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B. K. Bernard ˣ
E. R. Finkelstein

Section of Pharmacology and Toxicology
School of Pharmacy
University of Connecticut
Storrs, CT 06268

Received March 5, 1974.
Accepted for publication July 8, 1974.
Supported in part by a grant from the University of Connecticut Research Foundation to B. K. Bernard.
ˣ To whom inquiries should be directed.

Influence of Solute Properties on Release of *p*-Aminobenzoic Acid Esters from Silicone Rubber: Theoretical Considerations

Keyphrases □ Silicone matrix—chain-length effect on *in vitro* release of *p*-aminobenzoates, theory, equations □ *p*-Aminobenzoic acid esters—*in vitro* release from silicone matrix, effect of solute properties, chain length, theory, equations □ Chain-length effect—*in vitro* release of *p*-aminobenzoates from silicone matrix, theory, equations

To the Editor:

The use of silicone rubber as a carrier for therapeutic agents is well documented (1–5). The release of drug from such an inert matrix is dependent upon certain solute properties, *i.e.*, solubility and diffusivity, along with other parameters independent of the particular drug in question. Examples of the latter are the geometry of the matrix, the diffusion layer thickness, the amount of drug per unit volume in the matrix, the particle size, and the filler content.

A mathematical model describing drug release from homogeneous and heterogeneous systems was originally presented by Higuchi (6). Within the assumptions of the model, equations were derived that predict a linear dependence of the amount released, Q, upon the square root of time, $t^{1/2}$. Subsequently, the model was extended and equations were derived that consider the solvent boundary diffusion layer as an additional diffusional pathway (7). According to this extended model, plots of Q *versus* $t^{1/2}$ may not be linear during the early stages of the release process. This has been experimentally verified (8) with a series of progestins. Nonlinear behavior was also observed for chlormadinone acetate (9) and for ethynodiol diacetate (10). However, a systematic evaluation of the influence of the properties of a homologous series on the release rate has not been reported.

This communication utilizes these derived mathematical relationships to describe the effect of chain length of esters of *p*-aminobenzoic acid on the *in vitro* release of drug from a silicone matrix. The assumptions and conditions of the model are: *(a)* pseudo-steady state exists; *(b)* diffusion is rate controlling rather than dissolution of drug particles; *(c)* total concentration of drug within the matrix, A, is substantially greater than its solubility, C_s, in the matrix phase, *i.e.*, $A \gg C_s$; *(d)* transport of the drug species occurs through the matrix phase; and *(e)* ideal sink conditions exist in the dissolution media. The amount released per unit area, Q, from a planar surface as a function of time, t, is given by the following expression (7):

$$Q = \frac{-D_s h_a K A \epsilon}{D_a \tau} + \left[\left(\frac{D_s h_a K A \epsilon}{D_a \tau}\right)^2 + \frac{2AD_s C_s \epsilon t}{\tau}\right]^{1/2} \quad \text{(Eq. 1)}$$

where:

A = total concentration of drug in matrix (milligrams per square centimeter)
D_a = diffusion coefficient in aqueous phase (square centimeter per minute)
D_s = diffusion coefficient in matrix phase (square centimeter per minute)
K = partition coefficient (C_s/C_a)
C_a = solubility (milligrams per milliliter) in dissolution media
C_s = solubility in matrix phase (milligrams per milliliter)
h_a = boundary diffusion layer (centimeters)
ϵ = volume fraction
τ = tortuosity

Differentiating Q with respect to time yields the rate equation:

$$\frac{dQ}{dt} = \text{rate} = \frac{\alpha C_s}{2(\beta^2 K^2 + \alpha C_s t)^{1/2}} \quad \text{(Eq. 2a)}$$

where:

$$\alpha = \frac{2AD_s\epsilon}{\tau} \quad \text{(Eq. 2b)}$$

$$\beta = \frac{D_s h_a A \epsilon}{D_a \tau} \quad \text{(Eq. 2c)}$$

For a homologous series of moderate chain length, D_s and D_a can be considered to be relatively constant (11); thus, α and β are constant for a given set of experimental conditions. For this situation, the release rate (Eq. 2*a*) is dependent only upon C_s and C_a (or, alternatively, C_s and K). As the carbon chain length

Table I—Solubility (Milligrams per Milliliter) Data for Esters of *p*-Aminobenzoic Acid (12)

Ester	Water (C_a)	Silicone Oil (C_s)	Partition Coefficient (K)
Methyl	3.82	0.79	0.208
Ethyl	1.68	1.38	0.817
Propyl	8.42×10^{-1}	2.31	2.75
Butyl	3.32×10^{-1}	3.44	1.03×10^{1}
Pentyl	9.32×10^{-2}	3.69	3.95×10^{1}
Hexyl	2.37×10^{-2}	2.48	1.05×10^{2}
Heptyl	5.88×10^{-3}	2.35	4.00×10^{2}
Octyl	9.96×10^{-4}	1.48	1.48×10^{3}

is increased regularly in the homologous series, the ratio of C_s/C_a (which is approximately equivalent to the partition coefficient K) changes in an incremental fashion; *i.e.*, $K_n = K_0\, 10^{\pi n}$, where K_n is the partition coefficient for the *p*-aminobenzoic acid ester of chain length n, K_0 is the partition coefficient of a hypothetical reference member with no methylene groups, and π is the logarithmic change of the partition coefficient per methylene unit (11). Since π is dependent only upon the matrix and solvent properties, it is constant for all homologous series. For silicone oil–water, $\pi = 0.54$ (12). If the log of C_a also changes in a regular fashion with chain length, then $C_s = f[C(s_0), n]$, where $C(s_0)$ is the solubility of the hypothetical homolog with no methylene groups and f is the appropriate simple function (11). For the purposes of this communication, it suffices to deal with C_s and K directly as expressed by Eq. 2*a*.

Table I shows reported (12) solubility data for the *p*-aminobenzoic acid esters. Theoretical release rate data were generated for each homolog in the series

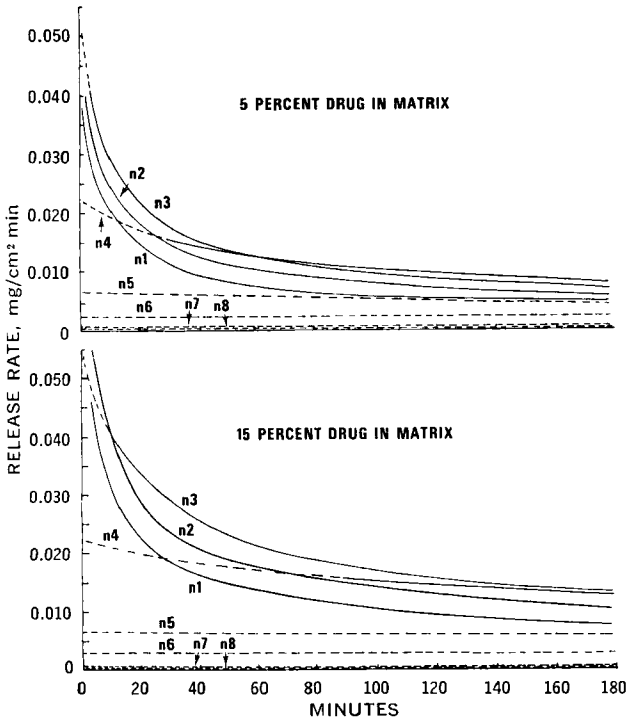

Figure 1—In vitro *theoretical release rates of esters of* p-*aminobenzoic acid from silicone rubber disks at two different concentrations of drug within the matrix* (n = *number of carbons in alkyl chain*).

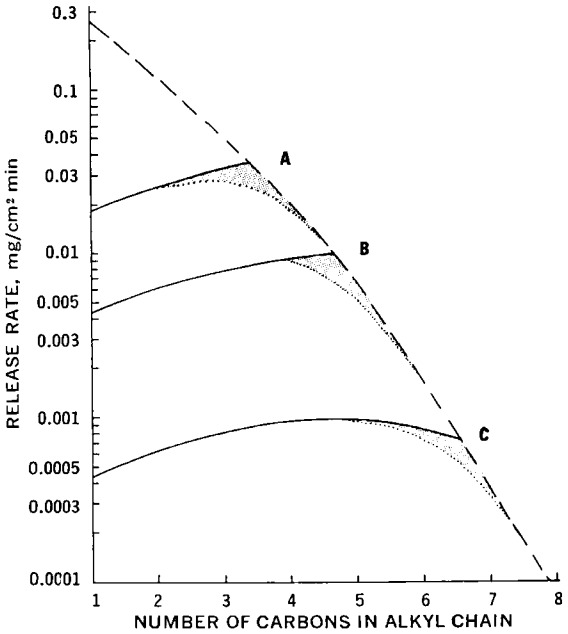

Figure 2—In vitro *theoretical release rates of esters of* p-*aminobenzoic acid as a function of chain length at three different times: A, 10 min; B, 3 hr; and C, 12.5 days. Key: ---, diffusion layer control rate (Eq. 7);* ——, *matrix control rate (Eq. 6); and* · · ·, *expected rate (Eq.* 2a).

with the assumption that C_s can be approximated by the solubility of the ester in silicone oil, and by setting:

$$\frac{D_a}{h_a} = 0.68 \times 10^{-1}\ \frac{\text{cm}}{\text{min}} \qquad \text{(Eq. 3)}^1$$

$$D_s = 1.6 \times 10^{-4}\ \frac{\text{cm}^2}{\text{min}} \qquad \text{(Eq. 4)}^2$$

$$A = 55 \text{ or } 165 \text{ mg/ml} \qquad \text{(Eq. 5)}^3$$

with ϵ and τ assumed to be unity[4].

Figure 1 shows the theoretical release rate profile as a function of time for the esters (methyl through octyl) at two different concentrations of drug within the matrix. The shape of the curves and the magnitude of the release rates are clearly dependent upon chain length. From methyl to butyl, rates decrease significantly with time due to drug transport through an increasing thickness of the depleted drug layer (7). At long times, butyl is released faster because it has a higher matrix solubility than the shorter chain congeners. In other words, at long times, Eq. 2*a* reduces to:

$$\text{rate} = \left(\frac{AD_sC_s\epsilon}{2t\tau}\right)^{1/2} \qquad \text{(Eq. 6)}$$

This is the matrix-controlled case as proposed by Higuchi (6). At higher chain lengths (pentyl through octyl), release rates are essentially constant, approximating a zero-order process. This is described as dif-

[1] A reasonable average value for D_a in dilute aqueous media for the homologous series calculated from the Sutherland-Einstein (13) equation is 4.8×10^{-4} cm²/min, while in a well-stirred system h_a may be around 70×10^{-4} cm (7).

[2] Value taken from Ref. 11.

[3] Equivalent to 5 or 15% (w/w) with the density of the matrix equal to 1.1.

[4] The values of ϵ and τ depend upon the heterogeneity of the matrix, *e.g.*, the filler content. For simplicity, they are assumed to be unity. Data have been presented that show that this is a reasonable assumption for certain matrixes (8, 14).

fusion layer control since diffusion away from the matrix is rate controlling. This behavior results when K is large, *i.e.*, $\beta^2K^2 \gg \alpha C_s t$, and Eq. 2*a* simplifies to:

$$\text{rate} = \frac{D_a C_a}{h_a} \qquad \text{(Eq. 7)}$$

The dashed lines in Fig. 1 indicate that period for which the diffusion layer contribution to the overall release is substantial (*i.e.*, until the time when $\alpha C_s t = \beta^2K^2$), while the continuous lines represent that period when the release is primarily under matrix control. The crossover of the curves results because the transition of diffusion layer to matrix control occurs at different times. Comparison of the 5 and 15% loading doses indicates that release rates are independent of drug concentration at longer chain lengths. However, the shorter chain lengths do exhibit a dependence on concentration which follows Eq. 6 at long times. Also, at the higher concentration, diffusion layer control is operative for a longer time (Fig. 1).

Figure 2 shows the applicability of Eq. 2*a* from a different viewpoint. Here, rate is plotted as a function of the number of carbons *(n)* in the alkyl chain. The dashed line is the rate calculated from Eq. 7 and is directly proportional to C_a. The continuous line is the rate calculated from Eq. 6 and is proportional to $(C_s)^{1/2}$ at a given time. The expected rate given by Eq. 2*a* is represented by the dotted line, and the shaded area is the transition region.

Based upon the model discussed here, factors such as particle size or polymorphic forms of the drug which may influence C_s and/or C_a would be expected to alter the release profile. A forthcoming publication[5] will experimentally test the applicability of these equations.

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T. J. Roseman ˣ
S. H. Yalkowsky

The Upjohn Company
Kalamazoo, MI 49001

Received May 17, 1974.
Accepted for publication July 8, 1974.

ˣ To whom inquiries should be directed.

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Bioavailability of Digoxin in Presence of Antacids

Keyphrases □ Digoxin—bioavailability in presence of antacids □ Antacids—effect on bioavailability of digoxin □ Bioavailability—digoxin, effect of concurrent antacid administration

To the Editor:

Considerable attention has recently been focused on the problem of bioavailability of digoxin (1–5), and several factors have been reported as responsible for the observed therapeutic effect (6–8). This communication reports the effect of some antacids on the dissolution of digoxin tablets[1] in an attempt to predict the bioavailability of the drug.

Recently, a number of reports (4, 5, 8) confirmed the existence of a close correlation between *in vitro* dissolution and the plasma digoxin level. Shaw *et al.* (4), using seven brands of digoxin tablets, found a good correlation between the percentage of dissolution at 30 min and the plasma digoxin level. Fraser *et al.* (5) reported that both the amount of digoxin dissolved in 1 hr and the reciprocal of the time for 50% dissolution ($1/t_{50\%}$) agreed well with the bioavailability data as computed from the mean area under the serum concentration–time curve. Therefore, dissolution experiments were carried out in the present work to reflect bioavailability.

The dissolution apparatus and procedure adopted were as reported previously (4). The liquid antacid preparation was incorporated in the dissolution medium (water), and an aliquot of 5 ml per digoxin tablet was used. Dissolution tests were performed at 37 ±

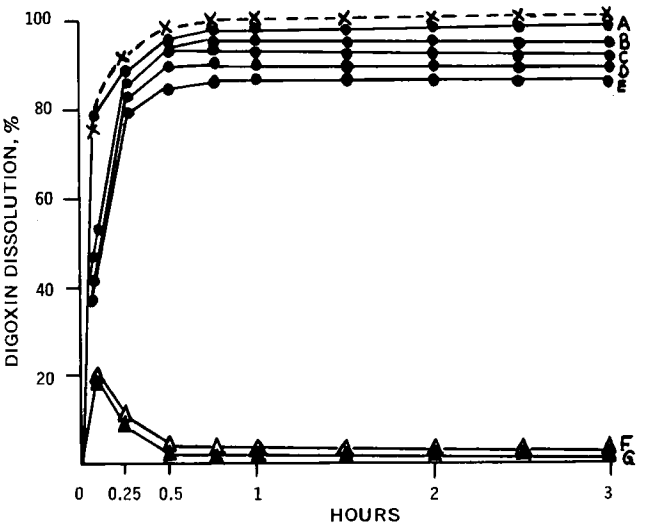

Figure 1—*Effect of some liquid antacid preparations on the dissolution rate of digoxin tablets at 37 ± 0.2° (average of four replicates). Key: – – –, dissolution in the absence of antacids; and ——, dissolution in the presence of antacids. For key to antacid preparations, see Table I.*

[1] Lanoxin tablets (0.25 mg), Batch 2042 X, Burroughs Wellcome & Co., Kent, England.