

Diffusivities of Dichloromethane in Poly(lactide-co-glycolide)

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ABSTRACT: Diffusion of dichloromethane in poly(lactide-co-glycolide) (PLGA), the rate-limiting step in the later stages of drying of microparticles formed in common encapsulation processes, was studied by the step-change sorption technique in a dynamic vapor sorption apparatus. Methods were developed to create films of polymer with the appropriate thicknesses for accurate diffusion determination over a wide range of solvent composition. Mutual diffusivities were measured at 5, 25, and 35°C from 10 to 70 wt % solvent. Values range from 2×10^{-10} m²/s at high solvent compositions to as low as 1×10^{-13} m²/s at solvent compositions just above the glass transition of the mixture. Equilibrium sorption isotherms were measured in the same

apparatus and agreed favorably with Flory-Huggins theory using a value of $\chi = 0.31$. The glass transition temperatures of the system were measured over the range of 0–11 wt % solvent content by modulated differential scanning calorimetry. The composition dependence was fit to the Fox equation, which estimated values of the pure polymer and the solvent T_g to be 39.3 and -131°C , respectively. These values, along with the diffusivity data, were used to deduce the free-volume parameters specific to PLGA. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 112: 1622–1629, 2009

Key words: biodegradable; polyester; diffusion; glass transition; drug delivery systems

INTRODUCTION

Microparticles of poly(lactide-co-glycolide) (PLGA), a biodegradable aliphatic polyester, are a proven vehicle for the sustained delivery of peptide and protein biopharmaceuticals.^{1,2} Injectable drug-loaded PLGA microparticles have been successfully prepared at both the bench and the commercial scale using several manufacturing processes, including emulsions, cryogenic entrapment, and spray drying. At the commercial scale, spray drying offers some distinct advantages over the other methods. Whereas alternative processes require large quantities of solvents and multiple processing steps and may expose protein to denaturing aqueous-organic interfaces and significant thermal stress, spray drying offers a rapid, efficient, and easily scalable method for encapsulation under mild processing conditions.^{3,4} However, a better understanding of drying kinetics

is required to design a PLGA microparticle spray drying process that remedies the current low and variable product yields.⁵

In spray drying, droplets of a dilute polymer and drug solution are dried in a chamber and collected as discrete particles. Typically, dichloromethane (DCM) is the solvent used for spray drying PLGA because of its high volatility.⁶ The particles must be dried below the glass transition before they contact the vessel walls to prevent agglomeration and adhesion to surfaces.⁷ Although dilute polymer solution droplets initially dry rapidly because of the high volatility of the solvent, their overall drying time is dominated by the later stage of evaporation where the mass transport of solvent becomes limited by diffusion through the concentrated polymer.⁸ Therefore, the solvent diffusion rate through the polymer as a function of both composition and temperature is critical for selecting the geometry and the operating parameters of a microparticle spray drying process.

Diffusion in mixtures of amorphous polymers and compatible solvents has been thoroughly characterized for commodity and engineering thermoplastics over a broad range of temperature and composition.⁹ In the liquid state, the mutual diffusivity of most polymer-solvent systems typically has values near 10^{-10} m²/s. As the solvent concentration decreases, the viscosity of the mixture increases resulting in a gradual but large decrease in the

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diffusivity, typically several orders of magnitude, between the dilute liquid state and the glass transition.¹⁰

Above the glass transition, the self-diffusion coefficient for a solvent (denoted as subscript 1) in a polymer (denoted as subscript 2) is well described by the free-volume theory^{11,12}:

$$D_1 = D_0 \exp \left[\frac{-E}{RT} \right] \times \exp \left[\frac{-\left(\hat{V}_1^* \omega_1 + \xi \hat{V}_2^* \omega_2 \right)}{\frac{K_{11}}{\gamma} (K_{21} - T_{g1} + T) \omega_1 + \frac{K_{12}}{\gamma} (K_{22} - T_{g2} + T) \omega_2} \right] \quad (1)$$

where D_0 is a constant preexponential factor, E is the activation energy for a jumping unit making a jump into a hole of free-volume, \hat{V}_i^* is the specific volume of component i at 0 K, ω_i is the mass fraction of component i , T_{gi} is the glass transition temperature of pure component i , ξ is the ratio of the molar volume of the solvent and polymer jumping units, and γ is the free-volume overlap factor. K_{11} and K_{21} are free-volume parameters for the solvent. The values of K_{11}/γ and K_{21} for many solvents are determined by Zielinski and Duda⁹ through comparison of diffusion theory with the viscosity data. K_{12} and K_{22} are the free-volume parameters for the polymer. K_{12}/γ and K_{22} are related to the Williams, Landel, and Ferry parameters for the temperature dependence of viscosity¹³ and so these can be estimated from the viscosity data, if available. The mutual diffusion coefficient of the polymer-solvent mixture is related to the self-diffusion coefficient given in eq. (1) using the Flory-Huggins description of the activity as follows:

$$D = D_1 \phi_2^2 (1 - 2\chi \phi_1) \quad (2)$$

where ϕ_i is the volume fraction of component i and χ is the enthalpic interaction parameter.

Until now, there are no published estimates of the free-volume parameters for PLGAs and no temperature- and composition-dependent diffusivity data available for their estimation. Recently, Eser and Tihminlioglu¹⁴ used inverse gas chromatography to measure diffusivities of several solvents, including DCM, at infinite dilution in PLGA. These measurements were made at elevated temperatures well above the T_g of the polymer and thus above temperatures relevant to spray drying. Without composition-dependent diffusion data at temperatures relevant to spray drying, modeling of particle drying kinetics is not possible.

In this work, the mutual diffusivity of amorphous PLGA and DCM was measured using the transient

sorption technique because it can be applied over a broad range of compositions. During transient sorption, the mass change of a film of thickness l in response to an instantaneous change in the surrounding vapor composition is¹⁵:

$$\frac{m - m_0}{m_f - m_0} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp \left[-\frac{(2n+1)^2 \pi^2 D t}{4l^2} \right] \quad (3)$$

Here, D is the mutual diffusivity and m_0 and m_f are the initial and final equilibrium film mass before and after the step. Early in the transient, the mass change in eq. (3) varies as $t^{1/2}$, and therefore the mutual diffusivity is determined experimentally from:

$$D = \frac{\pi}{4} \left[\frac{l}{(m_f - m_0)} \frac{dm}{d\sqrt{t}} \right]^2 \quad (4)$$

valid for $(m - m_0)/(m_f - m_0) < 0.6$.

Diffusivities were measured using the modified version of a commercially available dynamic vapor sorption (DVS) apparatus. The goal was to collect sufficient data over a wide range of compositions near the glass transition temperature of the polymer to develop accurate estimates of the free-volume parameters for interpolation and extrapolation of values in regions relevant to spray drying. Techniques were developed to measure the diffusivity in films that are fluid above the T_g because of the low molecular weight of the polymer and high solvent content.

A large number of parameters are required for the fit of diffusivity data to free-volume theory. To reduce the number of unknowns, independent measurements of several parameters were made. The glass transition temperatures of the pure polymer and pure solvent were determined from the T_g measurements at various polymer-solvent compositions. The Flory-Huggins enthalpic interaction parameter was also estimated from equilibrium sorption data. With these data, the first estimates of free-volume parameters for PLGAs were obtained.

EXPERIMENTAL

Equipment

The glass transition temperatures of the polymer-solvent mixtures were measured with a DSC Q100 modulated differential scanning calorimeter (DSC) (TA Instruments, New Castle, DE). The heat flow data were fitted using Universal Analysis software (TA Instruments, New Castle, DE).

A DVS Advantage 1 (Surface Measurement Systems, London, UK) was used to measure the equilibrium contents and diffusion coefficients of PLGA-DCM mixtures. A schematic of the DVS is shown in

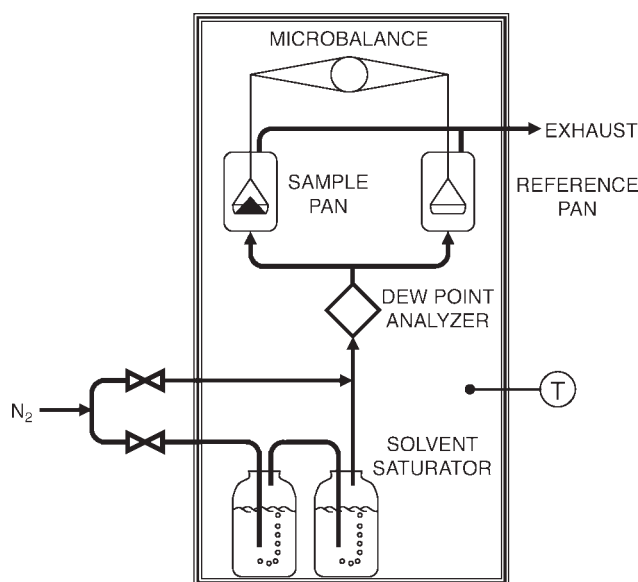


Figure 1 A schematic of the dynamic vapor sorption apparatus as modified for this work.

Figure 1. The DVS consists of a solvent vapor generator, a sample and a reference chamber, and a microbalance, all housed inside a temperature-controlled incubator. The incubator can be operated between 5 and 60°C with a stability of $\pm 0.1^\circ\text{C}$. The DVS generates solvent vapor of various concentrations by mixing a dry nitrogen stream with a second nitrogen stream saturated with solvent in a sparger bottle inside the incubator. The instrument changes the concentration of the mixed vapor stream in a series of user-defined steps by controlling the flow of the two nitrogen streams. The total flow rate Q is typically 100–200 mL/min. The dew point temperature of the mixed vapor stream is measured with a chilled mirror hygrometer and converted to an activity (a_1 , the ratio of the solvent partial pressure and its saturation vapor pressure at the sample temperature) using a temperature-dependent vapor pressure correlation for DCM.¹⁶ The stream is then split and equal portions are sent to the sample and reference chambers. Both chambers contain identical sample pans hanging from opposite arms of the microbalance. The chambers have volumes V of about 80 mL. Mass changes in the sample are measured with a resolution of 0.1 μg .

The DVS is an ideal instrument for step-change diffusion measurements since rapid changes in vapor concentrations can be implemented because of the fast response of the flow controllers and the small volume of the sample chamber. The transient in the vapor concentration within the sample chamber is a first-order response with a time constant $\tau = Q/2V$, which is less than 1 min at typical operating conditions. However, the DVS can exhibit significant overshoots in the vapor compositions at the begin-

ning of vapor transients because of the changes in solvent temperature in the sparger bottles induced by different evaporative cooling rates at each new flow setting. This is especially pronounced with the highly volatile DCM. Therefore, the DVS was modified in these experiments to include two or more spargers in series to mitigate the effects of the temperature drop in the first sparger. The temperature of the final sparger was monitored to assure stability during flow changes.

Materials

Resomer® RG502H PLGA (50 : 50 lactide : glycolide, carboxylic acid-terminated, lot # 1009848, intrinsic viscosity = 0.19 dL/g, number-average molecular mass = 4260 Da, mass-average molecular mass = 11 kDa, density = 1360 kg/m³) was obtained from Boehringer Ingelheim Pharma (Ingelheim am Rhein, Germany). HPLC-grade DCM was used.

Differential scanning calorimetry

Polymer samples with varying fractions of DCM were prepared in hermetically sealed DSC pans. Clean, empty pans and lids were weighed, and ~5 mg of dried polymer was added into each pan followed by one drop of DCM. Care was taken not to contaminate the sealing surfaces with the solution. The open pans were placed in a nitrogen-purged vacuum oven where the temperature was ramped from 40 to 55°C over 3 days to slowly evaporate the solvent from the resulting polymer film. Samples were periodically removed from the oven and sealed using an encapsulation press. Samples were then returned to the oven for 3 days of annealing at 55°C to allow the DCM to evenly distribute throughout the polymer. Samples were weighed to an accuracy of 0.2 μg immediately before DSC analysis to determine the solvent content to a precision of 0.1 wt %. Additional samples were prepared without the added DCM for comparison. Thermograms were acquired from -15 to 60°C using a ramp rate of 1.5°C/min, a modulation amplitude of $\pm 1.0^\circ\text{C}$, and a period of 40 s. The onset, midpoint, and offset T_g values were determined from the reversing heat flow.

Sorption equilibrium

For the sorption equilibrium experiments at low solvent compositions, thin films were required to obtain equilibrium within reasonable times. Two 13 mm diameter, flat-bottom glass sample pans (Surface Measurement Systems), one for the sample chamber and one for the reference chamber, were cleaned thoroughly and dried to a constant weight in the DVS. After a balance calibration with a 100 mg

standard, ~8 mg of RG502H in dry powder form was loaded onto the sample pan and the initial mass was noted in a dry nitrogen environment. The polymer sample was then exposed to a gas mixture with solvent activity a_1 of 0.90 for over 2 h. The DCM was absorbed, which then plasticized the polymer, allowing it to flow into a clear and occlusion-free film on the pan, with a dry film thickness of ~25 μm . The vapor activity was then lowered stepwise in increments of 0.05 from 0.90 to ~0.30. The duration of the steps varied from 2 to 48 h depending on the time required for the sample mass to reach equilibrium. In some tests, the desorption steps were followed by absorption steps to check for hysteresis in the equilibrium solvent concentrations.

Diffusivity

Diffusivities were measured with the DVS using the time-dependent mass data from desorption transients performed with uniform films of known thickness. To assure that the diffusivity was accurately represented by the $t^{1/2}$ region, the thickness of the film l was chosen so that $l^2/D\tau > 20$.¹⁵ Therefore, films of two thickness ranges were prepared using two different techniques. These techniques accommodated the fluid nature of this low-molecular weight polymer at the high solvent contents used in this work.

For the low diffusivity conditions, 70 to 150 μm thick films were prepared by dispensing and spreading ~100 μL of 10 wt % polymer solution from a syringe onto 12 mm diameter glass cover slips. The deposited films were allowed to dry in the open laboratory until they were no longer fluid. A coated cover slip was then loaded onto a 13 mm diameter sample pan in the DVS, preequilibrated to the desired temperature. An uncoated cover slip was placed in an identical pan in the reference chamber. The vapor composition in the DVS was programmed to make several downward going steps, each with sufficient duration for the film mass to reach a new equilibrium. The solvent activity in the vapor, a_1 , ranged from ~0.70 to 0.30, and the change in a_1 was typically no more than 0.05 for each step. The sample mass, vapor composition, and chamber and saturator temperatures were all measured at a frequency of 1/min during the desorption transients. Upon completion of the DVS program, the coated cover slip was removed from the chamber and dried to lower the DCM content by placing in a 60°C oven for more than 24 h. Thickness profiles of dried films were measured by fracturing the coated cover slips on a diagonal and imaging the cross section with an Eclipse E800 optical microscope (Nikon, Melville, NY) outfitted with a C5810 CCD camera and image analysis system (Hamamatsu, Bridgewater, NJ).

Thickness measurements were recorded at ~1 mm intervals across the radius, and then the volume-weighted average thickness was calculated.

For high diffusivity conditions, films of ~1 and 2 mm thickness were prepared by dispensing a known volume of 20 wt % polymer solution from a syringe into flat-bottomed, vertical-walled aluminum sample pans of 6.2 mm in diameter and 1 and 2 mm tall. Using the equilibrium isotherm data, the appropriate volume of solution was added to make the contents level with the top edge of the sample pan at the midpoint of the sorption transient. This minimized meniscus effects as the fluid interline was confirmed by microscopy to always remain at the pan rim, regardless of whether the free surface was above or below the edge. As these films were very fluid and volatile, they were not characterized for thickness. For films of this type, a separate sample was prepared for each sorption transient because of the large volume changes experienced during desorption steps in this composition range.

For both film preparation techniques, the solvent weight fraction in the sample ω_1 at the beginning and end of each step was determined from the equilibrium sorption data at the corresponding vapor activity, a_1 . For diffusivity calculations, the film thickness was corrected based on the solvent composition using a DCM density¹¹ of 1317 kg/m^3 and assuming volume-additive mixing. Data from each transient were plotted versus $t^{1/2}$, and a single diffusivity was calculated using eq. (4).

RESULTS AND DISCUSSION

Glass transition temperature

The glass transition temperatures were measured for PLGA-DCM mixtures over the range of solvent compositions from $\omega_1 = 0$ –0.106. The onset, midpoint, and offset T_g are plotted in Figure 2 as a function of ω_1 , showing ~3.3°C drop in T_g for every 0.01 increase in DCM mass fraction. The data were fit to the Fox equation;

$$\frac{1}{T_g} = \frac{\omega_1}{T_{g1}} + \frac{\omega_2}{T_{g2}} \quad (5)$$

predicting a value for midpoint $T_{g1} = -131^\circ\text{C}$ and for the midpoint $T_{g2} = 39.3^\circ\text{C}$. The value for T_{g1} is comparable with those for similar solvents.⁹ The Fox equation accurately captures the slight positive curvature evident in the data.

Equilibrium isotherms

Equilibrium sorption isotherms were measured at 5, 25, and 35°C for solvent mass fractions ω_1 ranging from 0.10 to 0.74. Results of three experiments

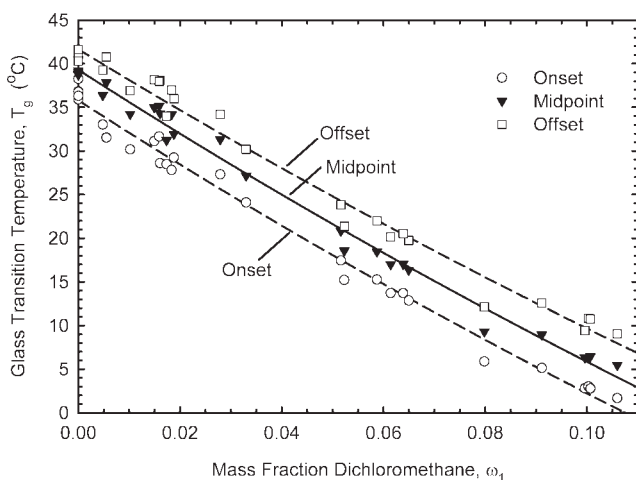


Figure 2 The onset, midpoint, and offset glass transition temperatures measured as a function of dichloromethane content in PLGA. The lines are the best fit of the Fox equation for each case.

performed at 25°C on three different films are plotted in Figure 3. The data are plotted with the solvent vapor activity a_1 on the ordinate and the volume fraction of the solvent in the polymer ϕ_1 on the abscissa to be consistent with the Flory-Huggins description of the polymer–solvent equilibrium

$$a_1 = \phi_1 \exp[(1 - 1/r)\phi_2 + \chi\phi_2^2] \quad (6)$$

where r is the ratio of the molar volumes of the solvent and the polymer. Equilibrium was determined

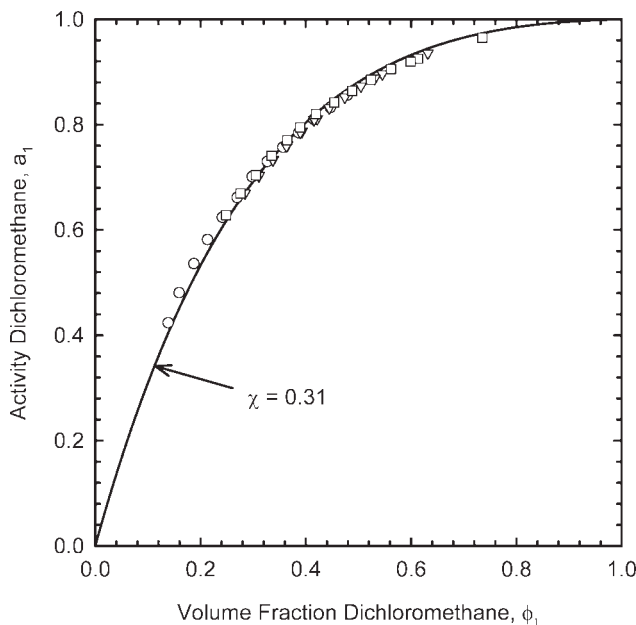


Figure 3 Sorption isotherms for the PLGA–dichloromethane system measured in three separate experiments at 25°C to demonstrate reproducibility, where the solid line is the best fit of the Flory-Huggins equation.

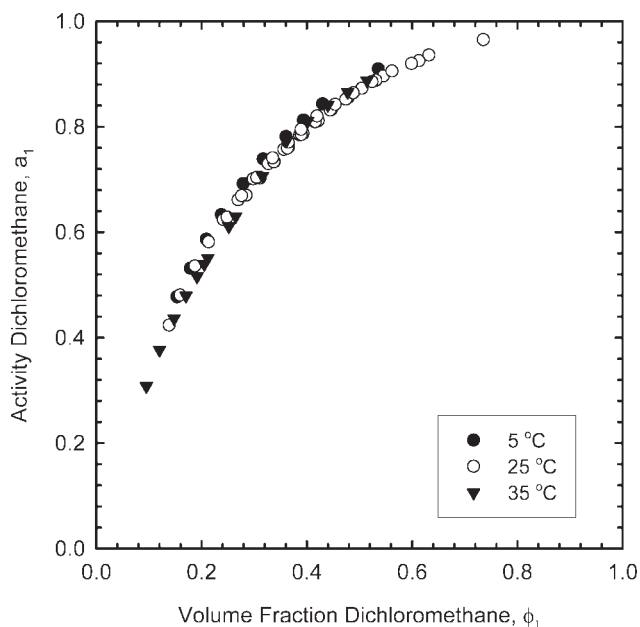


Figure 4 Sorption isotherms for the PLGA–dichloromethane system measured at 5, 25, and 35°C.

when the sample mass change over 30 min was below the noise level of $\sim 1\text{--}20\ \mu\text{g}$, depending on the experimental conditions. No measurable hysteresis in the equilibrium was observed as the steady-state mass fractions on absorption and desorption were within 0.01 at the same vapor activity. This is consistent with the completely amorphous nature of the PLGA-DCM mixture where morphological inhomogeneities that can lead to metastable states, and thus hysteresis, are not present.

The 25°C isotherm data are fit to the Flory-Huggins expression with $\chi = 0.31$. A value of $r = 48.6$ is used based on the ratio of the molar volumes determined from the DCM density and the number-average molecular weight of the polymer. Since equilibrium was achieved, it is assumed that the activity of the solvent in the polymer is equivalent to that in the vapor. The theoretical result is plotted in Figure 3, demonstrating good agreement with the data across the entire composition range. The value of χ is consistent within 9% for the three experimental determinations.

The equilibrium isotherms at 5, 25, and 35°C are shown in Figure 4. The value of χ is 0.39 at 5°C and 0.30 at 35°C, demonstrating only a modest decrease with increasing temperature. The values of χ are below 0.5, the critical value above which phase separation at low polymer content is predicted, and so are indicative of the excellent miscibility of DCM and PLGA. Indeed, no phase separation was observed at any composition in this temperature range. The value of χ at 25°C measured here is consistent with that predicted from Hildebrand

solubility parameters, where a value of 0.29 is estimated using group contribution methods for the solubility parameter of PLGA.^{17,18}

The values of χ measured here compare favorably to an extrapolation of those measured by Eser and Tihminlioglu¹⁴ at higher temperatures. The parameter χ is expected to vary inversely with temperature and, using this form, the high temperature data extrapolate to $\chi = 0.33$ at 25°C, in good agreement with our measured value. However, the temperature dependence of χ measured here is significantly smaller and the inverse of that observed by Eser and Tihminlioglu and so interpolation between the two regions should not necessarily be trusted. In fact, our values for χ are obtained from equilibrium data in the 0.1–0.7 weight fraction range, whereas those of Eser and Tihminlioglu are obtained at infinite dilution of solvent.

Diffusivity

Diffusion measurements were performed at 5, 25, and 35°C. Compositions ranged from $\omega_1 = 0.12$ –0.64. Typical desorption transients performed in the 1 mm tall pans at high solvent composition, one at 5°C and one at 35°C, are shown in Figure 5(a) plotted as a function of $t^{1/2}$. The solvent vapor activities at the beginning and end of each step are listed in the figure. The mass data were normalized with respect to the initial and final equilibrium mass at each step. In this figure, the mass transient data were shifted slightly backward in time so that the linear portions, fitted with dashed lines on the plot, pass through the origin. This shift is typically less than 2 min and accounts for the time constant τ of approximately this duration associated with the vapor mixing in the sample chamber and the associated tubing. The sigmoidal shape is typical of the transients produced in response to the noninstantaneous change in vapor composition.¹⁵ The diffusivities estimated by the slope of the linear portion of the plots are 5.1×10^{-11} m²/s for the 5°C transient and 6.6×10^{-11} for the 35°C transient. The value of $l^2/D\tau$ is 270 for the 5°C transient and 290 for the 35°C transient, well above the threshold for ensuring accuracy in the diffusivity measurement using this method.

The same data are plotted directly as a function of time in Figure 5(b). The slight oscillations in the sample mass are due to periodic variations in the chamber temperature with an amplitude of 0.2°C, which cause small variations in the solvent vapor activity. Theoretical estimates of the mass response, using eq. (3) and the diffusivities determined in the mass versus $t^{1/2}$ plots, are shown as dashed lines in Figure 5(b). The excellent agreement of the duration of the transients confirms that the diffusion is Fickian and that the diffusivity does not change signifi-

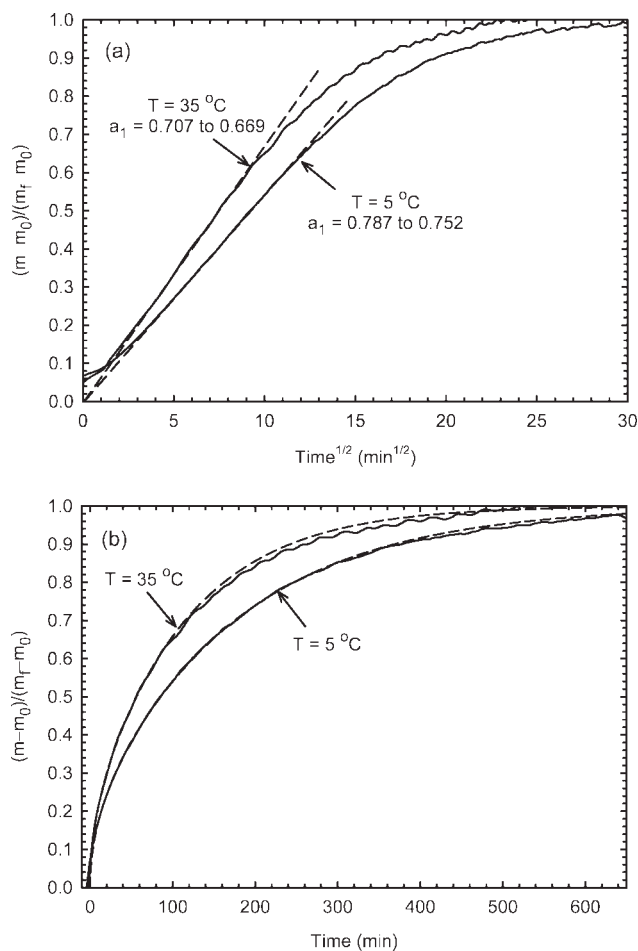


Figure 5 Normalized mass transients for two desorption step-change experiments: (a) as a function of $t^{1/2}$, where the dashed lines are the best fit to the linear portion and (b) as a function of time, where the dashed lines are theoretical fits using eq. (3) and the derived diffusivities. The values of a_1 are the initial and final vapor-phase solvent activities before and after the step.

cantly over the range of the composition steps used in these experiments.

The effect of film thickness on the measured diffusivity at these high solvent compositions was tested at 25°C by repeating experiments near $\omega_1 = 0.45$ with the two different pan depths. The 1 mm deep pan yielded a diffusivity of 1.5×10^{-10} m²/s and the 2 mm deep pan gave 1.7×10^{-10} m²/s at the same composition. This is within the measurement error of the technique, where the largest source of error is the estimation of an average film thickness.

The diffusivities calculated from the transient desorption experiments are plotted in Figure 6 as a function of solvent composition for the three temperatures examined. The data follow the composition dependence observed with other amorphous polymers, namely the large and gradual drop in diffusivity as the T_g is approached. A clear temperature dependence is apparent in the data, with a 15-fold

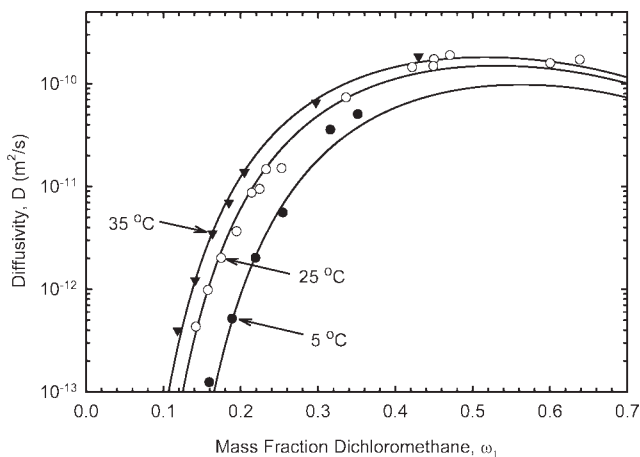


Figure 6 Mutual diffusivity in the PLGA–dichloromethane system as a function of the dichloromethane mass fraction for 5, 25, and 35°C. The lines are theoretical estimates at each temperature using the free-volume parameters listed in Table I.

difference in diffusivity between 5 and 35°C at the lower compositions.

The data in Figure 6 were fit with free-volume theory using the strategy suggested by Duda et al.¹⁹ and Zielinski and Duda.⁹ Twelve parameters are required for the fit: D_0 , E , \hat{V}_1^* , \hat{V}_2^* , ξ , K_{11}/γ , K_{21} , K_{12}/γ , K_{22} , T_{g1} , T_{g2} , and χ . To reduce the number of adjustable parameters, several approximations can be made. In the temperature range between the T_g and about 100°C above the T_g , energy effects are often found to be negligible and so E is assumed to be zero.^{9,19,20} The Arrhenius term and the preexponential term then collapse into one temperature-independent term, D_{01} , which determines the magnitude and not the shape of the fit. In lieu of the Arrhenius term, temperature effects are adequately modeled with the free-volume portion of eq. (1). The specific volumes of the solvent and polymer at 0 K can be estimated from group contribution methods.⁹ The free-volume parameters D_{01} , K_{11}/γ , and K_{21} are derived from the viscosity data of many solvents, including DCM, and are listed elsewhere.^{9,20} The glass transition temperatures, T_{g1} and T_{g2} , and the enthalpic interaction parameter χ measured here are used. Values for the estimated and measured parameters used to fit the diffusivity data are listed in Table I.

With the above estimates and measurements, the number of adjustable parameters necessary for the fit of eqs. (1) and (2) reduce to three: ξ , K_{12}/γ , and K_{22} . These remaining parameters are obtained from a fit to the diffusivity data. The best-fit values are listed in Table I. The parameter ξ has a significant effect on the curvature in the data between $\omega_1 = 0.2$ and 0.4,²⁰ and so its value was determined from a best fit of the data in this region. The resulting value

of $\xi = 0.68$ is consistent with the value of 0.73 obtained from the correlation that indicates that the polymer jumping unit is 3/2 of the monomer segment⁹:

$$\xi = \frac{2\tilde{V}_1^0}{3\hat{V}_2^*M_{\text{mono}}} \quad (7)$$

where \tilde{V}_1^0 is the solvent molar volume at 0 K and M_{mono} is the molecular mass of the monomer unit. The parameter K_{12}/γ affects the temperature dependence of the diffusivity, whereas K_{22} affects the composition dependence of the diffusivity just above the T_g ,²⁰ allowing for accurate independent determination. The value for K_{12}/γ is consistent with many other polymers listed in the literature. The value for K_{22} is somewhat smaller than is typical for other polymers, perhaps because of the low molecular weight and high mobility of the PLGA used in these experiments. The values of the diffusivity near the maximum are most strongly affected by D_{01} . The D_{01} used in the theoretical fit determined from independent viscosity measurements provides confidence that the magnitude of the diffusivity measured in the range above $\omega_1 = 0.4$ is accurate. As far as we can determine, these are the first estimates of the free-volume parameters for PLGA in the literature.

To compare these data with those of Eser and Tihminlioglu at higher temperatures, eqs. (1) and (2) are evaluated at 100°C using the free-volume parameters listed in Table I. At 100°C and at infinite dilution ($\omega_1 = 0$), a value of $D = 1.9 \times 10^{-14}$ m²/s is obtained, nearly three orders of magnitude lower than the value of 9.1×10^{-12} m²/s reported by Eser and Tihminlioglu at the same condition. This large discrepancy may be explained by the large Arrhenius temperature dependence in the high-temperature data, which is not included in the free-volume fit. It is well understood that polymer–solvent diffusivity exhibits Arrhenius behavior above the T_g but

TABLE I
Values of the Free-Volume Parameters Used to Fit the Diffusivity Data in Figure 6

Property	Value	Source
E	0	Refs. 9,19, and 20
D_{01}	3.88×10^{-8} m ² /s	Refs. 9 and 20
V_1^*	5.85×10^{-4} m ³ /kg	Ref. 9
V_2^*	5.33×10^{-4} m ³ /kg	Ref. 9
K_{11}/γ	1.05×10^{-6} m ³ /(kg K)	Refs. 9 and 20
K_{21}	80 K	Refs. 9 and 20
T_{g1}	142 K	Fit of T_g data
T_{g2}	312.3 K	Fit of T_g data
χ	0.31	Fit of equilibrium data
ξ	0.68	Fit of diffusion data
K_{12}/γ	3.3×10^{-7} m ³ /(kg K)	Fit of diffusion data
K_{22}	15 K	Fit of diffusion data

abruptly deviates toward an increasingly weaker dependence at temperatures below the T_g .²¹⁻²³ An Arrhenius fit of Eser and Tihminlioglu's data yields $E/R = 1.21 \times 10^5$ K, making $E/RT \gg 1$ for nearly pure polymer above the T_g . In contrast, the largest comparable term in the free-volume expression is $\xi \hat{V}_2^* \gamma / K_{12} = 1.1 \times 10^3$ K, demonstrating a much weaker dependence on temperature in this region. This comparison demonstrates why diffusion data in one region cannot be accurately extrapolated to other temperatures and compositions, especially in this critical area just above the T_g of the polymer.

CONCLUSIONS

We measured the mutual diffusivity of PLGA-DCM mixtures at temperatures near the T_g of the pure polymer and over a broad range of compositions. Measurements were performed using the transient sorption technique in the modified version of a commercially available DVS apparatus. Techniques were developed to accommodate the large variation in diffusivities over the composition and temperature ranges examined. The measured diffusivity exhibited the expected gradual but large decrease in value with decreasing solvent concentration and varied from 2×10^{-10} m²/s at high solvent compositions to as low as 1×10^{-13} m²/s at lower compositions just above the T_g .

To extrapolate the data to other values of temperature and composition, the data were fit to the free-volume expressions for diffusion in polymers. Twelve parameters are required for the fit. Several of these are specific to the solvent and were found in the existing literature, whereas others are estimated from group contribution methods. Three parameters, the T_g for the two pure materials and the Flory-Huggins χ parameter, are found from independent measurements of the T_g and the vapor sorption equilibrium of polymer-solvent mixtures. The three remaining polymer-specific free-volume parameters were determined by comparison of theory to the diffusivity data, making these the first estimates of the free-volume parameters for PLGA. The values of these parameters agree well with those for other amorphous polymers.

Attempts to extrapolate the diffusivity and χ to literature values at higher temperatures and at infinite dilution of solvent met with only limited success. The value of χ matched an extrapolation of the high

temperature data but the temperature dependence in our data was smaller in magnitude and the inverse of what was observed elsewhere. Extrapolation of the diffusivity data by 50°C or more to the higher temperature data using the free-volume fit proved inaccurate. This was attributed to a large temperature dependence of the diffusivity far above the T_g , which was not included in our modeling of the data near the T_g .

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