Some Filler Effects on Diffusion in Silicone Rubber

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Synopsis

The diffusion of ethyl p-aminobenzoate in silicone rubber membranes containing varying amounts of a high surface area fumed silica filler is described, as is a new apparatus for assaying multiple samples. It is shown that increased filler loading results in what appears to be a linear decrease in transmission rate, but that apparent diffusivities fall off drastically as a result of adsorption of the permeant on the filler. Distribution coefficient measurements suffer from the same result. The results suggest that neither an unmodified time lag technique nor a direct solubility method can be used to determine diffusivities of polar or unsaturated molecules in silicone rubbers, since they generally contain silica fillers.

INTRODUCTION

The relatively high diffusivities and minimal body tissue response exhibited by polydimethylsiloxane rubber has led to its exploitation as an implantable sustained-release carrier for medicaments.[1-3]

Diffusion coefficients have been calculated for a number of hydrocarbons and gases in silicone rubber,[4-9] but in general, in spite of the considerable current interest in drug diffusion, little effort has been made to determine the relationship between observed transmission rates and diffusivities.

Before a steady state is reached, there is a variation of permeant concentration within the membrane with respect to time, and a time lag is experienced before any permeation into the desorbing medium is observed and before the mass flux becomes constant. This time lag has been used by Daynes[10] and Barrer[11] to develop what has in the past been the most popular method for experimentally determining diffusivity and solubility terms.

EXPERIMENTAL

Dow Corning vinyl-functional polydimethylsiloxane and Cabot Corporation Cabosil MS-75 were used in preparing permeation cell membranes. Ethyl p-aminobenzoate, purchased from Aldrich Chemical Co., Inc., was used in the permeation cell in dry form as supplied, with an average particle size of 60–110 μ. Freshly distilled water was used as desorption medium.

The fillerless membranes were prepared by adding tert-butyl perbenzoate, 0.4000 g, to the gum, 100.0 g; blending thoroughly on a two-roll mill; and molding between Teflon without release agent at 138°C and 2000 psi for 10
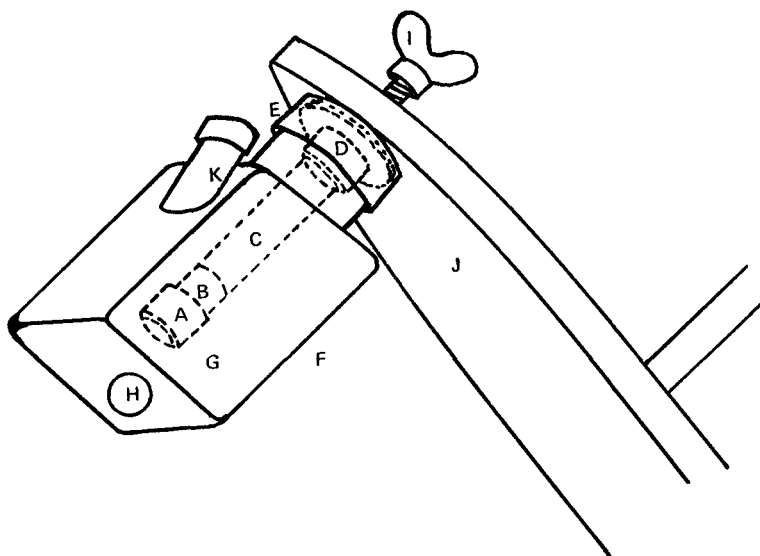
Fig. 1. Permeation cell assembly.   (See text for key.)

min.   The filled membranes were prepared by milling vinyl-functional polydimethylsiloxane gum with the filler, total 100.0 g, and blending thoroughly with 2,5-dimethyl-2,5-di(*tert*-butylperoxy)hexane, 0.5000 g, on a two-roll mill.   The stocks so prepared were molded between Teflon without release agent at 100°C for 1 hr at 2000 psi followed by 10 min at 177°C.   All membranes were postcured 16 hr at 150°C, cut from the vulcanized sheet with a cork borer, and rinsed with ethanol.   A schematic view of the permeation cell assembly is shown in Figure 1.   A nickel-plated or aluminum screw top cap (A) with a centered hole of 1.00-cm diameter sealed the membrane to the end of the permeant-containing chamber (B) attached to a glass tube (C).   The glass tube was held by friction fit to a Teflon gasket (D) inside the cap (E) of a 2 oz.   French square bottle (F) containing 25.0 ml of desorbing solution (G) and a 0.5 in. diameter stainless steel ball (H).

A machine screw soldered to the cap was secured by a wing nut (I) to a large aluminum disc (J) designed to accomodate 12 permeation cells of the described size.   The disc was inclined at an angle of 35° to the horizontal and was rotated at a rate of 30 rpm by an air motor with reducing gear box. The permeation cells were at all times submerged in a Sargent Model S-8470 water bath at 27.0°C.   A side arm (K) with screw cap and Teflon gasket was provided for ease of sampling at intervals.   Measurements were effected by periodically stopping the rotation of the disc, blowing dry the underlip portion of the sidearm cap, withdrawing a small sample, and immediately directly assaying for permeant at 285 mμ.   The sample was then returned to its cell and incubation was continued.   The motion of the rotating disc was resumed during the assay period.   Ultraviolet spectra

were obtained using a Cary Model 14 recording spectrophotometer, employing a 0.0–0.2 slideware for nonsteady state measurements for the fillerless membrane, or a Beckman DU-2 spectrophotometer. Four or six replicate samples were used for each membrane.

Distribution coefficients between an aqueous solution of ethyl p-aminobenzoate, 5.30 μmoles/ml, and silicone membranes were determined by washing the carefully weighed rubber, ca. 5 g, twice in distilled water, then in ethanol; drying at 70°; and immersing in 35.0 ml of aqueous benzoate solution at 27°C in the previously described permeation cells. The samples were kept in the constant temperature bath four days, a period found sufficient for equilibrium distribution, and the aqueous solution was analyzed at 285 mμ. The ratio of ethyl p-aminobenzoate concentration in the rubber, found by difference of drug in the aqueous phase before and after, to that in the final aqueous solution was taken as the solubility coefficient.

RESULTS AND DISCUSSION

Ethyl p-aminobenzoate was chosen as a model for the work reported herein because it has reasonable solubility in both aqueous and nonaqueous systems, possesses a satisfactorily high extinction coefficient in the ultraviolet (λ_{max} 285 mμ, ϵ 18,200 ± 600, water), and is a relatively small drug molecule, hence commanding a fairly high diffusivity.

Although a quasisteady state system was employed, it was found that the correction for nonlinearity in the benzocaine–water system was so small
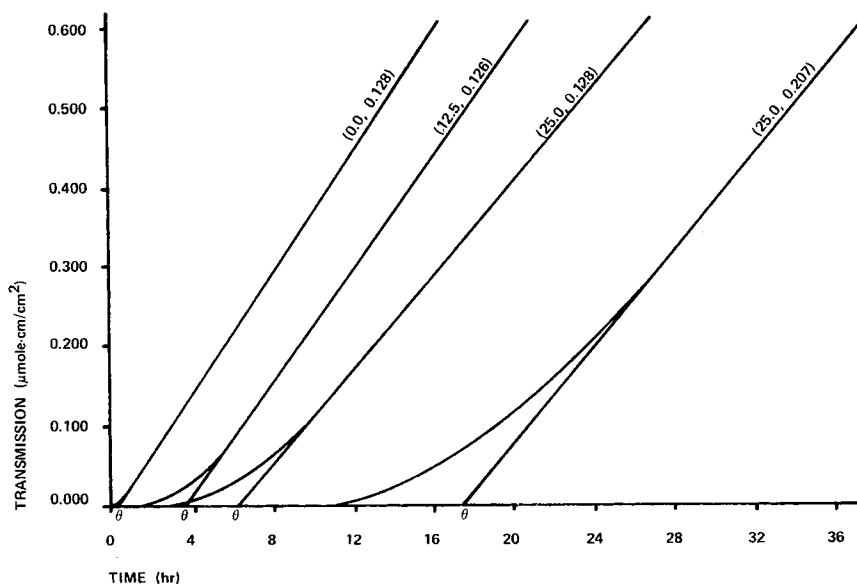

Fig. 2. Time lag plots for ethyl p-aminobenzoate in membranes with varying filler content. Parenthetical expressions refer to % filler, thickness of membrane.

as to be negligible for the illustrated period and was therefore ignored.   A further assumption was that a diffusion coefficient would probably be constant inasmuch as ethyl p-aminobenzoate is soluble only to the extent of 4.5–5.4 μmoles/cm^3 in high molecular weight silicone fluids.

Cabosil MS-75 is a fumed silica with no internal surface area[12]; hence its entire surface area of 265 m^2/g is readily available to the silicones present and to the permeant.   In preparing the membranes, attention was given to thorough milling and heating processes during membrane preparation in order to obtain the good filler–polymer contact essential to illustrating the phenomena reported herein.

The curves in Figure 2 illustrate the transmission of ethyl p-aminobenzoate through membranes with varying amounts of filler.   The transmission rates shown in Table I were calculated from the slopes of the steady state portions of such curves, and the time lag diffusivities according to Daynes[10] and Barrer[11] were calculated from the equation

$$D = \frac{l^2}{6\theta}$$

wherein l is the membrane thickness and θ is the time lag obtained by extrapolating the steady state portion of the curve to the time axis.

TABLE I
Composition and Properties of Silicone Rubbers

Filler, wt-%	Thickness, cm	Transmission rate,[a] (μmole·cm) ·(hr·cm^2)$^{-1}$	Time lag, min	Apparent diffusivity,[a] cm^2/hr
0.0	0.128	0.038 ± 0.003	25	0.0064 ± 0.0005
12.5	0.139	0.035 ± 0.003	220	0.00087 ± 0.00005
15.0	0.197	0.033 ± 0.001	749	0.00052 ± 0.00001
15.0	0.134	0.033 ± 0.001	396	0.00053 ± 0.00001
25.0	0.207	0.030 ± 0.001	1054	0.00041 ± 0.00001
25.0	0.128	0.030 ± 0.001	375	0.00043 ± 0.00001

[a] 95% Probability level.

A good agreement in values between membranes of different thickness for both transmission rates and apparent diffusivities is observed in Table I, indicating that initial absorption of the permeant into the rubber and desorption therefrom are not rate-limiting steps and that Fick's laws are obeyed.

Contemplation of Figure 2 and Table I immediately makes evident a severe displacement of time lag values for membranes containing filler. The disparity in time lag intervals is reflected in a considerable diminuation of calculated diffusivities, as compared to the moderate decrease in transmission rates as filler loading is increased.   For example, comparing the unfilled membrane with that containing 25.0% of filler, a 15-fold decrease
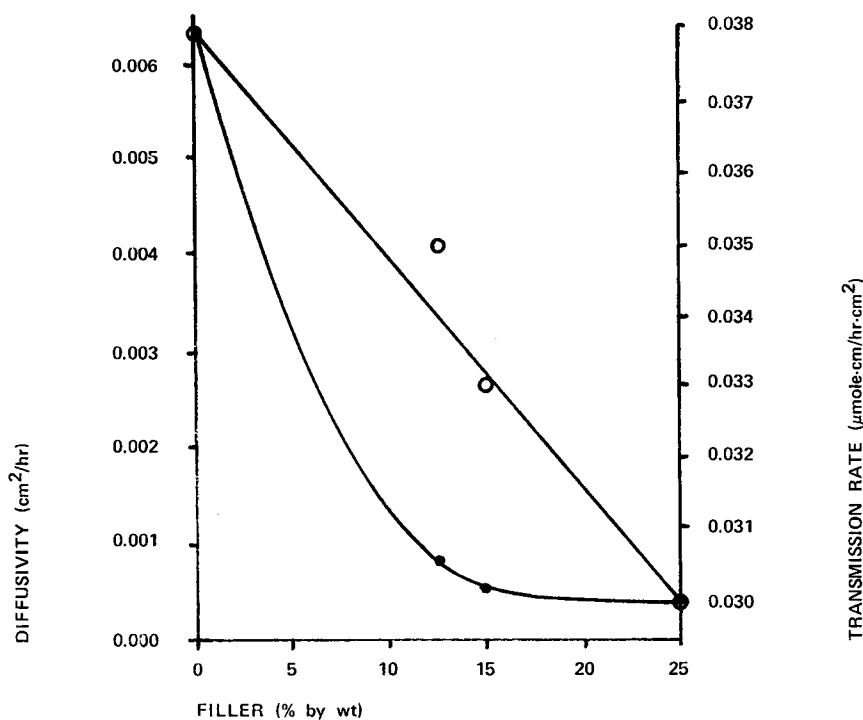
Fig. 3. Change in transmission rate and diffusivity as a function of filler content: (●) diffusivity; (○) transmission rate.

in diffusivity is observed whereas only a 21% drop in transmission rate is seen. This relationship is graphically depicted in Figure 3. Such results can be attributed to adsorption of permeant on the filler, the adsorbed permeant no longer taking part in the diffusion process. Such a conclusion is quite reasonable in that the nonsteady state period, during which adsorption of permeant on silica occurs, should be more susceptible to variation than the steady state.

It is obvious that in the systems described, wherein a solid permeant is in contact with the membrane, a direct measurement of a solubility coefficient can't be made. However, in order to further demonstrate the highly adsorptive capacity of the silica, distribution coefficients were measured as a function of an aqueous solution containing 5.30 μmoles/ml of the permeant. The coefficient so obtained was 0.97 ± 0.02 for the fillerless rubber, but 3.8 ± 0.2 for the rubber containing 25.0% filler, thus giving additional evidence for the filler adsorption phenomenon.

Barrer and co-workers[4–7] have recorded small differences in diffusivities in silicone rubber when the time lag method is compared to solubility methods. That such differences were slight is probably the result of the relatively nonpolar character of the gases used since, although almost all classes of organic compounds can be separated by silica gel chromatography, the

more highly adsorptive capacity of silica depends on interaction of its surface hydroxyls with polar or unsaturated molecules.[13]   It is probable that all chemicals which are good candidates for silica gel column chromatographic methods of purification would show a more or less severe time lag displacement in a diffusion experiment.   Thus, for polar and unsaturated chemicals in general, it is suggested that an unmodified time lag technique will not be valid for determining diffusivities in silicone rubbers, which generally contain silica fillers.   It also appears that use of a direct solubility technique will also be inapplicable for the same reason.   One is led to anticipate that for the time lag method of determining diffusivities in silica-filled membranes as compared to membranes containing a nonadsorbing filler, Fick's second law would require modification by terms which are functions of filler surface area and activity.

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