ACKNOWLEDGMENTS AND ADDRESSES

Received August 24, 1973, from the *Department of Experimental Therapeutics, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, NY 14203*

Accepted for publication October 4, 1973.

Supported by Core Program Grant CA-13038 from the National Cancer Institute, U.S. Public Health Service, and Institutional General Research Support Grant 61124 from the U.S. Public Health Service.

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Evaluation of Mathematical Models for Diffusion from Semisolids

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Abstract □ Models used in the description of diffusion processes were applied to drug release from semisolids. Two models, an exponential model for finite systems and a nonexponential model for semi-infinite and infinite systems, are evaluated for their suitability in describing literature data for release of substances from semisolids. The regression lines calculated for these data are evaluated using analysis of variance and examination of residuals. Evaluation of these models using these data indicates that the exponential model derived for finite systems is applicable in all the literature cases while the nonexponential model has restricted applicability.

Keyphrases □ Diffusion, drugs from semisolids—exponential and monoexponential models evaluated using literature data, regression lines calculated □ Semisolids—evaluation of mathematical models used to describe drug diffusion □ Ointments—evaluation of mathematical models used to describe drug diffusion □ Drug diffusion from semisolids—exponential and monoexponential models evaluated using literature data, regression lines calculated

Diffusion of drug agents from different solid and semisolid vehicles has been the subject of numerous reported investigations. During work in this laboratory with the diffusion of local anesthetics through semisolid dosage forms, it became necessary to evaluate mathematical models commonly used to describe diffusion. Several authors (1–3) described diffusion models which quantitate the diffusion process under various experimental conditions. For example, point, plane, and spherical sources of diffusion in finite, semi-infinite, and infinite systems in one, two, or three dimensions have been described. The terms finite, semi-infinite, and infinite are descriptive terms which locate the boundaries to diffusion in the x direction when a drug diffuses from a dosage form bounded between the planes $x = 0$ and $x = j$, while the semi-infinite system extends from a bounding plane at $x = 0$ to $x = +\infty$ and the infinite svstem extends to infinity in the $+x$ and $-x$ directions (3). In the case of diffusion in one dimension for a finite system, the desired solution for the amount diffused is given by the equations (4, 5):

$$M_t = M_\infty\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)}\exp\left(-(2m+1)^2 D\pi^2 t/l^2\right)\right] \quad \text{(Eq. 1)}$$

where:

M_t = amount diffused up to time t
M_∞ = amount diffused to time ∞
D = diffusion coefficient
t = time
l = thickness of membrane or layer

$$Q_{0,t} = C_0AH\left\{1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}\left[\frac{1}{(2m+1)^2}\exp\left(-\frac{(2m+1)^2\pi^2 Dt}{4H^2}\right)\right]\right\} = C_0AH\left\{1 - \frac{8}{\pi^2}\left[\exp\left(-\frac{\pi^2 Dt}{4H^2}\right) + \frac{1}{9}\exp\left(\frac{-9\pi^2 Dt}{4H^2}\right) + \ldots\right]\right\} \quad \text{(Eq. 2)}$$

where:

$Q_{0,t}$ = amount diffused between time = 0 and t
C_0 = initial concentration in phase from which the substance diffuses
A = area over which diffusion occurs
H = thickness of diffusing region
D = diffusion coefficient
t = time

It should be noted that $1 + (1/9) + (1/25) + \ldots = 8/\pi^2$. A model for semi-infinite and infinite systems (6) was suggested by Higuchi (7) as a simplified model for percutaneous absorption from an ointment. This model has the form:

$$Q = (2A - C_s)\left[\frac{Dt}{1 + 2(A - C_s)/C_s}\right]^{1/2} \quad \text{(Eq. 3)}$$

where:

Q = amount absorbed at time t per unit area of exposure
A = concentration of drug expressed in units per cubic centimeters
C_s = solubility of drug in units per cubic centimeter in external phase of ointment
D = diffusion constant of drug in external phase

Equation 3 may take the form (6) used in the analysis of diffusion of medicaments from semisolid dosage forms (8–11):

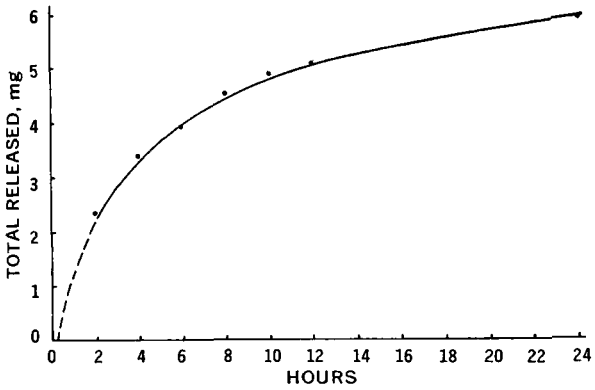

Figure 1—*Release of 0.025% fluocinolone acetonide from a water-soluble gel.*

$$Q_{0,t} = 2C_0A\sqrt{\frac{Dt}{\pi}} \qquad \text{(Eq. 4)}$$

where:

$Q_{0,t}$ = amount diffused between time = 0 and t
C_0 = initial concentration in semisolid dosage form
A = area for diffusion
D = diffusion coefficient
t = time

A similar form is (12):

$$M_t = \frac{4M_\infty}{l}\left(\frac{Dt}{\pi}\right)^{1/2} \qquad \text{(Eq. 5)}$$

The purposes of this report are: *(a)* to compare these models of diffusion, various forms of which are used in the analysis of diffusion experiments; *(b)* to use these models to describe various literature data; and *(c)* to evaluate these two models for statistical goodness of fit of the data.

MODEL THEORY AND GENERAL DESCRIPTION

Development of a model for diffusion should have some applicability in quantitating physical phenomena as well as in estimating a future course of diffusion under conditions like those under which the diffusion parameters were determined. Parameters that can be determined include the ultimate concentration or amount diffused, the thickness of the region from which diffusion is taking place, and the diffusion coefficient.

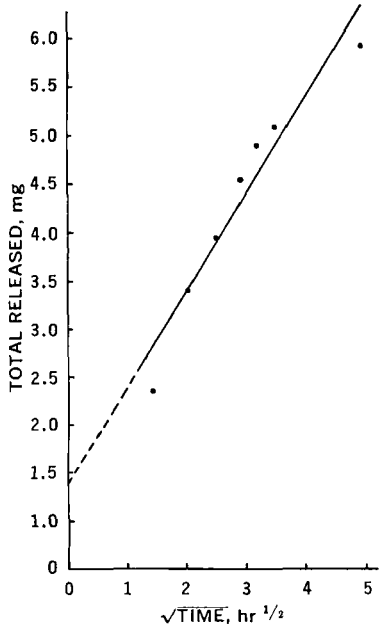

Figure 2—*Release of fluocinolone acetonide from a water-soluble gel.*

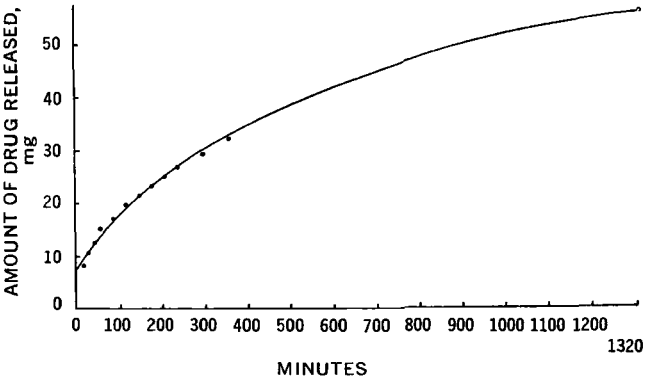

Figure 3—*Release of 0.126* M *pyridine from water/oil emulsion.*

The use of the nonexponential model (Eqs. 4 and 5) is of primary utility in the estimation of D from the initial gradient of sorption or diffusion due to the approximately linear behavior of diffusion *versus* square root of time up to $M_t/M_\infty \approx \frac{1}{2}$ for most systems (13). The total amount diffused at infinite time (M_∞) and the diffusion coefficient (D) can be obtained from Eq. 5 by noting that:

$$M_\infty = \frac{b_1 l \pi^{1/2}}{4D^{1/2}} \qquad \text{(Eq. 6)}$$

where b_1 = slope of the calculated line.

The diffusion coefficient may then be found by rearranging Eq. 5 or 4 to yield:

$$D = \frac{b_1 l \pi}{16M_\infty^2} \qquad \text{(Eq. 7)}$$

or:

$$D = \frac{b_1^2 \pi}{4C_0^2A^2} \qquad \text{(Eq. 8)}$$

where b_1 = slope of the line.

Problems associated with obtaining diffusion parameters by this method include lack of knowledge concerning, or the necessity of determining experimentally, M_∞. The linear model is useful only for the period from the end of the lag time to that time when $M_t \approx \frac{1}{2}M_\infty$, which is difficult to ascertain if M_∞ is unknown. In some cases, this relationship has been extended beyond $M_t \approx \frac{1}{2}M_\infty$ (14, 15).

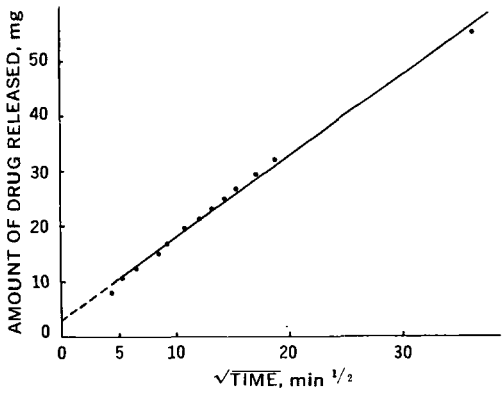

Figure 4—*Release of 0.126* M *pyridine from water/oil emulsion.*

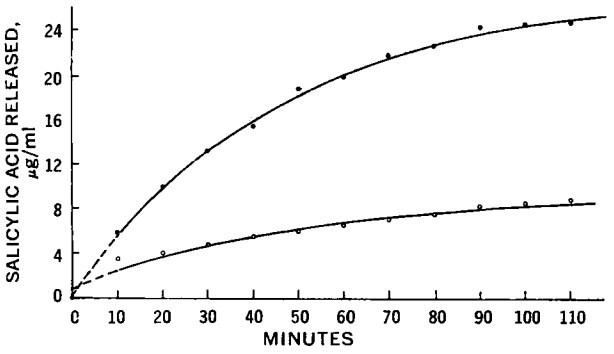

Figure 5—In vitro *release of salicylic acid from ointment bases. Key (ointment base): ●, hydrophilic cream; and ○, white petrolatum USP.*

Another error that may be made is the assumption that the curve must pass through the origin, *i.e.*, neglecting the effect of a lag time. Depending on the plotting procedure used, this results in a significant curvature in the straight line or a systematic negative deviation, assuming lag phase is complete. If this relationship is used prior to the end of the lag phase, the error appears as a curvature or a systematic positive deviation.

Several nonlinear curve-fitting procedures are available which readily permit estimation of the necessary parameters to describe the diffusion process using the exponential model. In practical use of Eqs. 1 and 2, summation beyond $m = 0$ may be ignored unless the term $(\pi^2 Dt/l^2)$ is sufficiently small that a significant contribution of this exponential term is made in the region(s) of interest (16, 17). In cases where terms with $m > 0$ must be included, inclusion of only $m = 0$ and $m = 1$ is sufficient for adequate estimation of the parameters. If terms beyond $m > 0$ are ignored, the diffusion model reduces to:

$$M_t = M_\infty - \frac{8M_\infty}{\pi^2} \exp\left(-\frac{D\pi^2 t}{A}\right) \qquad \text{(Eq. 9)}$$

Use of the single exponential term results not only from the lack of necessity for use of further members of the series but also from the frequent lack of sufficient experimental data for adequate elucidation of the parameters in the second and greater terms. It can be seen that the second term of the series is $(8M_\infty/\pi^2)(1/9)\ \exp\{-9\pi^2 Dt/l^2\}$. The preexponential term is one-ninth the previous term and the exponent has a ninefold greater absolute magnitude. Therefore, the contribution of this term is negligible, except at small times at which data are usually lacking. If a fit using the second exponential term is forced upon a data set with insufficient values at small times, the estimated parameters: *(a)* do not have their theoretical relationship, *(b)* are very "volatile," or *(c)* cannot be calculated due to singular or ill-conditioned normal equations (18).

Regardless of the number of terms retained in Eqs. 1 and 2,

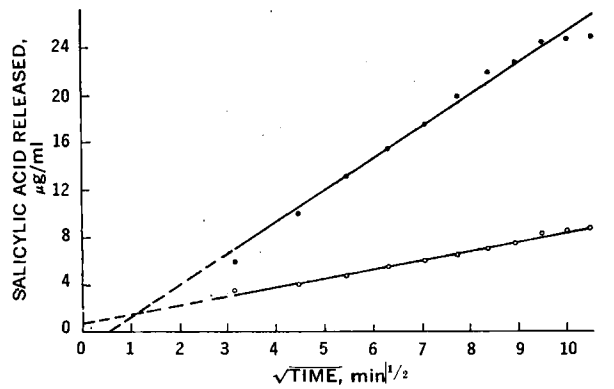

Figure 6—In vitro *release of salicylic acid from ointment bases. Key (ointment base): ●, hydrophilic cream, and ○, white petrolatum USP.*

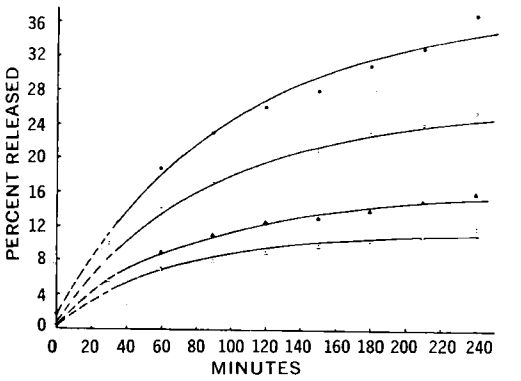

Figure 7—*Release of sodium radioiodide from ointment bases. Ointment bases containing: sodium salt of lauryl ether sulfate 1% (●); sodium salt of lauryl ether sulfate 2% (○); triethanolamine lauryl sulfate 3% (▲); and stearamidopropyl dimethyl β-hydroxyethylammonium nitrate 3% (△).*

M_∞ or C_0AH is estimated as the asymptote of the exponential equation. The term C_0AH implies that no equilibrium distribution of material that is diffusing will be attained but all will diffuse out. The term M_∞, however, is the equilibrium amount that diffuses out, which includes the above-mentioned terms as well as those terms giving the equilibrium conditions. It is also apparent that estimates of D may be found from each exponent portion of the series used in Eqs. 1 and 2. From the first term of the series, $D = B_3 l^2/\pi^2$ or $4B_3H^2/\pi^2$, where B_3 = estimated exponential parameter and is estimated or known independently. If further terms of the series are used, D may be estimated from each term using $D = B_i l^2$ (or $4H^2)/\pi^2\ (2m + 1)^2$, where B_i = estimated exponential parameter and $m = 1, 2, \ldots, \infty$. If several exponential terms are used, a weighted average using a term such as some function of $1/m$ or of the number of observations contributing to the estimate of D would be appropriate. Some indication of the constancy of D may be obtained by inspection or formal regression of the time dependency of D.

The lag time prior to establishment of steady-state diffusion may be estimated from both models. The presence of a lag time results in nonconformance of the preexponential factor(s) to theory in the exponential model and in a nonzero intercept for the square root of time model. Barrer (19) and Jacobs (20) noted that lag time is proportional to D and membrane thickness. This expression for lag time is sufficient if the diffusing substance is dis-

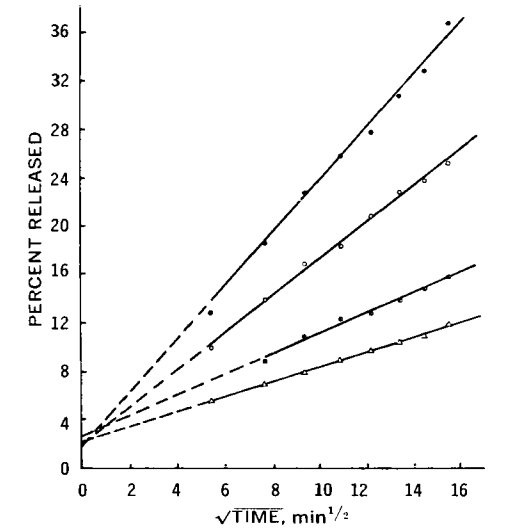

Figure 8—*Release of sodium radioiodide from ointment bases. Ointment bases containing: sodium salt of lauryl ether sulfate 1% (●); sodium salt of lauryl ether sulfate 2% (○); triethanolamine lauryl sulfate 3% (◐); and stearamidopropyl dimethyl β-hydroxyethylammonium nitrate 3% (△).*

Table I—Statistical Parameters for the Linear Model

Diffusion System	Intercept	Standard Error of Intercept	Slope	Standard Error of Slope	Sum of Squares Linear Regression (*df*)	Sum of Squares Quadratic Deviation (*df*)	Sum of Squares Residual (*df*)	Sum of Squares Cubic Deviation (*df*)	Sum of Squares Combined Quadratic and Cubic (*df*)	Sum of Squares Residual (*df*)
Fluocinolone acetonide[a]	1.370	0.390	1.019	0.127	7.906 (1)	0.600 (1)	0.013 (4)	0.001 (1)	0.600 (2)	0.013 (3)
Pyridine[b]	3.186	0.474	1.473	0.031	1778.378 (1)	6.874 (1)	1.569 (10)			
Salicylic acid, ●[c]	−1.589	1.033	2.689	0.133	401.978 (1)	6.956 (1)	1.934 (8)	0.897 (1)	7.853 (2)	1.037 (7)
Salicylic acid, ○[c]	0.705	0.199	0.767	0.026	32.704 (1)	0.198 (1)	0.132 (8)	0.043 (1)	0.242 (2)	0.088 (7)
Sodium radioiodide ($Na^{-131}I$), ●[d]	1.821	0.825	2.197	0.071	400.857 (1)	0.505 (1)	2.003 (5)	0.898 (1)	1.398 (2)	1.105 (4)
$Na^{-131}I$, ○[d]	1.937	0.469	1.540	0.040	196.566 (1)	0.311 (1)	0.498 (5)	0.002 (1)	0.313 (2)	0.496 (3)
$Na^{-131}I$, ▲[d]	2.657	0.509	0.858	0.042	33.818 (1)	0.062 (1)	0.335 (4)	0.247 (1)	0.309 (2)	0.876 (3)
$Na^{-131}I$, △[d]	2.194	0.112	0.619	0.010	31.734 (1)	0.002 (1)	0.044 (5)	0.002 (1)	0.004 (2)	0.043 (4)
Radioiodide from rectum[e]	0.034	5.096	9.280	0.840	4126.682 (1)	278.141 (1)	26.087 (8)	0.072 (1)	278.213 (2)	26.015 (7)

[a] Figure 2. [b] Figure 4. [c] Figure 6. [d] Figure 8. [e] Figure 10.

solved and in contact with the membrane. If, however, dissolution or some physical change, such as disintegration or dissolution of a dosage form, is necessary prior to diffusion, a more complex proportionality between lag time and D and the membrane thickness exists. This is apparent since the surface area for diffusion is changing. For adherence of the model to theory, a transformation of the independent variable, time or square root of time, to (time − lag time) or (time − lag time)$^{1/2}$ would be required.

MODEL EVALUATION

Sets of literature data for drug movement across a membrane, real or virtual, were evaluated[1] using Eqs. 1 and 4.

Experimental data reported for diffusion experiments were analyzed for goodness of fit to the mathematical models described by Eqs. 1 and 4. Examination of the parameters estimated from the experimental data for the two models can be compared using accepted statistical methods such as analysis of variance (ANOVA) and analysis of residuals. In using ANOVA methods, both linear regression and deviations from linear regression, calculated as the quadratic and cubic regression components, were examined. Analysis of residuals examines the deviations from regression for a nonrandom distribution about the calculated line. In the determination of the significance of lack of fit, the F-ratio of the mean square of interest to the residual mean square is examined. Significant lack of fit is defined when the F-ratio, as described, is greater than the appropriate tabular value at the $p < 0.05$ level. That these deviations from linearity are often not due solely to the quadratic (second-order) term would indicate that the choice of region of fit is not completely responsible for this lack of fit but also that a deficiency in the model is likely at fault. From an examination of the F-ratios generated by the mean squares computable from the sums of squares tabulated, significant lack of fit of the data to the linear model is apparent for most data sets. Indeed, some data reported by Higuchi (8) are the only ones that do not exhibit either significant or highly suggestive lack of fit.

Lack of fit or model deficiencies for the exponential model can be estimated only when an estimate of pure error, obtained from replications, is available. In all systems reported here, only a single determination was available for each point because the data were taken from graphs presented in the literature.

The effect of vehicle composition on the *in vitro* release of fluocinolone acetonide from a water-soluble[2] gel in direct contact with isopropyl myristate was reported (21) and subsequently (22) found to correlate with diffusion through human abdominal skin *(in vitro)* and vasoconstriction in the forearm *(in vivo)*. The data points for diffusion into isopropyl myristate are shown in Fig. 1. The solid line is that predicted from Eq. 1, when the values of $m = 0, 1$ are included. This line is $M_t = 7.102 - 3.701 \exp [0.2114 (\pm 0.0175)t] - 2.471 \exp (-0.0322t)$. The determination of lack of fit for the nonlinear estimation is not obvious from examination of the graph. Examination of residuals shows no evidence of nonrandom distribution of residuals about the estimated line. Figure 2 shows the data points for this study and the solid line predicted by using Eq. 4. The data points in the graph exhibit a sigmoid-shaped scatter about the estimated line. By using ANOVA, this observation is substantiated in that significant deviation from linear regression is observed (Table I).

Diffusion of pyridine from a water-in-oil emulsion through a cellophane membrane into an aqueous sink was measured (14), and the data are shown in Figs. 3 and 4. The solid line in Fig. 3 was generated with Eq. 9, and random scatter about the line can be observed. In Fig. 4, a significant deviation from linearity, determined by ANOVA as the quadratic regression component, is evident (Table I). The calculated line was determined using Eq. 4.

Figures 5 and 6 show the data (23) and calculated lines for the dialysis of salicylic acid from white petrolatum and a hydrophilic cream[3]. Figures 7 and 8 show the data (24) and predicted lines for the diffusion of sodium radioiodide ($Na^{-131}I$) from various surfac-

[1] All calculations were performed using library computer programs of the OS-3 system at Oregon State University. In particular, the programs SIPS (Statistical Interactive Programming System) and CURVFIT (Non-Linear Curve-Fitting Program) were utilized.

[2] Carbopol 934.

[3] Acid Mantle Creme.

Table II—Statistical Parameters for the Exponential Model

Diffusion System	M_∞ (C_0AH)	Standard Error of M_∞ (C_0AH)	Preexponential Factor	Standard Error of Preexponential Factor	Exponent	Standard Error of Exponent
Pyridine[a]	59.570	1.815	−51.182	1.689	−0.0019	0.0001
Salicylic acid, ○[b]	27.736	0.573	−27.552	0.534	−0.0216	0.0012
Salicylic acid, ●[b]	9.464	0.845	−8.630	0.766	−0.0200	0.0048
Sodium radioiodide ($Na^{-131}I$), ●[c]	37.690	2.934	−35.955	2.824	−0.0101	0.0022
$Na^{-131}I$, ○[c]	26.112	1.320	−25.170	1.372	−0.0116	0.0018
$Na^{-131}I$, ▲[c]	16.1525	0.578	−16.022	0.688	−0.0124	0.0014
$Na^{-131}I$, △[c]	11.450	0.639	−10.889	0.801	−0.0145	0.0029
Radioiodide from rectum[d]	76.918	1.188	−81.613	1.864	−0.0468	0.0072

[a] Figure 3. [b] Figure 5. [c] Figure 7. [d] Figure 9.

tant-containing ointment bases[4]. In each case, the drug was diffused through a cellophane membrane into an aqueous sink. A systematic sigmoidal deviation can be seen for one product in Fig. 6, but the data points all exhibit a random scatter in Figs. 5, 7, and 8. In the cases with random distribution of the residuals, the data appear to be equally well described by Eq. 1 or 4.

Riegelman and Crowell (25) described an *in vivo* method for investigating the rectal absorption of drugs in rats and reported the percent of the dose remaining in the rectum *versus* time. Those data were converted to amount diffused from the rectum and are plotted in Figs. 9 and 10. The sigmoidal deviation of the data points from the predicted line is clearly evident in Fig. 10 and exhibits a significant quadratic regression component (Table I).

CONCLUSION

Models describing diffusion have been discussed and compared. Their advantages and usefulness in various experimental conditions including *in vitro* diffusion with no membrane present, *in vitro* diffusion through cellophane membranes, and *in vivo* absorption from the rat rectum have been described. The advantages of the linear model (Eq. 4) include the ease of analysis and interpretation of linear relationships. The usefulness is in the region up to $M_t \approx \frac{1}{2}M_\infty$ for time greater than the lag time. A disadvantage lies in the necessity of estimating, if M_∞ is not known, when $\frac{1}{2}M_\infty$ is achieved. Furthermore, a high degree of dependence of estimation of M_∞ and D must occur since these are calculated from the same parameter. The nonlinear model, however, is useful over the entire diffusion time from the end of lag time to infinite time since, if sufficient terms of the series are retained, it is an exact physical model for a finite system. The errors inherent in the application of the linear relationship (Eqs. 4 and 5) appropriate for infinite and semi-infinite systems to systems more properly viewed as finite are avoided. The primary advantage in the use of the nonlinear model is that the parameters M_∞ and D are estimated as separate terms in the fitting procedure. Disadvantages lie in the greater unfamiliarity with nonlinear estimation procedures and in the iterative fitting techniques. These disadvantages can be overcome utilizing established estimation methods and the computer. Estimation of goodness of fit is somewhat more difficult since the statistical procedures are not rigorous but do provide a measure of comparison. However, examination of residuals can provide rigorous quantitative information concerning goodness of fit, if desired, or qualitative indications regarding suitability of the model. Models are often developed with the hope that they can be used beyond the end-points of experimental data and with some concern for the accuracy of estimation of the parameters of the physical process that the model describes. The asymptotic nature of the diffusion process is considered in the nonlinear model and is, therefore, useful in these

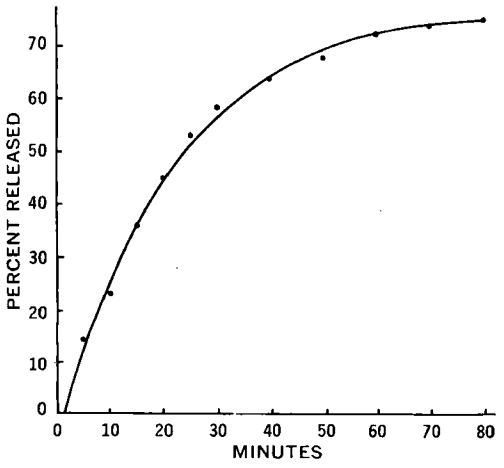

Figure 9—*Diffusion of radioiodide from rectum.*

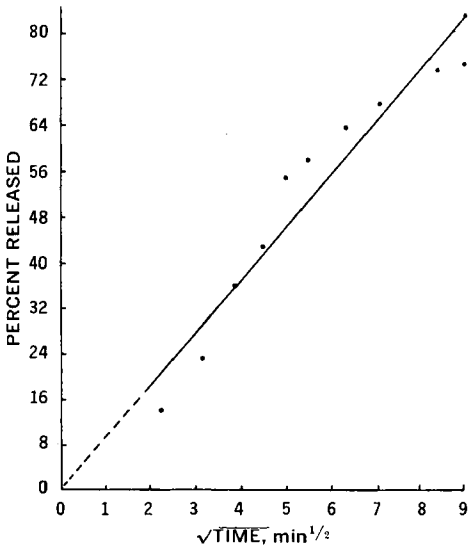

Figure 10—*Diffusion of radioiodide from rectum.*

[4] The bases used were the sodium salt of lauryl ether sulfate (Sipon ES), triethanolamine lauryl sulfate (Maprofix TLS), and stearamidopropyl dimethyl β-hydroxyethylammonium nitrate (Catanac SN).

respects. That all the data *generated* are used in parameter estimation, rather than merely that up to about $\frac{1}{2}M_\infty$, strengthens the parameter estimates.

It is anticipated that this evaluation will provide a basis for the use of the described models when the use of a physically exact or a general model is contemplated.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 16, 1973, from the *Department of Pharmaceutical Science, School of Pharmacy, Oregon State University, Corvallis, OR 97331*

Accepted for publication October 11, 1973.

Supported in part by Grant 30-260-0179 from the Research Council of Oregon State University.

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Substituted Piperazinoquinazolones: Relationship between Selective Inhibition of Nicotinamide Adenine Dinucleotide-Dependent Oxidations and Anticonvulsant Activity

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Abstract □ Several substituted piperazinoquinazolones were synthesized, characterized, and tested for their ability to affect the respiratory activity of rat brain homogenate. All piperazinoquinazolones were found to inhibit selectively nicotinamide adenine dinucleotide (NAD)-dependent oxidations of pyruvate, citrate, DL-isocitrate, β-hydroxybutyrate, α-ketoglutarate, and NADH while the NAD-independent oxidation of succinate remained unaltered. Inhibition of the oxidation of pyruvic acid by piperazinoquinazolones was concentration dependent, but added NAD, while stimulating the respiratory activity of brain homogenate, reduced the inhibition produced by these compounds. Some of these piperazinoquinazolones possessed anticonvulsant activity; however, this activity was found to be unrelated to their ability to inhibit the respiratory activity of the rat brain homogenate.

Keyphrases □ Piperazinoquinazolones—synthesis, anticonvulsant activity, and relationship to NAD-dependent oxidations □ Structure-activity relationships—piperazinoquinazolones, anticonvulsant activity, rats □ Inhibition of respiratory activity, NAD-dependent oxidations—synthesis and evaluation of piperazinoquinazolones □ Oxidation of pyruvate, citrate, DL-isocitrate, β-hydroxybutyrate, α-ketoglutarate, NADH, and succinate—effect of piperazinoquinazolones

Piperazinoureas possessing central nervous system (CNS)-depressant activity were recently shown to inhibit the oxidation of pyruvic acid by rat brain homogenate (1). Adrenergic, hypotensive, and antihistaminic activities were also reported for several 2-methyl-3-alkyl or piperazinoalkyl-4-quinazolones (2). Furthermore, selective inhibition of nicotinamide adenine dinucleotide (NAD)-dependent oxidation of pyruvic acid and other substrates of the tricarboxylic acid cycle by 2-methyl-3-*o*-tolyl-4-quinazolone (3–5) possessing hypnotic (6) and anticonvulsant properties (7) led to the synthesis of substituted pipera-