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Characterization of Solute Diffusion in a Polymer Using ATR-FTIR Spectroscopy and Bulk Transport Techniques

Kathleen Cogan Farinas, Lisa Doh,
Subbu Venkatraman, and Russell O. Potts*

Cygnus Therapeutic Systems, 400 Penobscot Drive, Redwood City, California 94063

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Introduction

Sorption and desorption have important consequences in material science and polymer physics. In addition, when the solute is a drug, diffusion out of a polymer matrix has important applications in the controlled release delivery of therapeutic agents. In each case, measurement of the mutual diffusion coefficient is crucial to both an understanding of the physical mechanisms controlling transport, as well as an ultimate prediction of the transport rate.

A number of experimental techniques have been devised to measure the diffusion coefficient (D) of a solute by monitoring either the release from, uptake into, or permeation through a polymer layer.[1] Some of these bulk transport methods require periodic sampling, and subsequent analysis by spectroscopic, chromatographic, or radiometric techniques to identify and quantify the concentration of the permeant molecule in a solution in contact with the polymer. In contrast, the ATR-FTIR spectroscopy technique enables the direct and unequivocal identification and quantification of the permeant concentration in an adhesive polymer film *in situ*. Furthermore, the transport of multiple species can be simultaneously measured provided the individual components have IR-distinguishable absorbance bands. Similar experiments have been reported in the literature.[2–4] More recently, ATR-FTIR techniques have been used to measure the mutual diffusion of small molecules in gels[5] and polymer films,[6–8] while others have measured polymer/polymer interdiffusion.[9,10]

In this paper, we describe the use of ATR-FTIR spectroscopy to monitor the uptake of urea into a silicone polymer. Analysis of the time-dependent changes in the infrared (IR) absorbances of urea and silicone leads to an estimate of D for urea which is in close agreement with a value obtained using a bulk transport method. To our knowledge, this is the first direct comparison of the ATR method with an independent technique. The results demonstrate that the spectroscopic technique provides an accurate and precise measurement of diffusant transport and holds the potential to evaluate changes in polymer swelling and polymer–solute interactions.

Materials and Methods

I. Experimental Methods. Materials. The permeant donor solution contained polyethylene glycol 300 (Union Carbide) saturated with urea (Aldrich). Polyethylene glycol was chosen as the inert carrier because of its low solubility in silicone adhesive. Medical grade silicone pressure-sensitive adhesive (X7-4201, 60% solids in heptane) was purchased from Dow Corning. To obtain identical samples for both the ATR-FTIR and radiolabeled diffusion experiment, films of silicone were solvent cast onto a fluoropolymer-coated polyester, "non-stick" sheet (release liner 1022, 3M) using a Gardner knife and then dried in an oven at 70 °C for 30 min to remove the residual heptane. The thicknesses of the resulting films, measured with a micrometer, were 75, 150, and 200 μm.

ATR-FTIR Diffusion Experiments. Spectra were obtained using a Nicolet 730 spectrometer (Nicolet Instruments) with a liquid nitrogen-cooled, mercury–cadmium telluride detector. The spectrometer was maintained in a climate-controlled room where the temperature was kept at 20 ± 1 °C. The optical bench included a Spectra Tech. (Stamford, CT) Out-of-Compartment Model Contact Sampler, which directed the IR radiation from the spectrometer up to the beveled input face of the horizontally-oriented, rectangular (1 × 7 cm) ATR crystal (ZnSe, 60° reflection angle; Spectra Tech). After multiple internal reflections, the Contact Sampler directed the beam to the detector. The silicone film was applied to the flat ATR detection surface, extending well beyond the area of contact with the crystal. An aluminum slab (thickness ~1 cm) with an open rectangular interior (1.5 × 8.5 cm) was then placed on top of the film with the interior opening centered above the area of film-optical contact. This aluminum barrier was held in place over the polymer film with clamps and formed a reservoir to retain the permeant solution directly above the silicone in contact with the ATR optics.

Each experiment was started by pipetting 4 mL of the donor solution containing urea in polyethylene glycol onto the film within the reservoir. Spectra (sample minus background spectra of air) were then obtained at predetermined time intervals throughout the experiment. The urea and silicone absorbance peaks were well resolved and did not require deconvolution techniques for spectral analysis. The urea (1540–1680 cm^{-1}) and silicone (2800–3030 cm^{-1}) absorbances were integrated using a two-point base line correction (Spectra Calc, Galactic, Salem, NH). The donor solution remained saturated with urea throughout the experiment due to the presence of excess urea.

Diffusion Experiments with Radiolabeled Permeant. The silicone samples and urea solutions used were identical to those used in the ATR-FTIR experiments except for the inclusion of tracer amounts of ^{14}C-urea (New England Nuclear) in the solution. A circular piece of silicone adhesive film with an impermeable plastic sheet attached to one side was mounted in a side-by-side diffusion apparatus. The diffusion chamber with the exposed silicone adhesive surface was filled with the solution of radiolabeled urea in polyethylene glycol 300 and allowed to equilibrate overnight. The urea containing solution was then removed from the diffusion cell and the chamber was rinsed quickly several times with solvent until negligible radioactivity was measured in the removed solvent. The chamber was subsequently filled with solvent. Aliquots were removed for liquid scintillation counting (Model 1600TR, Packard Instruments) at predetermined intervals and the chamber was replenished with fresh solvent.

II. Data Analysis. In ATR spectroscopy, radiation propagating through an optical medium of high refractive index (n_1) undergoes total internal reflection at an interface with a medium of lower refractive index (n_2) when the incident angle exceeds the critical angle.[12] At the interface between the two media, an evanescent wave is established within the medium of lower refractive index. When energy is absorbed in this medium (through spectral absorbance, for example), the reflected beam contains information characteristic of the absorbing molecules.

The intensity (E) of the evanescent wave decreases exponentially with increasing depth into the medium of lower refractive index ($E = E_0 \exp[-\gamma x]$). The depth constant γ is defined for weak absorptions by eq 1:

$$\gamma = \frac{2\pi}{\lambda_1}(\sin^2 \Theta - \sin^2 \Theta_c)^{1/2} \qquad (1)$$

where $\lambda_1 = \lambda/n_1$ is the wavelength of the incident radiation in the denser medium, and the critical angle (Θ_c) is defined as $\Theta_c = \sin^{-1}[n_2/n_1]$.

In the experiments described here, we assume that the saturated donor solution, placed in contact with the polymer, instantaneously establishes a constant concentration C_0 in the polymer at the solution/polymer interface ($x = 0$). The polymer thickness is denoted by l and does not change appreciably during

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* Corresponding author.

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the course of these experiments since the permeant and solvent both have low solubility in the silicone film. The lower surface of the polymer film ($x = l$) is in contact with the ATR optics which is impermeable and, hence, the concentration gradient at that point is zero [$(\mathrm{d}c/\mathrm{d}x)_{x=l} = 0$]. The permeant concentration as a function of depth and time within the polymer [$C(x,t)$] can be determined from a solution of Fick's law of diffusion, subject to these boundary conditions, and is given in eq 2,[1] where $K = 2k + 1$.

$$\frac{C(x,t)}{C_0} = 1 - (4/\pi^2)\Sigma[(-1)^k/K]\exp[-K^2\pi^2Dt/4l^2]\cos[K\pi x/2l] \quad (2)$$

The spectral absorbance (A) is given by the convolution of the evanescent wave and the concentration profile as described by eq 3, where ϵ is a constant related to the optical properties of the absorbing substance.

$$A = \epsilon \int_0^l C(x)E^2(x)\mathrm{d}x \quad (3)$$

Substitution of eqs 1 and 2 into eq 3 yields an expression for A versus time for the experiments described here. In the limit as γ/l approaches zero, the integration simplifies to eq 4, where A_{eq} represents the equilibrium absorbance at times approaching infinity.

$$A/A_{\mathrm{eq}} = 1 - (4/\pi)\sum[(-1)^k/K]\exp[-K^2\pi^2Dt/4l^2] \quad (4)$$

Since γ^{-1} is typically on the order of 1 μm, while l was greater than 75 μm in these experiments, eq 4 is well justified. In addition, at sufficiently large time ($t > 4l^2/\pi^2D$) the first term in the sum of eq 4 dominates and A/A_{eq} can be expressed as eq 5:

$$A/A_{\mathrm{eq}} = 1 - (4/\pi)\exp\left[\frac{-\pi^2Dt}{4l^2}\right] \quad (5)$$

Results

The ATR-FTIR spectrum of silicone polymer shows distinct bands around 3000 cm^{-1}, whereas urea absorbs near 1650 cm^{-1} (data not shown). Figure 1a displays the time dependence of the integrated intensity for these peaks in an experiment using a 200 μm thick polymer film. The silicone peak shows a rapid increase in the first 10 000 s, while the contribution of urea to the integrated intensity near 1650 cm^{-1} is negligible during this time period. The subsequent increase in the integrated intensity near 1650 cm^{-1} is a consequence of urea diffusing from the donor solution though the polymer film to a distance within micrometers of the polymer/ATR optics interface.

It is common in ATR spectroscopy to employ band ratioing techniques to improve quantitative analysis when the degree of contact between the optics and the sample is difficult to control or reproduce.[12] This entails normalizing the absorbance of interest by another absorbance that serves as an internal standard. Since the solubility of urea in the silicone film is small (1.6%), we have normalized the absorbance near 1650 cm^{-1} by the silicone absorbance around 3000 cm^{-1} ($R = A_{\mathrm{u}}/A_{\mathrm{Si}}$). This corrects for changes in the polymer/optical contact during the time course of the experiment. We have also subtracted the non-urea contribution to the absorbance near 1650 cm^{-1} measured at the start of the experiment [$A = R(t) - R(0)$] to obtain a quantitative measure of urea concentration (Figure 1b).

The relationship between the time dependence of the urea spectral absorbance and its diffusion coefficient (eq 5) involves two additional parameters, the polymer film thickness and the absorbance of urea once the film has equilibrated with the donor solution (A_{eq}). We used a measured value for the film thickness and determined the A_{eq} value that minimized the least squared error of ln[$\pi/4(1 - A/A_{\mathrm{eq}})$] versus time. Figure 2 shows a linear dependence for the data of Figure 1b, yielding a diffusion coefficient of 5.7 × 10^{-9} cm^2/s.

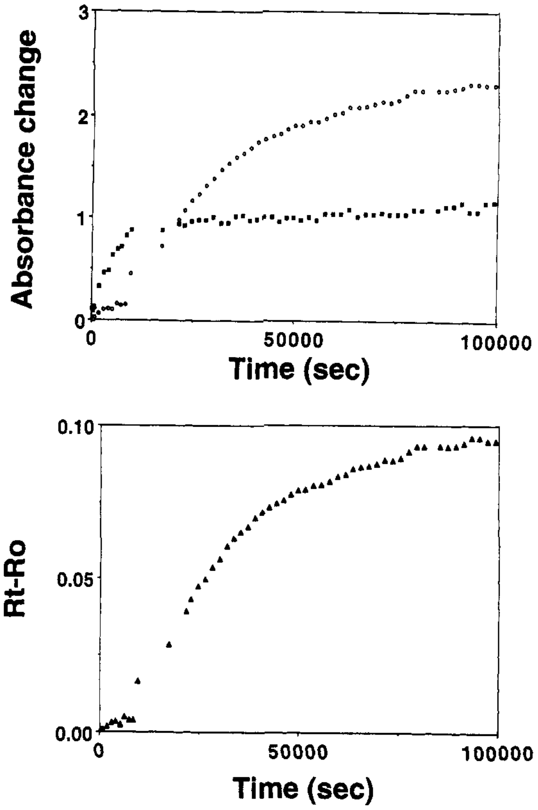

Figure 1. (a) The change in IR absorbance of urea (■) and silicone (○) as a function of time for diffusion into a film of 200 μm thickness. The integrated intensity at zero time was 22.3 and 1.9, respectively, for the silicone and urea absorbances. (b) The ratio of the urea to silicone absorbance minus the value at zero time, as a function time.

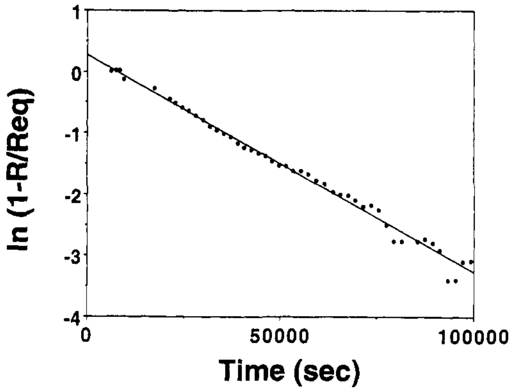

Figure 2. A plot of the data from Figure 1b as ln($1 - A/A_{\mathrm{eq}}$) vs time.

Results were also obtained in triplicate for polymers of 75 μm thickness. The mean value (plus selected values of the SEM) of A/A_{eq} versus time are shown in Figure 3. These results show that the SEM seldom exceeded 10% of the measured value. Analysis of the average data yielded a D value of 5.2 × 10^{-9} cm^2/s. The solid line drawn through these data are the simulated values of A/A_{eq} versus time, generated using the first five terms in eq 4 and the values of D and A_{eq} derived experimentally. The fit of the data to the simulation at all time points is within the standard error estimate for most individual points.

Also shown in Figure 3 are data obtained for polymer film thicknesses of 150 and 200 μm. These data were analyzed to yield D values of 4.0 and 5.7 × 10^{-9} cm^2/s,

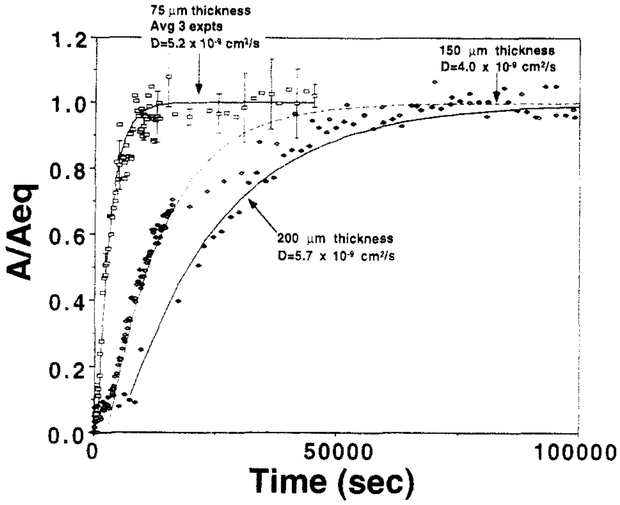

Figure 3. Simulated and experimental values of A/A_{eq} vs time generated using the first five terms in eq 4 and the experimentally determined of D and A_{eq} values.

respectively. Again, the simulation of A/A_{eq} data conforms well to the data. The average value (±SEM) of D for these five determinations is 5.2 (±0.8) × 10^{-9} cm^2/s. Thus all experiments provided a similar value of D, within error, and, as illustrated in Figure 3, thicker samples exhibited delayed appearance and equilibrium as predicted from diffusion theory. Finally, the A_{eq} value varied little in these experiments with an average value (±SEM) of 0.083 (0.004), showing that the same equilibrium concentration of urea was obtained, regardless of the sample thickness.

The values of D obtained by the spectroscopic technique were compared with values obtained by bulk transport experiments using identical polymer samples to those used in the ATR studies. The cumulative amount of ^{14}C released from a silicone sheet of uniform thickness followed precisely the square-root of time dependence predicted for one-directional diffusion from a polymer slab.[1] The diffusion coefficient was estimated from the slope of cumulative appearance versus $t^{1/2}$. The average value (±SEM) for six determinations was 7.9 (±1.0) × 10^{-9} cm^2/s. In addition, from the total amount released, the equilibrium urea concentration was determined to be 16 mg/cm^3.

Discussion

A number of investigators have evaluated diffusion in polymers using similar ATR-IR techniques to those presented here. This study differs significantly from those earlier studies, however, by the direct comparison of the spectroscopic results with those obtained for the same diffusant and solvent in an *identical polymer film*. Similar D values were obtained, 7.9 (±1.0) × 10^{-9} and 5.2 (±0.8) × 10^{-9} cm^2/s, from the tracer and ATR-FTIR diffusion experiments, respectively.

A model system was chosen in this study to fulfill the assumptions associated with the data analysis employed. In particular, urea and silicone polymer were selected because of their dissimilar chemical nature, and hence, the low measured solubility (1.6%). Indeed, there is little evidence of polymer swelling which would result in decreased IR absorbance of silicone.

The silicone polymer investigated here exhibits an IR absorbance increase during the initial portion of the ATR-FTIR diffusion experiment. We have observed an initial change in the polymer absorbance in experiments with several types of pressure-sensitive adhesives, possibly due to the relaxation of the adhesive under the weight of the donor solution. A measure of the change in diffusant concentration within the polymer can be obtained from the absorbance ratio of the diffusant to polymer peaks. In this way, the polymer spectral absorbance served as an "internal standard", in accord with common ATR spectroscopy practice.[12] A similar "internal standard" was used to measure the diffusion of acetone into polyisobutylene.[4]

The results presented here demonstrate the usefulness of the ATR-FTIR technique to rapidly and accurately measure diffusion in a polymer matrix. The spectroscopic technique also has several potential advantages over the release assay. The IR spectrum allows unequivocal analysis of the diffusing molecule. Release assays must ultimately rely upon analytical techniques. In addition, the IR spectrum provides direct information on the polymer and hence, allows insight into potential drug–polymer interactions. While there are many sources of potential error in each technique, it seems likely that the solute analysis methods required in the bulk transport studies offer significant opportunity for the introduction of error. By contrast, analysis of the solute concentration is an integral part of the ATR-FTIR method. Finally, the greatest single source of error in the spectrometric experiments may well be the precision with which films of uniform thickness can be prepared and measured.

In conclusion, we provide experimental verification of an ATR-FTIR technique to rapidly and accurately determine solute diffusion within a polymer matrix. The technique has broad potential application provided distinct spectral absorbances exist for both the diffusant and polymer.

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