# Membrane Transport of Alkyl Homologs: Role of Fluid Flow in Aqueous Diffusion Region

**ASHOK C. SHAH** *x **and KENNETH G. NELSON** ‡§

Received April 4, 1979, from the *Pharmacy Research Unit, The Upjohn Company, Kalamazoo, MI 49001, and the ‡College of Pharmacy, University of Minnesota, Minneapolis, MN 55455. Accepted for publication August 24, 1979. §Present address: Pharmacy Research Unit, The Upjohn Company, Kalamazoo, MI 49001.

**Abstract** □ Passive drug transport across a membrane involves the resistances in series offered by the membrane and the liquid layer immediately adjacent to it. The liquid layers generally are referred to as unstirred aqueous diffusion layers, suggesting that solute transport across these layers occurs solely by molecular diffusion. In accord with convective diffusion theory, recent studies showed that the transport from either a dissolving surface or a membrane surface depends not only on molecular diffusion but also on fluid convection in the liquid adjacent to the membrane. Membrane permeation rates were determined for a series of alkyl *p*-aminobenzoates, and the results correlated with a model comprised of membrane diffusion and convective diffusion in the adjacent liquid region.

**Keyphrases** □ Drug transport—alkyl *p*-aminobenzoates, membrane permeation, fluid flow in aqueous diffusion region □ *p*-Aminobenzoates—membrane permeation, fluid flow in aqueous diffusion region □ Permeation—*p*-aminobenzoates, membrane transport, fluid flow in aqueous diffusion region

Passive drug transport across a membrane involves the resistance offered by the membrane itself as well as by the passage through the liquid immediately adjacent to the membrane. At steady state, the two processes occur simultaneously; because they are in series, limiting cases exist in which one process or the other may be rate limiting. Recent studies demonstrated that under conditions of aqueous boundary layer control, the permeation rate of butamben through a dimethicone membrane was described accurately by a mathematical model based on convective diffusion theory (1).

Models for steady-state transport across membranes generally have been based on the assumption of unstirred solvent layers adjacent to the membrane (2). Such layers are included as a resistance in series with the membrane. However, this concept of a static liquid layer adjacent to a solid and continuous with a moving liquid has been criticized (3) on the basis of empircal evidence as well as hydrodynamic theory.

The purposes of this work were to study the membrane permeation of a series of alkyl *p*-aminobenzoates and to evaluate the data in terms of a model comprised of membrane diffusion and convective diffusion in the adjacent liquid.

## EXPERIMENTAL

The permeation studies for the methyl through pentyl *p*-aminobenzoates were carried out using a dimethicone membrane (thickness of 0.0254 cm) in a laminar flowcell (1, 4). On the donor side of the membrane, a well-stirred aqueous suspension of the permeant provided the source at a constant concentration. On the other side, water flowing under laminar conditions removed the solute from the vicinity of the membrane and also served as the means to monitor the permeation rate spectrophotometrically.

Table I gives the aqueous solubilities and partition coefficients for the compounds studied. The aqueous solubilities at 25° were determined previously (4). The partition coefficients were obtained by equilibrating dimethicone membranes with aqueous suspensions of the esters for 48 hr at 25°, extracting the ester from the membrane by successive equilibration with water, and analyzing the extract spectrophotometrically ($\lambda_{max}$ 285 nm) to determine the ester concentration in the membrane. Partition coefficients were taken as the ratio of the concentration in the membrane to the aqueous solubility.

## THEORETICAL

The diffusional resistance, $R_m$, of the circular membrane is given by:

$$R_m = \frac{h}{D_m K \pi r^2} \qquad \text{(Eq. 1)}$$

where $h$ is the membrane thickness, $D_m$ is the solute diffusivity in the membrane, $K$ is the partition coefficient of the solute in the membrane relative to water, and $r$ is the membrane radius. The analogous resistance term, $R_w$, for the convective diffusion transport through the liquid adjacent to the membrane may be expressed as:

$$R_w = \frac{1}{2.16 r^{5/3} D_w^{2/3} \alpha^{1/3}} \qquad \text{(Eq. 2)}$$

where $D_w$ is the aqueous diffusivity of the solute and $\alpha$ is the rate of shear adjacent to the membrane which is directly proportional to the fluid flow rate (4). The steady-state permeation rate is given by the concentration difference across the membrane divided by the resistance, which is the sum of the individual layer resistances for a classical composite membrane (5). If it is assumed that the resistances as given in Eqs. 1 and 2 are additive, the steady-state permeation rate, $J$, may be written as:

$$J = \frac{2.16 \pi r^{11/3} D_w^{2/3} \alpha^{1/3} D_m K C}{\pi r^2 D_m K + 2.16 h r^{5/3} D_w^{2/3} \alpha^{1/3}} \qquad \text{(Eq. 3)}$$

where $C$ is the constant solute concentration on the donor side of the membrane.

Two limiting cases of Eq. 3 are represented schematically in Fig. 1. In one case, diffusion across the membrane becomes rate controlling under conditions that favor minimizing Eq. 2 relative to Eq. 1, *e.g.*, a very large $\alpha$ or $h$, so that Eq. 3 becomes:

$$J = \frac{\pi r^2 D_m K C}{h} \qquad \text{(Eq. 4)}$$

Alternatively, if the resistance in the membrane (Eq. 1) is minimized with respect to that in the liquid (Eq. 2) by such factors as a small $h$ or a large $K$, then:

$$J = 2.16 r^{5/3} D_w^{2/3} \alpha^{1/3} C \qquad \text{(Eq. 5)}$$

This limiting case was discussed previously (1) and is the same expression as for the dissolution from a solid solute surface in the cell. Equation 3 in effect is an interpolation formula; it combines the two limiting cases to describe permeation for conditions in which the two resistances are comparable in magnitude.

Figure 1 was drawn ignoring the partitioning effect ($K = 1$). In Case II, the profile in the liquid is dependent on the distance along the mem-

**Table I—Aqueous Solubilities and Partition Coefficients of *p*-Aminobenzoate Esters at 25°**

| Ester | Aqueous Solubility, moles/liter | Partition Coefficient |
|---|---|---|
| Methyl | $1.04 \times 10^{-2}$ | 0.26 |
| Ethyl | $6.19 \times 10^{-3}$ | 0.78 |
| Propyl | $2.78 \times 10^{-3}$ | 2.59 |
| Butyl | $9.39 \times 10^{-4}$ | 9.61 |
| Pentyl | $2.72 \times 10^{-4}$ | 38.11 |



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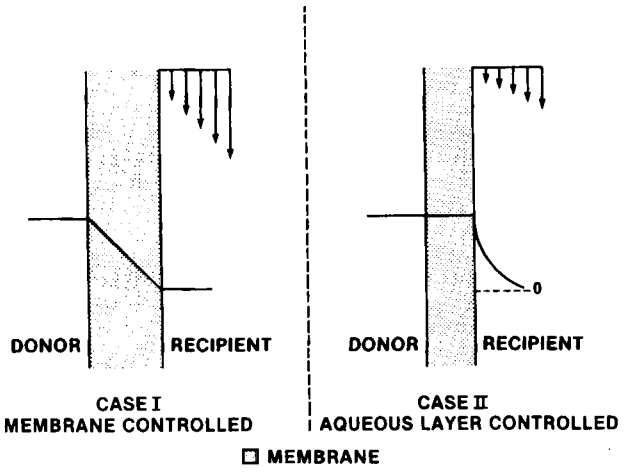


**Figure 1**—*Concentration profile for the two limiting cases of permeation according to Eq. 4 (Case I) and Eq. 5 (Case II). Arrows indicate the velocity of laminar liquid flow within the aqueous boundary layer.*

brane. Thus, the gradient would be steeper and the extent of penetration into the liquid would be less near the upstream edge of the membrane than at points along the membrane further downstream.

## RESULTS AND DISCUSSION

The steady-state permeation rates of the methyl through pentyl *p*-aminobenzoates were determined as a function of the fluid flow rate under laminar conditions. These rates are shown in Fig. 2 as the data points. Because the parameters on the right side of Eq. 3 are known independently, the rates predicted by Eq. 3 also are included in Fig. 2 as the solid lines. The experimental results are in reasonably good agreement with

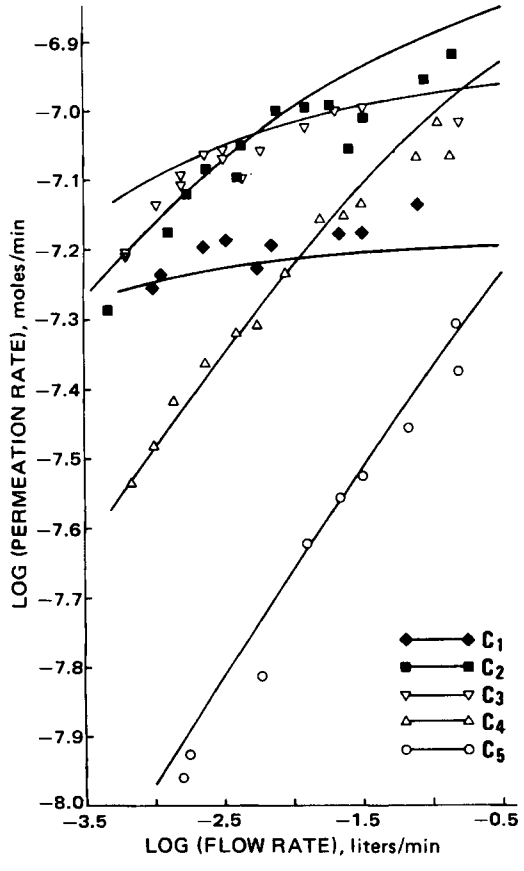


**Figure 2**—*Permeation rates of $C_1$–$C_5$ alkyl homologs of* p-*aminobenzoates determined as a function of the fluid flow rate. Curves represent relationships predicted by Eq. 3.*

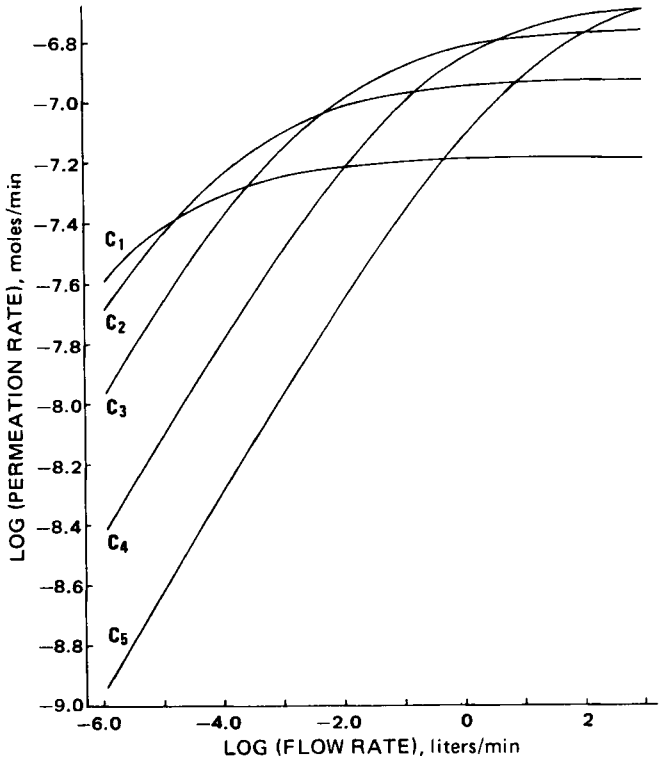


**Figure 3**—*Permeation rates of $C_1$–$C_5$ alkyl homologs of* p-*aminobenzoates estimated by Eq. 3 over a wide range of fluid flow rates.*

Eq. 3, especially for the butyl and pentyl esters. For the others, predicted trends exist in the rates of the various esters relative to each other.

To demonstrate the ramifications of Eq. 3, predicted rates are shown in Fig. 3 for a much wider range of fluid flow rates. At low flow rates, the lines became parallel with a slope of one-third because the solute transport rate was controlled by the simultaneous diffusion and convection in the liquid adjacent to the membrane, which is commonly termed the aqueous boundary layer control. This limiting case is given by Eq. 5. The

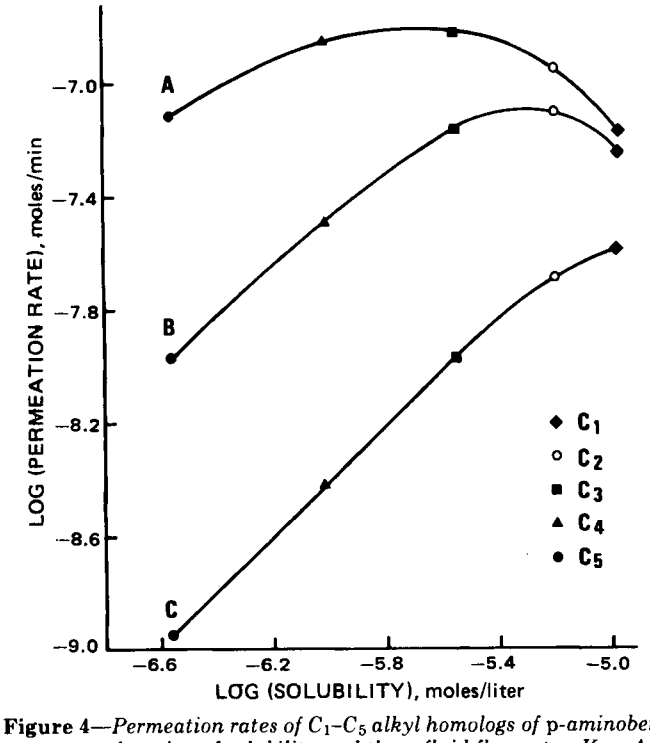


**Figure 4**—*Permeation rates of $C_1$–$C_5$ alkyl homologs of* p-*aminobenzoates as a function of solubility and three fluid flow rates. Key: A, 1 liter/min; B, $1 \times 10^{-3}$ liter/min; and C, $1 \times 10^{-6}$ liter/min.*

vertical spacing is governed by the solubilities of the various esters.

At high flow rates, the permeation rates leveled off and became independent of flow in accordance with Eq. 4, wherein the permeation rate becomes only a function of the transport across the membrane. Thus, $K$ and $C$ determined the relative positions of the plateaus in Fig. 3.

In the permeation simulations calculated with Eq. 3, values of $D_m$ and $D_w$ reported previously (2, 4) were assumed to be the same ($D_m = 2.72 \times 10^{-6}$ cm$^2$/sec and $D_w = 6 \times 10^{-6}$ cm$^2$/sec) for all members of the series because the change in molecular weight would change the diffusivity insignificantly (6) compared with the order-of-magnitude changes in the other parameters, *e.g.*, solubility and flow rate. Although the diffusivity was not evaluated as an independent parameter in the present work, it has been observed experimentally (7) that the resistance in the aqueous boundary layer film adjacent to a membrane is proportional to the diffusivity raised to the power −0.6. This observation is in reasonably good agreement with Eq. 2.

Equation 3 arises from an assumption that the resistances in the membrane and in the adjacent liquid are additive. This combination permits calculation of the permeation rate under conditions of membrane control or aqueous convective diffusion control or at intermediate points. It is apparent from the permeation data that the predictions were reasonably good. However, in the intermediate region, Eq. 3 should be considered as an interpolation formula rather than as an expression arising directly from basic theory because the instantaneous transport rate decreases somewhat with increasing distance along the membrane in the direction of flow. This decrease is a characteristic of convective diffusion theory. With intermediate cases, there would be a concentration gradient within the membrane in the direction of flow. This gradient is not accounted for in Eq. 3. However, such a gradient would be much smaller than the gradient normal to the membrane because of the relative distances involved and, therefore, may be ignored.

If the data in Fig. 3 are replotted as log permeation rate *versus* log solubility, the curves obtained at different flow rates appear as in Fig. 4. The maximum permeation rate is shifted to the left, *i.e.*, to permeants having a lower solubility, with an increase in flow rate. This is similar to the concepts of Flynn and Yalkowsky (2), who evaluated the effect of fluid flow agitation in terms of a change in the thickness of the stagnant or unstirred layer. The thickness of the unstirred layer is a model-dependent parameter; it cannot be measured independently of permeation experiments. In the present work, the effect of fluid flow is incorporated as the rate of shear adjacent to the membrane. Because hydrodynamic theory permits one to determine the shear rate from the fluid flow rate and the geometry of the cell, the effect of fluid flow on permeation and the position of maximum permeation can be calculated readily *a priori* for a given membrane thickness using Eq. 3.

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# Simultaneous High-Pressure Liquid Chromatographic Determination of Acetaminophen, Guaifenesin, and Dextromethorphan Hydrobromide in Cough Syrup


**W. O. McSHARRY *x and I. V. E. SAVAGE ‡**



Received April 12, 1979, from the **Quality Control Department, Hoffmann-La Roche Inc., Nutley, NJ 07110,* and ‡*Roche Products Pty. Ltd., Dee Why 2099, Australia.* Accepted for publication August 23, 1979.



**Abstract** □ Acetaminophen (I), guaifenesin (II), and dextromethorphan hydrobromide (III) were separated and quantitated simultaneously in cough syrup by high-pressure liquid chromatography. A chemically bonded octadecylsilane stationary phase was used with a mobile phase of 45% (v/v) aqueous methanol. The mobile phase pH was stabilized to 4.2 by adding formic acid–ammonium formate buffer (~0.4%). The internal standard was *o*-dinitrobenzene. Retention volumes were 4 ml for I, 6 ml for II, 11 ml for the internal standard, and 20 ml for III. Inactive syrup components did not interfere, permitting direct diluted sample injection. Results on active ingredients were essentially 100% of the claim, with standard deviations of ±1.5, 1.2, and 2.1% for I, II, and III, respectively.



**Keyphrases** □ High-pressure liquid chromatography—simultaneous determination of acetaminophen, guaifenesin, and dextromethorphan hydrobromide, analysis of cough syrup active ingredients □ Pharmaceutical preparations—simultaneous determination of cough syrup active ingredients by high-pressure liquid chromatography □ Acetaminophen—simultaneous determination with guaifenesin and dextromethorphan hydrobromide, high-pressure liquid chromatography □ Guaifenesin—simultaneous determination with acetaminophen and dextromethorphan hydrobromide, high-pressure liquid chromatography □ Dextromethorphan hydrobromide—simultaneous determination with acetaminophen and guaifenesin, high-pressure liquid chromatography


Characterization of numerous drugs (1–4) and analyses of specific dosage forms have been conducted through the use of high-pressure liquid chromatography (HPLC). Recent investigations of pharmaceutical preparations included acetaminophen (paracetamol)–chlorpheniramine maleate–dextromethorphan hydrobromide (5) and codeine phosphate–guaifenesin (glyceryl guaiacolate)–pheniramine maleate–phenylpropanolamine hydrochloride–pyrilamine maleate (6). A liquid chromatographic analysis of 29 drug compounds in acidic, neutral, and alkaline media included syrups containing phenylephrine hydrochloride, acetaminophen, guaifenesin, and dextromethorphan hydrobromide (4). However, it was not clear if the last three compounds could be analyzed using a single mobile phase.

Simultaneous determination of acetaminophan (I), guaifenesin (II), and dextromethorphan hydrobromide (III) in a liquid preparation has not been reported. Routine analysis of a cough syrup was required, and HPLC was the method of choice. A chemically bonded nonpolar-sta-




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