T_6 = 0.735$)	($T_6 = 0.735$)
C_7	3	0.825	0.760	0.809	0.755
	4	0.751	0.737	0.789	0.732
	4.5	0.648	0.688	0.746	0.682
	5	0.526	0.566	0.636	0.560
	6	0.172	0.171	0.216	0.167
	7	0.025	0.022	0.028	0.021
	7.8	0.0	—	—	—
			($T = 0.311$)	($T = 0.233$)	($T = 0.320$)
C_8	3	0.912	0.871	0.930	0.876
	4	0.881	0.857	0.922	0.863
	4.5	0.799	0.824	0.902	0.831
	5	0.696	0.736	0.846	0.745
	5.5	0.485	0.550	0.706	0.561
	6	0.266	0.305	0.464	0.315
	6.5	0.135	0.127	0.223	0.132
	7	0.062	0.045	0.084	0.057
	8.3	0.0	—	—	—
			($T = 0.146$)	($T = 0.074$)	$T = 0.139$)

[a] With the exception of $f(T)_{expt.}$, all $f(T)$ values were calculated using Eq. 11 and the T values in parentheses. With the exception of the average $T_{expt.}$ and T_6, all T values were calculated using Eq. 15.

In Table II the $f(T)_{expt.}$ values are compared to the $f(T)$ values calculated both from the average $T_{expt.}$ values and from T values calculated with Eq. 15 employing T_6 as the reference. With regard to the latter, an incremental partition constant of 3.15 for the methylene group was used as a first approximation. This value was taken from the work of Iwasa *et al.* (12) and Hansch *et al.* (13) on the partitioning of esters, alcohols, ketones, and ethers between *n*-octanol and water at 25°. With this value for n, the $f(T)$ did not correlate well with the $f(T)_{expt.}$. Even a generous 5% correction of this constant for the temperature change from 25° to the physiological 37° based upon a ΔH of oil–water transfer of 500 cal. mole^{-1} (14) for a methylene group was insufficient to improve the correlation. As shown in Table III, incremental partition constants determined from the data in Table I yielded much smaller values, with a mean of 2.33. With $n = 2.3$ and T_6 as reference, the agreement between the theoretical $f(T)$ and $f(T)_{expt.}$ was very good.

From the data in Table II, profiles of the absorption rate function $f(T)$ *versus* buffer pH of the drug solution were constructed (Fig. 2). The exceptionally good agreement between the numerical values and shapes of the theoretical curves and the experimental results probably represents the first explicit application of the physical model approach for the quantitative and mechanistic interpretation of the *in vivo* absorption of drugs. Only the absorption–pH curve for butyric acid follows the dissociation curve characteristic of

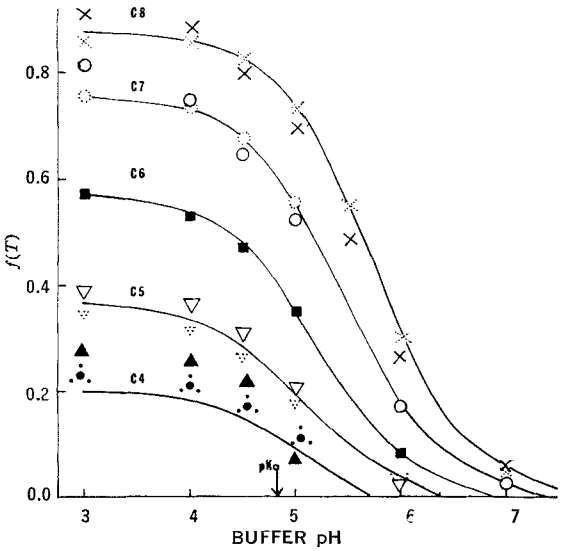

Figure 2—*Profiles of buccal absorption rate function* f(T) versus *buffer pH of the drug solution. Solid curves are* f(T) *based on* T_6 *with* n = *2.3.*

n-Alkanoic Acid	$f(T)_{expt.}$	f(T) *Based on Average* $T_{expt.}$
C_4	▲	△
C_5	▽	▽
C_6	■	□
C_7	○	○
C_8	×	×

these alkanoic acids. The increased rate in the absorption of the acids at constant buffer pH is attributable mainly to the partition coefficient characteristic of each acid. On the other hand, the shifts of the profiles of the homologous series to the right of the dissociation curve are due not only to the increasing lipid solubility but also to the presence of the aqueous diffusion layer on the mucosal side. These effects constitute a departure of real systems from the classical pH–partition theory for drug absorption.

In view of the preceding discussion, the absorption rate–pH profiles of the acids and also the extents of the pH shifts could be predicted *a priori* on the basis of the profile of one of the acids by employing Eqs. 11, 13, and 15. For example, when $f(T)_i = f(T)_{i+1}$ for i = number of carbon atoms,

$$\frac{1 + K_a/(H^+)_{1,i+1}}{1 + K_a/(H^+)_{1,i}} = \frac{T_i}{T_{i+1}} = \frac{P_{0,2,i+1}}{P_{0,2,i}} = n \qquad \text{(Eq. 16)}$$

In this case, if, for example, $K_a/(H^+)_{1,i+1}$ is large compared to unity, $(H^+)_{1,i}/(H^+)_{1,i+1} = n$. Thus, for the high pH data of the higher acids, the shifts are indeed observed to be rather constant (Fig. 2).

An interesting result of the theoretical analysis of the *in vivo* absorption data is the self-consistent factor, 2.33, for the buccal lipid membrane–aqueous incremental partition constant for the methylene group within a linear homologous series. This number is highly significant, since it is the first time to the authors' knowledge that a biophysically based and biologically meaningful factor has been deduced. Further investigations along these lines should lead to a mechanistic understanding of various structure–activity relationships based not upon simulated biological lipids but rather where the relevant membrane lipid in the dynamic real system is studied.

Table III—Buccal Lipid Membrane–Aqueous Incremental Partition Constant for the Methylene Group within the Homologous Series of *n*-Alkanoic Acids Derived from Buccal Absorption Experiments at 37°[a]

Buffer pH	Incremental Constant *n*			
	C_4–C_5	C_5–C_6	C_6–C_7	C_7–C_8
3	1.61	2.21	3.43	2.21
4	1.61	2.09	2.64	2.46
4.5	1.88	2.04	2.06	2.16
5	3.08	2.14	1.99	2.03
6	—	4.57	2.20	1.81
7	—	—	—	2.59
Average	2.05	2.61	2.47	2.21

[a] The incremental constant is calculated by $T_{expt.}$ values in Table I using Eq. 15.

Table IV—Estimates of the Buccal Membrane Permeability Coefficient of *n*-Alkanoic Acids from *In Vivo* Absorption Data

n-Alkanoic Acids	Average $T_{expt.}$	Membrane Permeability $P_{0,2}$, cm. sec.$^{-1}$, at 37°	
		Equation 9[a]	Equation 17[b]
C_4	3.208	5.20×10^{-4}	5.40×10^{-4}
C_5	1.90	8.77×10^{-4}	9.12×10^{-4}
C_6	0.735	2.27×10^{-3}	2.35×10^{-3}
C_7	0.3109	5.36×10^{-3}	5.57×10^{-3}
C_8	0.1459	11.43×10^{-3}	11.88×10^{-3}

[a] Calculations based on Eq. 9 using $D_{w,1} = 5 \times 10^{-6}$ cm.^{2} sec.$^{-1}$; $L_1 = 3 \times 10^{-3}$ cm. [b] Calculations based on Eq. 17 using $V = 25$ ml.; $A = 100$ cm.^{2}; $B_{1,expt.} = 6.931 \times 10^{-3}$ sec.$^{-1}$.

This number also implies that the lipoidal membrane of the buccal cavity is not strongly nonpolar. Consequently, *in vitro* partitioning studies with the hexane–water system or even the oleyl alcohol, octanol, or olive oil–water systems may not yield the expected information concerning the buccal situation. An incremental constant of 2.4–2.8 for the homologous series of *n*-alkyl acids, alcohols, and esters in the butanol–water system at 20°, as was shown by the studies of Collander (15, 16), appears to be appropriate. By considering a temperature correction to 37°, this *in vitro* system would probably provide good agreement with the present 2.33 factor. Collander and Barlund (17, 18) found incremental constants ranging from 1.7 to 2.5 per unshielded CH_2 group among chosen homologous pairs of an ether, alcohol, amide, and ester from permeation determinations using the plant cell *Chara ceratophylla.*

As described, the sequence of the quantitative analysis was based upon the apparent maximum absorption rate of 87.5% in 5 min., with the higher alkanoic acids in the series at pH < 3 in Fig. 1. This corresponds to $B_{1,expt.} = 6.93 \times 10^{-3}$ sec.$^{-1}$. To avoid the possible criticism that the 5-min. data for the higher acids are very close to 100% absorption and, therefore, unreliable for these calculations, an alternate method of data analysis was also used. Utilizing only the K_u *versus* buffer pH profile of hexanoic acid and calculating T_6 from the theory by

$$T_6 = \frac{K_{u,A} - K_{u,B}}{K_{u,B}[1 + K_a/(H^+)_B] - K_{u,A}[1 + K_a/(H^+)_A]}$$

$$[K_{u,A} \text{ at } (H^+)_A > K_{u,B} \text{ at } (H^+)_B] \qquad \text{(Eq. 17)}$$

the average $T_6 = 0.6564$ as compared to the average $T_6 = 0.7350$ in Table I, representing a difference of 10%. Using Eq. 8, one gets $B_{1,expt.} = 6.52 \times 10^{-3}$ sec.$^{-1}$, which is in good agreement with the $B_{1,expt.}$ determined before. Furthermore, the incremental constant found by the pH shifts of the absorption rate profiles by Eq. 16 is 2.22. Thus, the entire analysis is self-consistent.

In Table IV some estimates of the permeability coefficients for the buccal membrane are made. These were calculated with Eq. 9 using $D_{w,1} = 5 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ and $L_1 = 3 \times 10^{-3}$ cm. and also with

$$P_{0,2,i} = \frac{VB_{1,expt.}}{AT_{expt.}} \qquad \text{(Eq. 18)}$$

using $V = 25$ ml. according to Beckett and Moffat (5) and the area of the buccal cavity $A \sim 100$ cm.^{2}. It is significant that Eq. 18 permits the estimation of the $P_{0,2}$ value of an alkanoic acid from the experimental data alone and, in turn, with Eq. 13 predicts the $P_{0,2}$ values of other acids in the homologous series.

These $P_{0,2}$ values give rise to D_0 values of the order of 10^{-12} to 10^{-10} cm.^{2} sec.$^{-1}$ when $L_2 \simeq 100$ Å and reasonable values for K are employed. For example, for caproic acid, $K \simeq 50$ when the oil is oleyl alcohol or butanol; therefore, $D_0 = 4 \times 10^{-11}$ cm.^{2} sec.$^{-1}$.

Such small D_0 values are of the same order of magnitude as those values found when the rat gastrointestinal absorption data were treated (1, 2) and when data on drug transport across the hydrated *stratum corneum* were recently analyzed (19) by means of the physical model approach.

In summary, the physical model approach has been shown to be extremely successful in analyzing the buccal absorption data involving the alkanoic acids from C_4 to C_8. The mechanistic conclusions based upon the analysis appear to be very firm, because the agreement between the appropriate physical model and experiments was very good.

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[5] In Fig. 10 of *Reference 1*, the diffusion efficiency coefficient T should read T^2.

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Steroid Release from Silicone Elastomer Containing Excess Drug in Suspension

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Abstract □ The *in vitro* release from a matrix consisting of silicone elastomer was studied for the purpose of testing release theories. The micronized steroid was suspended in silicone elastomer, and the release from a controlled surface area into an aqueous "sink" was experimentally determined. After a certain time period, the release from the matrixes displayed the predicted time and concentration dependencies. An initial period of apparent linear release was observed. The duration of this period was concentration and particle-size dependent. The amount released assumed square root of time dependency after the initial linearity period terminated. The observed results are inconsistent with the equations developed to describe the release of solutes from ointment bases and matrix systems. The concentration and particle-size effects on the duration of the linear release suggest that the release is dissolution rather than diffusion controlled.

Keyphrases □ Silicone elastomer—steroid release, *in vitro* □ Chlormadinone acetate release mechanism—silicone elastomer matrix □ Membranes, silicone elastomer—steroid transport rates □ Particle-size effect—steroid release from silicone matrix □ Colorimetric analysis—spectrophotometer

The behavior of simple diffusional processes is generally mathematically described in an adequate fashion by an equation containing a series of exponentials (1, 2). Diffusion of solutes through silicone elastomer membranes has recently been evaluated, and good predictive ability was achieved assuming that the drug solute diffused according to Fick's law (3–5). *In vitro* release of a solute dissolved in ointment bases was predicted by W. Higuchi (6) by applying equations similar to those used by Jost (2) and by restricting flux to a single direction. The mathematics of these processes is quite complex; for the formulator of ointment bases or similar drug delivery systems, a more practically usable equation was developed by T. Higuchi (7).

By assuming that diffusion is the slow step in the overall release process, Eq. 1:

$$Q = \sqrt{DC_s(2A - C_s)t} \qquad \text{(Eq. 1)}$$

was derived by T. Higuchi (8) to describe drug release from ointment systems into a receptor sink when excess drug is suspended in that system. The Q is the amount released at time t/square centimeter of surface contact with the receptor sink; D is the diffusion constant of the drug molecule in the ointment or matrix system, A is the concentration of drug in the ointment given in amount/cubic centimeter, and C_s is the solubility of the drug in the ointment expressed in amount/cubic centimeter.

This paper is a report of the results of release experiments from a drug–matrix system analogous to the one described previously (8). The validity of Eq. 1 is tested.