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Application of a Convective Diffusion Model to Membrane Transport

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Abstract □ Studies were carried out on the permeation rate of butamben through a dimethicone membrane. Under conditions of "aqueous diffusion layer control," the permeation rate was accurately described by a mathematical model based on convective diffusion theory. In accordance with the model, the rate of permeation from a saturated donor phase was shown to be equal to the rate of dissolution from a pure solid.

Keyphrases □ Diffusion, convective—model applied to permeation rate of butamben through dimethicone membrane □ Membrane transport—convective diffusion model applied to permeation rate of butamben through dimethicone membrane □ Permeation rate—butamben through dimethicone membrane, convective diffusion model □ Butamben—permeation rate through dimethicone membrane, convective diffusion model

One fundamental process that occurs during drug absorption is the transport of the active ingredient across various biological membranes. The study of membrane transport is thus of considerable interest, and the theoretical aspects of permeation models were recently reviewed (1).

In the model most frequently used to describe membrane transport, the membrane is considered to be in series with a stagnant or unstirred liquid diffusion layer on each side (2–5). For a liquid flowing past a surface, however, fluid flow occurs even at very small distances from the solid. Therefore, convective diffusion theory that accounts for fluid flow as well as diffusion should be applied (6). The differential equation of convective diffusion theory requires a mathematical description of the liquid flow past the dissolving surface. Although flow profiles are generally nonlinear, a constant velocity gradient can be assumed if the dissolving surface is relatively short (7, 8). Such a model recently was applied to describe drug dissolution into a moving liquid (9, 10). The purpose of this study was to evaluate the application of convective diffusion theory to membrane transport under conditions where transport across the dynamic liquid layer adjacent to the membrane is the rate-limiting step.

EXPERIMENTAL

The laminar flowcell was a modification of the dissolution cell described previously (10). The dissolution cell was adapted for membrane transport studies by constructing a donor compartment in the die such that the membrane would be positioned coplanar with the die surface. As shown in Fig. 1, the donor compartment consists of a cylindrical metal cup over which the membrane is positioned. When placed in the die as shown, the membrane made a watertight seal over the donor compartment. The donor compartment was stirred with a magnetic stirring bar.

The permeation rates were determined as follows using butamben as the permeating species. The donor cup was filled with an aqueous suspension of butamben and was mounted in the die with the membrane (thickness 0.025 cm) positioned as described. The membrane was prepared as described by Roseman (11). The die was placed in the flowcell, which was leveled and mounted on a vibration-free platform. Distilled
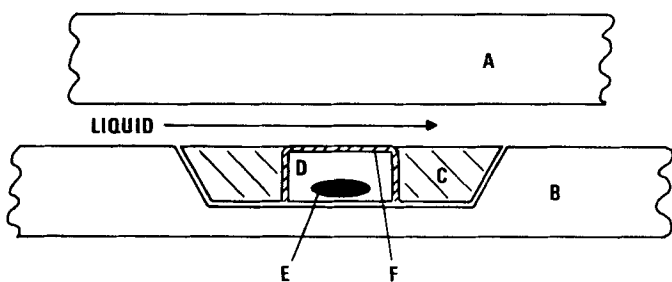
Figure 1—*Cross-sectional view of diffusion cell. Key: A, top plate; B, bottom plate; C, die; D, donor compartment; E, stirring bar; and F, membrane.*

water (25°) was pumped through the flowcell at a set flow rate with an infusion syringe pump[1], and the effluent was assayed spectrophotometrically[2] at 285 nm for the ester concentration. The ester concentration together with the flow rate permitted calculation of the permeation rate.

The permeation rate was studied as a function of the liquid flow rate and membrane area. The former was varied by changing the pump speed, while the latter was changed by using three donor cup–die assemblies with different radii (0.65, 1.0, and 1.25 cm).

RESULTS AND DISCUSSION

Figure 2 is a log–log plot of permeation rate *versus* flow rate. The initial rise followed by a plateau indicates that at low rates the permeation rate is influenced significantly by the transport in the liquid; at the higher flow rates, the major resistance to transport is offered by the membrane. The conditions corresponding to the former case are commonly called "diffusion layer control." Because the membrane offers only negligible resistance to permeation under these conditions, the aqueous concentration of solute at the interface between the membrane and the flowing liquid is equal to the concentration in the donor phase, which in this case is the solubility of the solute. Therefore, at low flow rates, the mathematical model describing the permeation rate should be the same as that used to describe the drug dissolution rate into a moving liquid (9, 10). The model, based on convective diffusion theory, gives the permeation rate, R, as:

$$R = 2.157D^{2/3}C_0\alpha^{1/3}r^{5/3} \qquad \text{(Eq. 1)}$$

where D is the diffusivity of the solute in water, C_0 is the solubility (or more generally the concentration of solute in the donor phase), α is the rate of shear over the membrane, and r is the radius of the membrane. The rate of shear immediately over the membrane is given by (10):

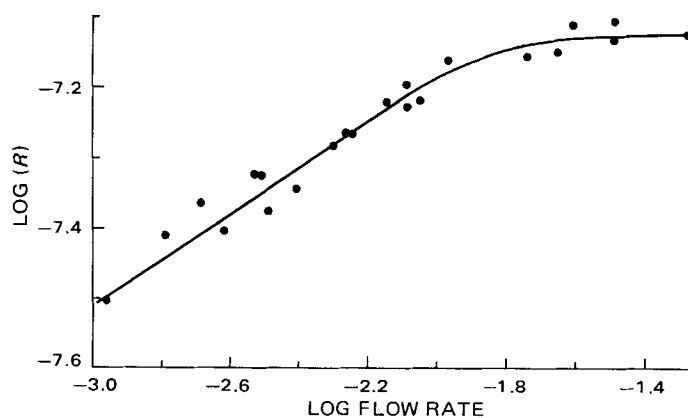$$\alpha = \frac{6Q}{H^2W} \qquad \text{(Eq. 2)}$$

Figure 2—*Log–log plot of the permeation rate, R, as a function of the fluid flow rate.*

Table I—Permeation Rate as a Function of Fluid Flow Rate

Flow Rate (Q) × 10^3, liters/min	Permeation Rate × 10^8, moles/min
1.00	3.126
1.60	3.880
2.05	4.328
2.38	3.934
2.92	4.740
3.03	4.692
3.24	4.180
3.92	4.497
5.00	5.176
5.50	5.455
5.68	5.400
7.17	5.985
8.12	6.405
8.25	5.886
8.83	6.033
10.70	6.827
18.20	6.967
22.00	7.044
24.30	7.752
32.25	7.295
32.50	7.840
52.50	7.490

where Q is the volumetric flow rate, and H and W are the height and width of the diffusion cell, respectively. Thus, Eqs. 1 and 2 would predict a straight line with a slope of one-third on a plot of log R *versus* log Q. In Fig. 2, a line with a slope of one-third is drawn through the data up to log $Q = -2.0$ to permit visual correlation between theory and experiment. The data are given in Table I, and a statistical analysis of the data up to log $Q = -2.0$ gives a least-squares slope of 0.297 ($SD = 0.0215$) with a correlation coefficient of 0.9626.

The permeation rate also was determined using the area of the membrane as a variable. Figure 3 shows a log–log plot of permeation rate *versus* membrane radius at a constant flow rate of 2.24 ml/min. The slope of this line is 1.66, which is in excellent agreement with the exponent of 5/3 on the radius in Eq. 1. These results indicate that, under conditions of diffusion layer control, the permeation rate is not directly proportional to area but to a somewhat reduced function of area ($r^{5/3}$) because of the interaction of diffusion and convection. Solute leaving the membrane near the upstream edge of the membrane enters liquid largely devoid of solute, whereas there is a buildup of solute further downstream. The model based on convective diffusion can quantitatively account for such phenomena.

A calculation of the permeation rate using Eqs. 1 and 2 further supports the applicability of the convective diffusion model. Independently determined values used for the calculation are: $D = 6 \times 10^{-6}$ cm^2 sec (12), $C = 9.4 \times 10^{-4}$ M (10), $r = 1.25$ cm, $H = 0.31$ cm, $W = 3.65$ cm, and $Q = 2.05$ ml/min. The permeation rate is calculated to be 4.88×10^{-8} mole/min, which corresponds quite well to the experimentally determined rate of 4.33×10^{-8} mole/min.
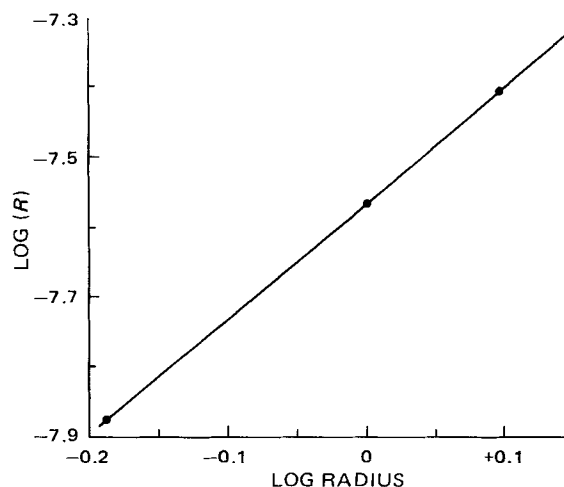

Figure 3—*Log–log plot of the permeation rate, R, as a function of the membrane radius.*

As in the studies on dissolution rates of drugs (9, 10), the model based on convective diffusion theory is able to describe quite accurately the membrane transport rate as a function of the physical–chemical parameters of the system. The convective diffusion model should apply to membrane transport for conditions intermediate between extremely low and high liquid flow rates. For the former conditions, as the flow approaches zero, it would be more appropriate to base a model on a non-steady-state differential equation; for the latter, the transport is "membrane controlled" and has been thoroughly discussed (1).

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Quick Specific Assay for Aspirin

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Abstract □ Use of the Schoenemann reaction for the assay of aspirin in pharmaceutical combinations is described.

Keyphrases □ Aspirin—colorimetric analysis using Schoenemann reaction, pharmaceutical combinations □ Colorimetry—analysis using Schoenemann reaction, aspirin in pharmaceutical combinations □ Analgesics—aspirin, colorimetric analysis using Schoenemann reaction, pharmaceutical combinations

Aspirin is often the most labile component in a combination-type analgesic compound. Therefore, its stability is often the initial concern in any formulation screening program. Preliminary screening of a large number of potential formulations can be arduous, since most current methods of analysis generally consist of several steps: extractions or column separations followed by UV, colorimetric, or GLC assay (1–4). The method proposed here is quite suited to large numbers of assays. It is straightforward and is not subject to interference from substances such as salicylic acid, caffeine, phenacetin, acetaminophen, and codeine. It is essentially a Schoenemann reaction with slight modifications (5, 6).

EXPERIMENTAL

Preparation of Sample—An amount of tablet granulation equivalent to 100 mg of aspirin is weighed into a 250-ml volumetric flask, and 200 ml of distilled water is added. The slurry is shaken for about 10 min; then the flask is diluted to volume with distilled water.

Standard—Aspirin, 0.4 mg/ml of water, is prepared freshly.

Equipment—A recording dual-beam spectrophotometer[1] was used at 455 nm with the recorder speed at 5 mm/min.

Reagents—o-Dianisidine hydrochloride[2] (3,3'-dimethoxybenzidine dihydrochloride) was obtained commercially[3]. Tribasic sodium phos-

phate, 3% hydrogen peroxide, and the various pharmaceuticals tested were all reagent or USP grade or good commercial grade. Acetone[4] was reagent spectrophotometric grade and was used without purification. Previous investigators warned that impure acetone leads to false results (5).

Assay—The reagents were mixed in the following order: 0.5 ml of o-dianisidine hydrochloride (0.5% aqueous solution), 3.0 ml of acetone, 1.0 ml of 3% hydrogen peroxide, 1.0 ml of standard, and 2.0 ml of 0.05 M tribasic sodium phosphate.

The maximum color developed was measured in a 1-cm cell against water in the reference beam of the spectrophotometer at 455 nm by recording absorbance as a function of time. The maximum always occurred within 5 min.

The entire procedure was repeated, substituting the sample solution for the standard.

The ratio of the maximum absorbances of sample and standard was used to calculate the amount of aspirin in the sample taken.

RESULTS AND DISCUSSION

Linearity—The maximum absorbance was determined for the standard over a concentration range from 0.1 to 1.6 mg/ml and found to be linear and directly proportional to concentration throughout this range.

Interferences—The specificity of the Schoenemann reaction for certain esters and anhydrides is well documented (8) and was confirmed by testing a wide range of pharmaceuticals likely to be present in aspirin formulations. Only salicylsalicylic acid interfered; it gave absorbance proportionate to its molar concentration when compared to aspirin. That is, the method should also be applicable to salicylsalicylic acid. Minor interference was noted with propylene glycol diacetate and acetylated mannitol.

Color of Blank—Initially, a reagent blank was routinely used in the reference beam during absorption scanning. However, it was unnecessary for aspirin samples, since the color change was negligible in the few minutes required to reach the maximum color of the sample.

Method Validation—The proposed method and a chromatographic method analogous to the NF procedure for aspirin, phenacetin, and caffeine tablets were used for the analysis of aspirin in stability samples of an experimental preparation containing aspirin, acetaminophen, and caffeine. The aspirin found (percent of label) with the chromatographic

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[1] Cary model 15.
[2] o-Dianisidine is a derivative of benzidine, a common reagent used in blood analysis. Although there is evidence that it is less carcinogenic than benzidine (7), it should be handled with usual precautions against skin contact.
[3] Eastman Kodak Co.

[4] Matheson, Coleman and Bell.