Distribution Coefficients and Diffusivities in Three Polymers for Nineteen Aqueous Nonvolatile Solutes

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ABSTRACT: Experimental results at 25°C are reported for infinite-dilution distribution coefficients for 19 nonvolatile solutes between aqueous solution and three kinds of polymer films, and for their diffusion coefficients in the polymer matrix. The experiments were performed by coupling UV spectroscopy and gravimetric measurements with mass balances. The solutes are aromatic nonvolatile compounds that are of interest in environmental technology and may serve as model compounds for drug-delivery systems. The polymers are ethylene-vinyl acetate copolymers with 33 (EVAc33) and 45 (EVAc45) weight percentage vinyl acetate, and poly(vinyl acetate) (PVAc) widely used in drug-delivery devices. For PVAc, a long time is required to reach equilibrium. Because the required time is too long for reasonable experimental studies, equilibrium distribution coefficients were calculated from finite-time data by using a diffusion model. The contribution of surface adsorption is shown to be negligible. Infinite-dilution distribution coefficients K_s, defined as the volume fraction of solute in the polymer divided by that in water, tend to increase with vinyl acetate content; they range from near unity to several hundred. Diffusion coefficients, determined from time-dependent sorption data, are significantly larger in EVAc copolymers (10^{-10} to 10^{-8} cm²/s) than in PVAc (10^{-12} cm²/s). These data may be useful for design of membrane processes, for controlled delivery of drugs, and for application in packaging and storage of food, chemicals, and pharmaceuticals. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 85: 2041–2052, 2002

Key words: diffusion; distribution coefficient; drug delivery systems; nonvolatile solutes; solution properties

INTRODUCTION

Numerous applications of polymeric materials concern polymer films in contact with an aqueous

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solution of heavy organic solutes (i.e., those with a negligible vapor pressure at room temperature). For example, in wastewater purification, polymer membranes enable the removal of small amounts of pollutants from water streams and the potential recovery of useful compounds. Polymeric bags, containers, and wrapping films are extensively used for packaging of food and storage of pharmaceuticals or other chemicals. Leaching of polymer-processing chemicals could contaminate the stored product. On the other hand, sorption of compounds from a stored pharmaceutical solution could compromise its effectiveness by lowering the compound's concentration.[1–3] Distribution-coefficient data are helpful for selection of suitable polymers for separation processes and packaging.

Most pharmaceuticals are organic compounds with very low volatility at room temperature. In controlled drug-delivery systems, polymers serve as a supporting matrix for a uniformly dissolved or dispersed solute (matrix systems) or as permeable barriers surrounding the stored drug (reservoir systems) as discussed, for example, by Langer.[4] The solubility of the solute in the polymer and the distribution coefficient between the aqueous phase and the polymer, together with the diffusion coefficient, are controlling properties in drug release to the surrounding media.[5] These properties affect the ability of a drug to reach significant concentration in the bloodstream for distribution into tissues.

The polymer–water distribution coefficient and the diffusion coefficient in the polymer are essential parameters for rational design of appropriate devices for specific purposes.

In this work, we report distribution coefficients for 19 nonvolatile organic solutes between a dilute aqueous solution and a polymer film at 25°C. For each solute, the diffusion coefficient in the polymer matrix is also obtained at the same temperature. The solutes are aromatic compounds with different functional groups with molecular weights ranging from 79 to 182 g/mol; most of them are solids at 25°C. They may be considered as models for typical pharmaceuticals.

Ten of the solutes are aromatic nitro compounds, an important class of substances with a variety of applications. They are used as solvents, fuel additives, intermediates in manufacture of dyes and explosives, etc. Nitroaromatics present a serious environmental hazard because of their high stability and tendency to leach into groundwater; they frequently appear on lists of high-priority pollutants. Under environmental conditions, they are encountered at very low concentrations.[6] Naphthols are used in the manufacture of dyes and are converted into tanning agents, antioxidants, and antiseptics; acetophenone is used in the perfumery industry, as a solvent and as an intermediate in organic synthesis. Benzophenone is used for pesticides, perfumes, pharmaceuticals, and as an organic ultraviolet (UV) absorber. Benzoic acid is mainly used in the dye and paint industries; benzyl alcohol is used in the soap, perfume, and flavor industries and as a solvent for inks and lacquers.

The polymers are two ethylene-vinyl acetate copolymers (33 and 45 wt % vinyl acetate) and poly(vinyl acetate). Ethylene-vinyl acetate copolymers (EVAc) find a variety of industrial applications thanks to their chemical resistance, flexibil-

Table I   Solute Properties: Name, Chemical Formula, Molecular Weight M_w (g/mol), Density ρ_s (g/cm³), Melting Point T_f (°C)

Solute	Formula	M_w	ρ_s^e	T_f
1-Naphthol[a]	$C_{10}H_8O$	114	1.220	95.0[g]
2-Naphthol[a]	$C_{10}H_8O$	114	1.280	120.4[g]
2-Nitroaniline[a]	$C_6H_6N_2O_2$	138	1.442	69.3[g]
3-Nitroaniline[a]	$C_6H_6N_2O_2$	138	1.430	113.8[g]
4-Nitroaniline[a]	$C_6H_6N_2O_2$	138	1.424	147.5[g]
2-Nitrophenol[b]	$C_6H_5NO_3$	139	1.495	44.8[g]
3-Nitrophenol[a]	$C_6H_5NO_3$	139	1.540[f]	96.8[g]
4-Nitrophenol[b]	$C_6H_5NO_3$	139	1.479	113.8[g]
2-Nitrotoluene[b]	$C_7H_7NO_2$	137	1.163	−3.8[h]
3-Nitrotoluene[a]	$C_7H_7NO_2$	137	1.157	16.0[h]
4-Nitrotoluene[b]	$C_7H_7NO_2$	137	1.392	51.6[g]
Acetophenone[c]	C_8H_8O	120	1.055	19.6[g]
Benzoic acid[a]	$C_7H_6O_2$	122	1.266	112.3[g]
Benzonitrile[a]	C_7H_5N	103	1.010	−12.8[g]
Benzophenone[d]	$C_{13}H_{10}O$	182	1.110	47.8[g]
Benzyl alcohol[d]	C_7H_8O	108	1.045	−15.5[g]
Nicotine[a]	$C_{10}H_{14}N_2$	162	1.010	−80.0[i]
Nitrobenzene[d]	$C_6H_5NO_2$	123	1.196	5.7[g]
Pyridine[d]	C_5H_5N	79.1	0.978	−41.6[g]

[a] Aldrich, Milwaukee, WI
[b] Acros, NJ
[c] Pfaltz, Stamford, CT
[d] Fisher, Fair Lawn, NJ
[e] All solute densities are at 20°C[12] except for 3-nitrophenol (25°C).
[f] Hamzaoui et al.[21]
[g] Domalski and Hearing.[22]
[h] Domalski and Hearing.[23]
[i] International Chemical Safety Card.[24]

ity, and excellent processability. Their biocompatibility and biological inertness make them appealing for biomedical applications. EVAc copolymers with 30–50% VAc content are FDA-approved materials employed as nondegradable polymers for drug-delivery systems.[7–10]

MATERIALS

Tetrahydrofuran (THF) was purchased from EM Science and used as a solvent to cast the polymer films. Ultrapure water (Barnstead NANOpure system) was used to prepare the aqueous solutions.

Table I lists the solutes; for each solute, Table I gives chemical formula, molecular weights, densities, and melting points T_f (°C). 1- and 2-naphthol are light sensitive. All solutes were used without further purification.

Table II   Polymer Properties: Average Molecular Weight M_w (g/mol), Density ρ_s (g/cm³), Composition (Comonomer Weight Percent), Glass-Transition Temperatures T_g (°C) and Purity

Polymer	M_w	ρ_s	VAc (wt %)	T_g	Purity (%)
PVAc	500,000	1.189	100	39.7 (±1.5)	>99
EVAc45	250,000	0.952	45	−80[a]	>99
EVAc33	150,000	0.936	33	−95[a]	>99

[a] Estimated using eq. (1) and T_g (PVAc) = 32°C, T_g (PE) = −125°C.[25]

Ethylene-vinyl acetate (EVAc) copolymers were obtained from Scientific Polymer Product, while PVAc was purchased from Aldrich. Table II gives the average molecular weight M_w, purity, composition, and glass-transition temperature. The glass-transition temperature for EVAc was estimated by using the Flory–Fox equation[11]:

$$\frac{1}{T_g} = \frac{w_{p1}}{T_{g,p1}} + \frac{w_{p2}}{T_{g,p2}} \tag{1}$$

where T_g is the glass-transition temperature of the copolymer, while $T_{g,p1}$ and $T_{g,p2}$ are the glass-transition temperatures of the parent homopolymers, and w_{p1} and w_{p2} are the mass factions of the parent monomers. Possible uncertainties in eq. (1) are not relevant for our measurements because the glass-transition temperature is much lower than 25°C. The glass-transition temperature of poly(vinyl acetate) (PVAc) was measured by modulated differential scanning calorimetry (DSC 2920, Modulated DSC, TA Instruments) at a heating rate of 3°C/min, with modulation amplitude of ±1°C and a period of 60 s.

The polymers are polydisperse. Experimental studies by Nguyen[12] have shown that the effect of M_w on K_s is negligible for rubbery polymers at a high degree of polymerization ($M_w > 80,000$). Polydispersity may affect the solubility and the distribution coefficient of a solute in a glassy polymer by increasing the glass-transition temperature and reducing polymer chain mobility. However, the EVAc copolymers and the water-presaturated PVAc (see the next section) used in this work are rubbery at room temperature[13]; therefore, polydispersity is not expected significantly to affect our results.

Polymer-film densities were determined by using a 10-mL pycnometer. The densities reported are averages over several measurements; typical uncertainty (standard deviation) is less than 2 wt %. Measured densities agree within the experimental error with those reported by the producer (the latter are 2% higher for EVAc copolymers, the same for PVAc).

Distribution Coefficient

In the following section, we present the experimental procedure to determine the distribution coefficient in EVAc33. For PVAc and EVAc45, we report only the variations applied to the procedure for EVAc33. Table III summarizes the characteristic features of preparation of the distribution-coefficient experiment for each polymer.

Experimental
EVAc33

To obtain the infinite-dilution distribution coefficient K_s^∞, the weighed polymer samples were put

Table III   Conditions for Polymer Film Preparation

Conditions	EVAc33	EVAc45	PVAc
THF solution concentration[a]	6%	8%	4%
Container	Aluminum pan	Pyrex dish	Aluminum pan
(diameter)	(63 mm)	(139 mm)	(63 mm)
ml solution/pan	20	84	10
Heating T (°C)	100	100	100
Heating time (h)	40	40	40
Cooling T (°C)	Room	−20	Room
Average film thickness (μm)	266 (±45)	421 (±94)	101 (±23)

[a] g polymer/ml THF.

into contact with a weighed dilute aqueous solution of the selected solute.

To reduce the time to reach equilibrium, the polymer samples were prepared as thin films. A liquid polymer solution was obtained by dissolving the polymer in THF. The polymer concentration in THF should be low to avoid problems with liquid transfer due to high viscosity, but not too low, lest the time for evaporating THF is too long. Typical polymer concentration was 6% (g polymer/mL THF). Consistent with the desired film thickness, a small amount of polymer/THF solution was poured into a 63-mm-diameter aluminum dish; 20 mL/pan was used for EVAc33. Each aluminum pan was then covered, put into an oven, and fluxed with nitrogen for a time of 40 h at 100°C. The drying temperature was chosen well above the normal boiling point of THF (66°C) and well above the glass-transition temperature of the polymer (estimated to be −95°C for EVAc33) to allow complete drying.[14] After that, the polymer melt in the aluminum pan was allowed to cool to room temperature for at least 8 h. Next, a polymer film was removed from the aluminum pan and cut into strips. For EVAc33, the average thickness of the polymer film was 0.266 mm (measured by MDC-1″Pf Micrometer from Mitutoyo).

Polymer films should be totally free of solvent after casting. Thermogravimetric analysis, using 5–10 mg polymer samples at heating rate 5°C/min, showed that all solvent in the polymer film is absent (TG 220 SSC/5200 SII Seiko Instruments).

EVAc45

EVAc45 films were cast from an 8% THF solution. Pyrex dishes (139-mm-diameter) were filled with 84 mL polymer solution each, covered, and heated to 100°C for 40 h under a nitrogen flux. The dishes were then stored at −20°C in the refrigerator for a minimum of 1 day. The cold polymer films were detached from the Pyrex container as soon as possible after removing the dishes from the refrigerator. Use of Pyrex dishes (instead of aluminum pans) combined with the cooling procedure and the use of a larger film thickness (0.421 mm) minimized problems in the recovery of the polymer films from the dishes caused by the adhesive properties of EVAc45. For EVAc33, it was easy to peel off the polymer film from the aluminum pan, but not for EVAc45.

PVAc

Ten milliliters of a 4% THF polymer solution were poured in each aluminum pan to obtain 0.101-mm-thick PVAc films. The temperature and the heating time are the same as those used for EVAc33. The polymer films, removed easily from the aluminum pans, were then placed into contact with nanopure water and allowed to equilibrate for 2 weeks. The water sorption lowers the glass transition temperature of the wet PVAc films; with roughly 2.5 wt % water content (smaller than the measured equilibrium value at 25°C), they become rubbery at room temperature.[15] Therefore, there is no glass transition during subsequent distribution-coefficient experiments. Moreover, preequilibration with water provides additional removal of possible impurities from the polymer films.

After the polymer films were prepared, several strips of EVAc33 (total weight ∼ 1 g) were placed into an equilibrium vial, in contact with a weighed amount of aqueous solution of the solute at known concentration. Because of the strong adhesion properties of EVAc45 and wet PVAc, the polymer strips tend to stick together, reducing the contact area with the aqueous solution. This compromises the reproducibility of the distribution-coefficient data, especially for those systems that require a long time to reach equilibrium. Therefore, for EVAc45 and PVAc, only one strip was used in each vial (∼ 0.5 and ∼ 0.2 g, respectively).

The optimum initial concentration of the solute in water was determined by trial and error for each solute-polymer pair. The concentration of the solute in the aqueous solution must not be too large lest the change in aqueous solute concentration before and after sorption become too small for accurate measurement. On the other hand, the concentration must not be too small lest the amount of sorbed solute be difficult to detect because of limits in analytic accuracy. To minimize loss of aqueous solution during repeated measurements at different times, the solution concentration should also allow direct UV spectroscopic measurement of absorbency without dilution. In this case, the sampled solution can be recovered for subsequent measurements. To minimize any error caused by evaporation of water in the equilibrium vial, each vial was completely filled with solution and polymer and then sealed with Teflon tape or septa and capped tightly. The equilibrium vials prepared for the sorption experiment were maintained in a thermostatic bath at 25 ± 0.1°C until equilibrium was nearly obtained. Time required for near-equilibrium was a minimum of a few days for EVAc copolymers, and more than 4–5 weeks for PVAc. As discussed in the appendix, the near-equilibrium data for PVAc were fit

to a diffusion model that permits rational extrapolation with time to obtain equilibrium distribution coefficients. For the light-sensitive solutes, precautions were taken to minimize the exposure to light by using brown glass vials for the sorption experiment and for storing aqueous solutions. To minimize the number of components in solution, we did not use any buffer to control solution pH. Therefore, solution pHs change slightly during sorption experiments.

Using an ultraviolet-visible spectrophotometer (Shimadzu UV-160), the solute concentration in water was measured prior to contact with the polymer films and then, as a function of time extending over several weeks, at regular intervals. These data, coupled with the known mass of solution and mass of polymer, were used to determine the concentration of solute in the polymer as a function of time.

Data Reduction

The ratio of solute concentrations (expressed as volume fractions) in the polymer and in the aqueous phases gives the time-dependent distribution constant K_s before extrapolation, as shown:

$$m_{s,p} = m_s^0 - m_{s,w} \qquad (2)$$

$$m_{s,p} = m_{\text{sol}}^0 w_{s,w}^0 - m_{\text{sol}} w_{s,w} = m_{\text{sol}}^0 w_{s,w}^0$$
$$- [m_{\text{sol}}^0 - (m_{s,p} + m_{w,p})]w_{s,w} \qquad (3)$$

$$w_{s,p} = \frac{m_{s,p}}{m_{s,p} + m_{w,p} + m_p^0} \qquad (4)$$

$$K_s = \frac{\Phi_{s,p}}{\Phi_{s,w}} = \left(\frac{w_{s,p}}{w_{s,w}}\right)\left(\frac{w_{s,w}/\rho_s + w_{w,w}/\rho_w}{w_{s,p}/\rho_s + w_{w,p}/\rho_w + w_{p,p}/\rho_p}\right)$$
$$(5)$$

where $m_{i,j}$ is the mass of component i in phase j; $w_{i,j}$ is the mass fraction of i in phase j; $\Phi_{i,j}$ is the volume fraction of i in phase j; i or $j = s$ (solute), w (water), or p (polymer); subscript sol stands for aqueous solution, and superscript 0 stands for initial. The densities ρ_i are for pure components; contributions from excess volume are neglected. To convert weight fraction into volume fraction, we introduced in eq. (5) the densities of the solutes in the actual state at the experimental temperature. Although a more rigorous calculation should use the density in a hypothetical liquid state for the solid solutes at 25°C, negligible errors are introduced by this approximation. The
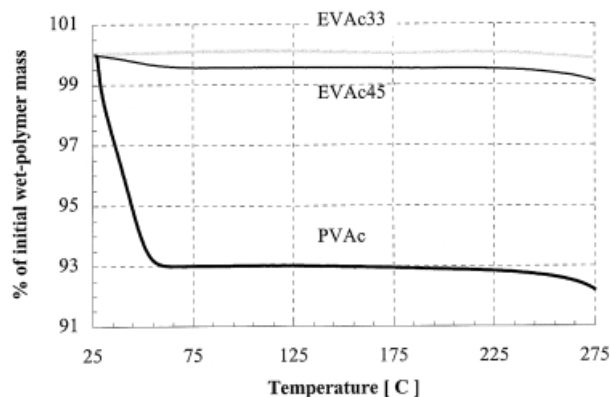

Figure 1 Water sorption in EVAc copolymers and PVAc. The initial decrease to the plateau region corresponds to the water weight fraction.

precise value of ρ_s in eq. (5) has no appreciable influence on the distribution coefficient because $w_{s,p}$ and $w_{s,w}$ are much smaller than $w_{w,w}$ and $w_{p,p}$.

For data interpretation through thermodynamic analysis, it is convenient to obtain the distribution coefficient at infinite dilution K_s^∞. For a particular polymer-solute pair, distribution-coefficient data were therefore obtained at five levels of dilute aqueous-solution concentration. Because the experimental distribution coefficients do not show any trend with the final solution concentration, the experimental points are considered to be inside the infinite-dilution regime and K_s^∞ was calculated as a simple average over these five values. More precisely, this procedure gives the ratio of concentrations $\Phi_{s,p}/\Phi_{s,w}$ at infinite dilution as a function of time. These data, in turn, were reduced to give the equilibrium (corresponding to infinite time) distribution coefficient K_s^∞ at infinite dilution as discussed in the appendix.

Water Sorption

To close the mass balance , the amount of water in the polymer at saturation is also required. It was obtained from a separate experiment with solute-free water and was assumed to be independent of the solute. Thermogravimetric analysis was performed to determine the water content of water-saturated polymer films. Fifteen days of contact were sufficient to reach saturation. The equilibrium water content was determined from the loss of weight of the water-saturated polymer sample after heating to at least 100°C, as illustrated in Figure 1. An independent measure of the polymer

Table IV   Water Content at Saturation (wt %)

Method	EVAc33	EVAc45	PVAc
Thermogravimetric	~0	0.43 (±0.04)	7.0 (±0.3)
Gravimetric	~0	0.42 (±0.05)	7.6 (±0.3)

weight before and after equilibration with water gives consistent results as indicated in Table IV.

Diffusion Coefficient

To determine the diffusion coefficients of the solutes in the polymer films, we used a short time approximation to the solution of the diffusion problem illustrated in the appendix[16]:

$$\frac{\Phi_{s,p}(\tau)}{\Phi_\infty} = (1 + \alpha)\left\{1 - \exp\left(\frac{\tau}{\alpha^2}\right)\text{erfc}\left(\frac{\tau}{\alpha^2}\right)^{1/2}\right\} \quad (6)$$

where $\Phi_{s,p}$ is the volume fraction of the solute in the polymer at time t; Φ_∞ is the equilibrium volume fraction of the solute in the polymer; $\tau = Dt/l^2$ and $\alpha = a/lK_s$; D is the diffusion coefficient of the solute in the polymer; a/l is the ratio of the volume of solution to that of polymer; and K_s is the equilibrium distribution coefficient.

Performing a Taylor expansion and applying the solute mass balance, eq. (6) simplifies to

$$\frac{\Phi_{s,w}(t)}{\Phi_{s,w}^0} = 1 - \frac{2}{\sqrt{\pi}}\sqrt{\frac{\tau}{\alpha^2}} = 1 - \frac{2K_s}{a\sqrt{\pi}}\sqrt{D}t^{1/2} \quad (7)$$

where $\Phi_{s,w}$ is the solute volume fraction in the aqueous solution. Equation (7) shows that for $t \rightarrow 0$ the solute concentration decreases linearly with $t^{1/2}$ and that the slope is proportional to the distribution coefficient and $\sqrt{D}$. Once the distribution coefficient was determined by using eq. (5), the diffusion coefficient can be calculated from the slope of the straight line when $\Phi_{s,w}(t)/\Phi_{s,w}^0$ is plotted against $t^{1/2}$.

The data required for eq. (7) were obtained by measuring as a function of time the decrease of the solute concentration in the aqueous solution near the beginning of the experiment every 2–5 min for 15–60 min for EVAc copolymers, and every 0.5–1 h for 6–10 h for PVAc. In these time intervals, the experimental solute concentrations are linear functions of the square root of time. Before contacting with the aqueous solution, PVAc films were saturated with water.

RESULTS AND DISCUSSION

Contribution of Surface Adsorption

Equations (2)–(5) do not distinguish between solute adsorbed on the polymer film surface and solute absorbed in the polymer bulk. Because our interest is in the bulk properties of the polymer/aqueous solution system, it is necessary to estimate the contribution of surface adsorption to the total sorption. This problem was addressed in two ways. First, sorption experiments were performed by varying the thickness of the polymer film while keeping constant the polymer mass as well as the mass and concentration of the aqueous solution. Second, the Langmuir adsorption isotherm was used to provide an upper bound estimate of the amount of adsorbed solute. For a conservative estimate, we assumed a large adsorption-energy parameter $K_{ads} = 100\text{-}1000$ to favor solute adsorption, and we estimated the monolayer coverage n_m as the ratio of the typical surface area of the polymer films to the projected van der Waals area[17] of a solute molecule.

The experimental approach is meaningful only if the measurements of solution concentration are at a long period of time, close to the equilibrium condition. Because the amount of solute diffused into the polymer at a given time is inversely proportional to the film thickness, the time-dependent distribution coefficient decreases with rising film thickness while the diffusion process is proceeding. At equilibrium, for films of varying thickness, the distribution coefficient attains a common value only if there is no surface adsorption. On the other hand, if the equilibrium distribution coefficient depends on film thickness (surface-to-volume ratio), there is significant surface adsorption contribution. At nonequilibrium conditions, the dependence of $\Phi_{s,p}/\Phi_{s,w}$ on the film thickness cannot be discerned from the eventual equilibrium surface adsorption contribution. For this reason, and to reduce the experimental effort, we used this experimental approach only for EVAc33 but not for the other polymers. Figure 2 shows typical results for EVAc33 with an aqueous solution of acetophenone, 2-nitroaniline, or 2-nitrophenol. The zero slope indicates that surface adsorption for all examined EVAc33/solute systems is negligible.

The calculation based on the Langmuir isotherm shows that for both EVAc copolymers and PVAc, the contribution of surface adsorption is less than 0.5% of the total sorption.

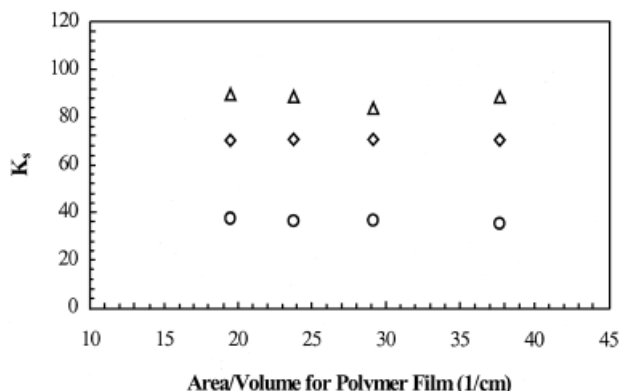Finally, the early-time measurements also indicate a negligible effect of surface adsorption.

Figure 2 Distribution coefficients for solutes in EVAc33. Acetophenone (after 20 days; circles), 2-nitroaniline (after 22 days; diamonds), and 2-nitrophenol (after 14 days; triangles). K_s is independent of the polymer's area/volume ratio, indicating that adsorption is negligible.

The typical equilibration time for surface adsorption of a small solute on a nonporous solid is on the order of a few minutes.[18] Therefore, a plot of the solute concentration in the aqueous solution as a function of the square root of the time should present a nearly instantaneous decline at the beginning, corresponding to the amount adsorbed. None of the systems studied here shows such a decline; see, for example, Figure 6. In conclusion, eq. (5) can be used to evaluate the bulk distribution coefficient without introducing any appreciable error due to surface adsorption.

Water Sorption

Table IV reports the measured water sorption in EVAc33, EVAc45, and PVAc. The weight percentage of water at saturation (at $T = 25°C$) increases with VAc content. The water content is negligible in EVAc33; it rises to ~ 0.4 wt % in EVAc45 and reaches 7.0% in PVAc. Our measured water contents in EVAc copolymers are in agreement with those reported by Chen and Lostritto,[19] who find less than 0.5% water content for copolymers with VAc content between 0 and 40%. Johnson et al.[15] showed that PVAc absorbs up to about 4 wt % water that is bound to the polymer and is responsible for the decrease of T_g below room temperature. Additional sorbed water (roughly 3 wt % in our PVAc films) fills microscopic cavities within the polymer matrix and has no effect upon T_g for PVAc.

Distribution Coefficient

Figure 3 shows distribution coefficients for three different solutes in EVAc33 as a function of the
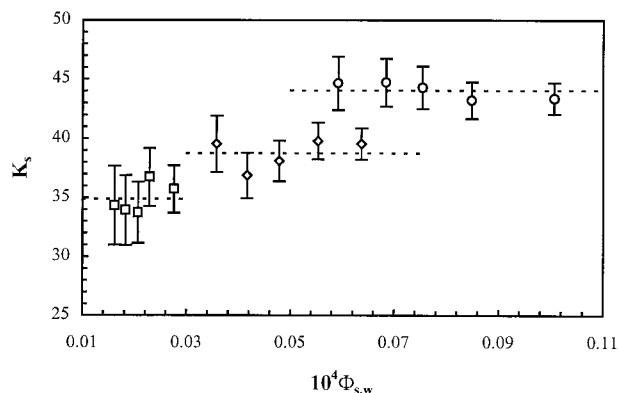

Figure 3 Distribution coefficients for three solutes in EVAc33. Squares are for 3-nitroaniline (after 23 days; $K_s = 34.9 \pm 1.3$), diamonds are for acetophenone (after 35 days; $K_s = 38.8 \pm 1.2$), and circles are for 3-nitrophenol (after 35 days; $K_s = 44.0 \pm 0.7$). The dotted line represents the average distribution coefficient K_s.

solute equilibrium volume fraction in the aqueous phase. In the experiments, the masses of both phases and the thicknesses of the polymer films were held constant. The error bars and the average distribution coefficient are also shown. Clearly, the measured distribution coefficients are independent of aqueous solute concentration for the concentration range considered here.

Figure 4 shows similar data for EVAc45; analogous conclusions can be drawn. In Figure 5 (PVAc), there is again no evident trend of the distribution coefficient with the solute concentration. Here, however, the concentration in abscissa
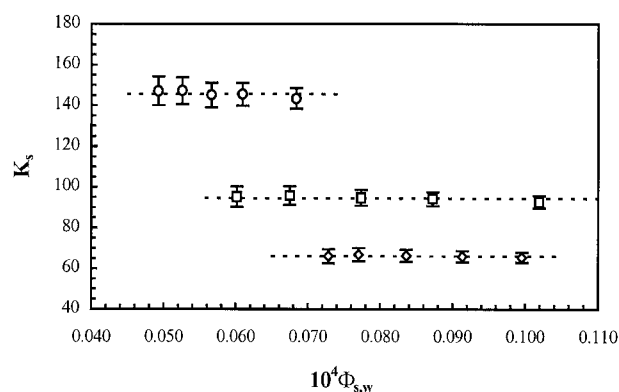

Figure 4 Distribution coefficients for three solutes in EVAc45. Diamonds are for acetophenone (after 14 days; $K_s = 66.1 \pm 0.5$), squares are for 2-nitrophenol (after 14 days; $K_s = 94.5 \pm 1.1$), and circles are for nitrobenzene (after 14 days; $K_s = 145.6 \pm 1.6$). The dotted line represents the average distribution coefficient K_s.
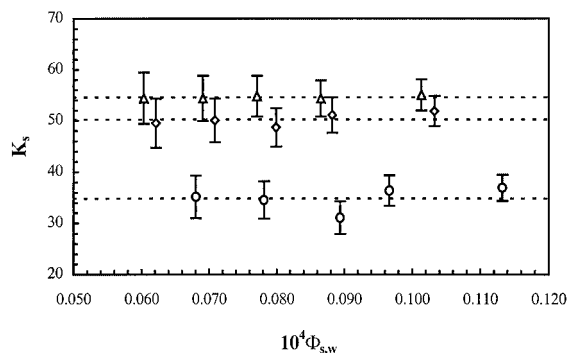
Figure 5 Effect of time on the distribution coefficient of acetopheneone in PVAc (circle: 7 days; diamond: 21 days; triangle: 40 days). K_s is independent of solute concentration at any time. The dotted lines represent the time-dependent average distribution coefficients.

is a nonequilibrium concentration because of the long time necessary to reach equilibrium. Comparing the ratio of solute volume fractions in the two phases at different times, the time-dependent distribution coefficient $\Phi_{s,p}/\Phi_{s,w}$ remains independent of dilution. Therefore, the assumption of infinite-dilution conditions for PVAc remains valid for all times up to the time required for equilibrium.

Table V lists distribution coefficients with corresponding standard deviations for all solutes in EVAc33, EVAc45, and PVAc. Because EVAc copolymers in contact with aqueous solutions reach equilibrium in a few days, extrapolation to infinite time is not required, and the reported K_s are simple averages of the final measurements. However, for PVAc systems, the diffusion process is much slower, and a long time is needed for equilibration. Therefore, the reported distribution coefficients are the average of the five values (corresponding to the five different solution concentrations) of the fitting parameter K_s appearing in the diffusion model used for time extrapolation (see Appendix). The experimental error is a few percentages of the corresponding K_s for all solutes except nicotine in EVAc45 and PVAc, and pyridine in PVAc, for which it is as high as 20–50%. These last data should be taken with caution.

In general, the distribution coefficient of a solute is affected primarily by two factors: the presence of functional groups on the solute molecule that may interact specifically with the VAc moiety, and the lipophilicity (hydrophobicity) of the solute.

Highly polar molecules such as pyridine and benzyl alcohol have indeed the lowest K_s values ($\sim$ 1–10), whereas benzophenone has the highest

($\sim 10^3$). For a given solute, K_s increases with VAc content in the polymer with few exceptions: namely 2- and 4-nitrotoluene and benzophenone; for these three solutes, EVAc45 gives the highest distribution coefficient. The addition of polar VAc moieties into the polyethylene backbone appears to increase the favorable interaction between the solute and the polymer. Each solute studied here has a polar functional group (nitro, amino, hydroxyl, carbonyl, carboxyl, etc.) attached to the aromatic ring; specific attractive interactions between these groups and VAc are likely. Maurin et al.[10] observed similar behavior for monosubstituted benzoic acids in EVAc copolymers. They explained their results on the basis of complex formation between the carboxylic group and the vinyl acetate moiety because experimental studies have shown that these aqueous monosubsti-

Table V   Equilibrium Distribution Coefficient K_s and Corresponding Standard Deviation for 19 Solutes in Two EVAc Copolymers and in PVAc

Solute	EVAc33	EVAc45	PVAc
1-Naphthol	599 (±8)	623 (±25)	2203 (±65)
2-Naphthol	372 (±5)	743 (±8)	1693 (±27)
2-Nitroaniline	66.3 (±2.7)	140 (±2)	350 (±3)
3-Nitroaniline	36.5 (±1.3)	80.1 (±1.3)	264 (±4)
4-Nitroaniline	25.2 (±0.3)	65.9 (±0.5)	322 (±2)
2-Nitrophenol	93.7 (±4.3) [a]	122 (±2) [a]	185 (±5) [a]
3-Nitrophenol	44.1 (±0.6)	94.2 (±1.1)	314 (±5)
4-Nitrophenol	33.9 (±0.2) [a]	87.3 (±2.6) [a]	374 (±7) [a]
2-Nitrotoluene	336 (±17)	483 (±1)	435 (±15)
3-Nitrotoluene	105 (±4) [a]	249 (±2) [a]	386 (±2) [a]
4-Nitrotoluene	345 (±11) [a]	471 (±10) [a]	423 (±3) [a]
Acetophenone	38.7 (±1.2)	41.5 (±2.2) [a]	55.7 (±0.7) [a]
Benzoic acid	5.18 (±0.45) [a]	13.9 (±1.9) [a]	53.4 (±0.5) [a]
Benzonitrile	43.9 (±0.7)	54.5 (±1.3)	77.1 (±3.1)
Benzophenone	1356 (±30)	2231 (±12) [a]	1782 (±37) [a]
Benzyl alcohol	2.79 (±0.08) [a]	10.8 (±1.7) [a]	23.4 (±3.3) [a]
Nicotine	1.42 (±0.08)	22 (±14) [a]	46 (±9)
Nitrobenzene	91.5 (±0.8)	145 (±2)	172 (±7)
Pyridine	1.09 (±0.11)	2.65 (±0.15)	5.32 (±1.32)

[a] At the end of the experiments for determining the distribution coefficient, we compared the UV spectrum of the aqueous solution for each solute before and after contacting with polymer. We define a ratio r of absorbences at two characteristic wavelengths. If there are no interfering factors and the only phenomenon occurring in the experiment is the solute sorption by the polymer, r_{before} / r_{after} must be equal to unity within experimental error. The systems labeled with subscript a have r_{before} / r_{after} different from unity by more than 10%, but usually not much more. The largest deviation was for benzyl alcohol in PVAc. The origin of this deviation is unknown. It could be due to a combination of factors such as release of some polymer impurities in solution, solubilization of a tiny amount of polymer, solute degradation, bacterial growth, etc.

Table VI Diffusion Coefficient D and Corresponding Standard Deviation for 19 Solutes in Two EVAc Copolymers (10^{-9} cm²/s) and in PVAc (10^{-12} cm²/s) (For PVAc, results from both early-time measurements and from the extrapolation procedure are compared)

| Solute | EVAc33 | EVAc45 | PVAc | |
			Early-time	Extrapolation
1-Naphthol	0.13 (±0.05)	0.46 (±0.21)	1.1 (±0.5)	4.4 (±0.3)
2-Naphthol	0.44 (±0.17)	0.66 (±0.30)	1.3 (±0.6)	6.6 (±0.8)
2-Nitroaniline	2.9 (±1.0)	3.9 (±1.7)	3.4 (±1.5)	9.3 (±1.3)
3-Nitroaniline	4.3 (±1.6)	5.1 (±2.3)	5.9 (±2.7)	11 (±1)
4-Nitroaniline	4.6 (±1.6)	6.2 (±2.8)	4.7 (±2.1)	12 (±1)
2-Nitrophenol	1.1 (±0.4)	10 (±5)	6.9 (±3.2)	14 (±1)
3-Nitrophenol	3.0 (±1.1)	2.5 (±1.2)	2.4 (±1.1)	12 (±2)
4-Nitrophenol	4.6 (±1.6)	1.5 (±0.7)	6.9 (±3.1)	13 (±2)
2-Nitrotoluene	2.2 (±0.8)	1.5 (±0.7)	8.2 (±3.8)	13 (±1)
3-Nitrotoluene	2.9 (±1.0)	2.9 (±1.3)	5.6 (±2.6)	16 (±1)
4-Nitrotoluene	1.2 (±0.5)	3.7 (±1.7)	8.2 (±3.8)	16 (±2)
Acetophenone	4.6 (±1.7)	13 (±6)	11 (±5)	13 (±2)
Benzoic acid	12 (±5)	7.2 (±3.8)	8.8 (±4.0)	6.6 (±1.3)
Benzonitrile	5.0 (±1.7)	15 (±7)	20 (±9)	28 (±2)
Benzophenone	0.10 (±0.03)	0.34 (±0.15)	1.4 (±0.6)	4.7 (±0.4)
Benzyl alcohol	56 (±22)	16 (±9)	10 (±6)	145 (±27)
Nicotine	3.1 (±1.1)	0.05 (±0.07)	0.19 (±0.12)	2.0 (±1.7)
Nitrobenzene	2.6 (±1.0)	5.5 (±2.5)	19 (±9)	17 (±1)
Pyridine	51 (±21)	26 (±12)	—	—

tuted benzoic acids have essentially zero partition coefficients in polyethylene.

4-Nitroaniline in EVAc copolymers exhibits a smaller K_s than nitrobenzene (92 and 145 in EVAc33 and EVAc45, respectively). The additional amino group decreases the lipophilicity of the solute, increasing its partition into the aqueous solution. When the amino group moves from the *para* to the *ortho* position, intramolecular interaction with the adjacent nitro group may reduce this effect, causing an increase in lipophilicity and in the distribution coefficient.

For all three polymers, the distribution coefficient of 2-nitrophenol is the same as that of nitrobenzene. The addition of a hydroxyl moiety has a parallel effect in EVAc copolymers; the *ortho*-substituted isomer has the higher K_s, whereas the *meta* and *para* isomers show nearly the same K_s.

For nitrophenols, PVAc presents an opposite trend, whereas for nitroanilines the behavior is more complex. For both solutes, the additional polar group raises K_s above that for nitrobenzene. The favorable interaction between polar moieties appears here to be the major driving force for partition into the polymer.

For nitrotoluenes, EVAc copolymers and PVAc show similar behavior. The methyl group favors partition into the polymer by increasing the lipophilicity of the solute.

Diffusion Coefficient

Table VI gives diffusion coefficients for all solutes in EVAc33, EVAc45, and PVAc as obtained with the method presented by eq. (7). The standard deviation is also reported. Typical experimental data are presented in Figure 6. The diffusion co-
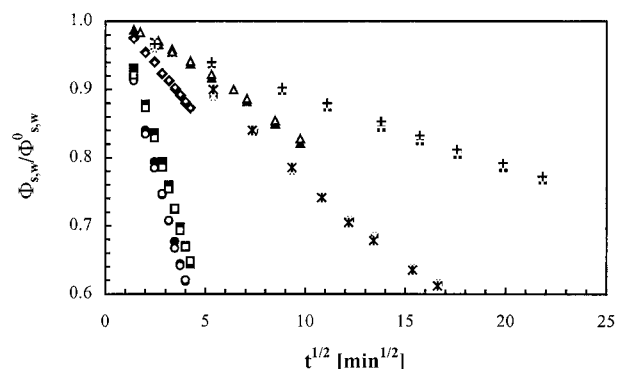
Figure 6 Short-time solute depletion in the aqueous solution. The vertical axis is the normalized solute volume fraction in solution. Circles are for EVAc33 + 2-nitroaniline; triangles are for EVAc33 + benzophenone; diamonds are for EVAc45 + 4-nitroaniline; squares are for EVAc45 + nitrobenzene; stars are for PVAc + 1-naphthol; and crosses are for PVAc + nitrobenzene. Open and filled symbols refer to two separate experiments for the same polymer/solute system.

efficients for solutes in EVAc45 and EVAc33 range from 10^{-10} to 10^{-8} cm^2/s, whereas for the wet PVAc, they are two orders of magnitude smaller. With few exceptions, diffusion coefficients in EVAc45 are somewhat larger than those in EVAc33.

Our data are in reasonable agreement with previous results for similar aromatic compounds. Chen and Lostritto[19] measured the diffusion coefficient of benzocaine ($M_w = 165.2$) in EVAc copolymers with different VAc content; their results for 28–40% VAc are on the order of 10^{-9}-10^{-8} cm^2/s, slightly increasing with %VAc. Maurin et al.[10] report diffusion coefficients for monosubstituted benzoic acids in EVAc copolymers at 37°C; they found $D \sim 10^{-9}$-10^{-8} cm^2/s and little change in the diffusion coefficient with VAc content in the range 0–40%. Kumar et al.[20] obtained diffusion coefficients for benzene, toluene, and xylene in EVAc with 18% VAc; here, the results are on the order of 10^{-7} cm^2/s. To the best of our knowledge, no diffusion-coefficient data have been reported in literature for aromatic solutes in wet PVAc.

Table VI also shows diffusion coefficients for solutes in PVAc obtained by the extrapolation procedure described in the appendix. Agreement between the two methods is fairly good (except for benzyl alcohol and nicotine). [Note that our primary goal is to determine distribution coefficients; diffusion coefficients D are secondary. For our purposes, agreement for D between the two methods is satisfactory inside a factor of 3 to 4.] The experimental uncertainty of the diffusion coefficient obtained through the extrapolation procedure is smaller than that obtained from the early-time measurements because in the former, the uncertainty in the film thickness is not taken into account.

For a given polymer/solute system, there is a weak correlation between the diffusion coefficient and the distribution coefficient. As the latter increases, the former decreases, as shown in Figure 7 for EVAc33. The stronger polymer/solute interaction in the systems (indicated by a higher distribution coefficient) retards solute motion in the polymeric matrix. Results for isomers of the same solute show some exceptions; however, these exceptions may not be significant because the uncertainties in the data are often quite large, perhaps as high as ±50%.

For benzoic acid, nicotine, pyridine, and the three nitrophenols, solute speciation may affect experimental K_s and D. For these solutes, solution pHs were calculated from the total solute concentration in the aqueous solutions measured
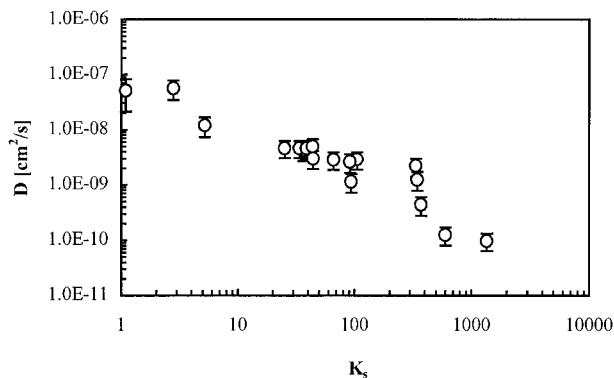

Figure 7 Double logarithmic plot of diffusion coefficients for 19 solutes in EVAc33 versus polymer/water distribution coefficients.

by UV spectroscopy. Benzoic acid (pK = 4.21 at 25°C) is almost completely dissociated (initial pH pH$_i$ = 5.5–5.9; final pH pH$_f$ = 5.6–6.0 for all three polymers in the distribution coefficient experiments), whereas, for pyridine, only 1% of the protonated form (pK = 5.23 at 25°C) is present in solution (pH$_i$ = 7.1–7.2; pH$_f$ slightly smaller). Maurin et al. have shown that for benzoic acid in EVAc copolymers, D is not sensitive to solution pH.

For 2-nitrophenol (pK = 7.23 at 25°C; pH$_i$ = 6.2–6.4; pH$_f$ = 6.4–6.65) and 4-nitrophenol (pK = 7.08 at 25°C; pH$_i$ = 6.25–6.4; pH$_f$ = 6.45–6.6), the degree of dissociation ranges between 15 and 30%, whereas for 3-nitrophenol (pK = 8.36 at 25°C; pH$_i$ = 6.6–6.8; pH$_f$ = 6.8–6.9), it is less than 10%. Nicotine in solution (pK = 6.16 at 15°C; pH$_i$ = 7.4–7.65; pH$_f$ = 7.35–7.6) is protonated to less than 6%. For the other solutes, ionization is negligible in our concentration ranges.

CONCLUSION

For 19 aqueous nonvolatile solutes, experimental results are reported for distribution coefficients at infinite dilution and diffusion coefficients in three polymers. Solutes are aromatics with a variety of functional groups; the polymers are two EVAc copolymers and PVAc. The solutes are of environmental interest and may serve as models for pharmaceuticals; EVAc copolymers are widely used as rate-controlling membranes in drug-delivery systems.

Surface adsorption is negligible. The distribution coefficients K_s increase with vinyl acetate content in the polymer because the vinyl acetate group interacts favorably with the polar func-

tional groups in the solute. The nature and position of functional groups in the solute affect K_s; if they augment lipophilicity, the distribution coefficient tends to increase in EVAc copolymers and vice versa. In PVAc, the effect appears to be more complex; polar moieties (hydroxyl and amino group) can raise K_s because of favorable interaction with the vinyl acetate group, but nonpolar groups (methyl) may give the same effect because of increased lipophilicity.

In EVAc copolymers, diffusion coefficients D depend weakly on VAc; they range from 10^{-10} to 10^{-8} cm^2/s. They are usually larger for the solute with lower distribution coefficient. In PVAc, the diffusion process is much slower ($D \sim 10^{-12}$ cm^2/s). As a consequence, the time to equilibrate the polymer with the aqueous solution of the solute is quite long (more than 4–5 weeks). Therefore, for solutes in PVAc, an extrapolation procedure with a suitable diffusion model has been used to obtain the equilibrium distribution coefficient and the diffusion coefficient.

APPENDIX: EXTRAPOLATION OF THE DISTRIBUTION COEFFICIENT TO INFINITE TIME

For PVAc systems, nonnegligible increases of the amount of absorbed solute were measured even after 40 days. To obtain the equilibrium value of the distribution coefficient K_s^{∞}, extrapolation to infinite time is necessary. Toward that end, we have chosen a mathematical model for diffusion that is consistent with our experimental conditions. The main features of this model are as follows:

1. The decrease of solute concentration in the aqueous phase is due only to diffusion of the solute into the polymer bulk (i.e., the contribution of surface adsorption is negligible).

2. The solute mass transfer into the polymer follows Fick's law with constant diffusion coefficient.

3. The solution volume is limited (i.e., the concentration of the solute in the solution falls as the solute enters the polymer film). This feature is essential because the solute uptake in the polymer is experimentally deduced by monitoring the concentration in the solution as a function of time.

4. The solute mass transfer in the aqueous phase is much faster than that in the polymer phase; the solute concentration in the aqueous phase is then uniform and depends only on time [$\Phi_{s,w}(t)$].

5. The polymer film is modeled as a plane sheet of infinite surface area with negligible border area. The only relevant dimension x is orthogonal to the plane surface.

6. Equilibrium is established instantaneously at the solution–polymer interface $x = \pm l$ [$\Phi_{s,p}(\pm l, t) = K_s\Phi_{s,w}(t)$], where $2l$ is the wet-film thickness.

Adsorption, discussed in the Results and Discussion section, is negligible. The assumption of constant diffusion coefficient is justified at infinite-dilution condition where $K_s = K_s^{\infty}$.

The fifth feature is easily tested by calculating the ratio of the border area A_b to the surface area A_s of the polymer films for a typical polymer thickness. A_b/A_s is always less than 1%.

Finally, the time-independent relation between solute concentration in the polymer film at the interface and that in the solution is reasonable for the highly dilute solutions used here.

The solute uptake in the polymer film as a function of time is obtained by solving the one-dimensional diffusion problem:

$$\frac{\partial \Phi_{s,p}}{\partial t} = D \frac{\partial^2 \Phi_{s,p}}{\partial x^2} \qquad (A.1)$$

with the initial conditions:

$$\begin{aligned} \Phi_{s,p} &= 0 & -l < x < l, \quad t = 0 \\ \Phi_{s,w} &= \Phi_{s,w}^0 & t = 0 \end{aligned} \qquad (A.2)$$

stating that at time $t = 0$ all the solute is in the aqueous solution phase with concentration $\Phi_{s,w}^0$. The boundary condition equates the rate at which the solute leaves the solution to that at which it enters the film at the surfaces $x = \pm l$:

$$V_w \frac{\partial \Phi_{s,w}}{\partial t} = A_p j_{s,p}\bigg|_{x=\pm l} = \mp A_p D \frac{\partial \Phi_{s,p}}{\partial x}\bigg|_{x=\pm l}$$

$$\frac{a}{K_S}\frac{\partial \Phi_{s,p}}{\partial t} = \mp D\frac{\partial \Phi_{s,p}}{\partial x} \quad x = \pm l, \quad t > 0. \quad (A.3a)$$

One of the boundary conditions in eq. (A.3) can be replaced by the symmetry condition:

$$\frac{\partial \Phi_{s,p}}{\partial x} = 0 \quad x = 0, \quad t > 0 \qquad (A.3b)$$

In eqs. (A.1)–(A.3), V_w is the solution volume, A_p is the surface area of the polymer film, $\Phi_{s,p}$ represents the solute volume fraction in the polymer film, D is the diffusion coefficient in the poly-

mer phase, x is the direction orthogonal to the polymer surface, t is time, $2l$ is the wet-film thickness, $\Phi_{s,w}$ is the solute volume fraction in the aqueous solution, $2a = V_w/A_p$ is the solution thickness, K_s is the distribution coefficient of the solute between polymer film and aqueous solution, defined in eq. (5) of the text.

The solution of the diffusion equation is[15]

$$\frac{\Phi_{s,p}(t)}{\Phi_\infty} = 1 - \sum_{n=1}^\infty \frac{2\alpha(1+\alpha)}{1 + \alpha + \alpha^2\lambda_n^2} \exp\left(-\frac{D\lambda_n^2 t}{l^2}\right)$$

(A.4)

In eq. (A.4), $\Phi_{s,p}(t)$ is the solute concentration in the polymer averaged over the film thickness at the time t; $\alpha = a/lK_s$ and $\Phi_\infty = (a/l)[\Phi_{s,w}^0/(1+\alpha)]$.

Equation (A.4) contains two parameters: diffusion coefficient D and equilibrium distribution coefficient K_s. We fit these parameters with a nonlinear least-squares algorithm minimizing the weighted sum S of the squares of the differences between calculated $\Phi_{\text{calc},i}$ and experimental $\Phi_{\text{exp},i}$ concentrations:

$$S = \sum_{i=1}^{npt} w_i(\Phi_{\text{calc},i} - \Phi_{\text{exp},i})^2$$

(A.5)

where npt is the number of measurements at different times and w_i is the weight corresponding to $\Phi_{\text{exp},i}$.

Because the contribution of the nth term is decreasing exponentially with increasing index n, only the first 10 terms of the series in eq. (A.4) were used in the calculation.

The parameter fitting is repeated for each of the five vials used in the experiments for determining the equilibrium value of K_s and the diffusion coefficient D. The average distribution coefficients and diffusion coefficients are reported in Tables V–VI, respectively, of the text along with their standard deviations.

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