

Variability of Water Uptake Studies of Biomedical Polymers

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ABSTRACT: Water uptake influences many properties of polymers and has been widely studied. In the context of polymeric biomaterials, several publications reported an unusual high variability of analytical results, without further investigating the cause for this phenomenon. Using selected polymers from the library of L-tyrosine-derived polyarylates and poly(D,L lactic acid), we showed that nonaged and nonannealed compression molded film samples exhibit the typical large variation in water uptake observed in previous reports. The introduction of an annealing step allows accurate and reproducible water uptake measurements for these polymers. We evaluated the use of ³H-radiolabeled water for the determination of water uptake, finding that the use of

radiolabeled water yields statistically indistinguishable measurements, compared to gravimetric methods, while providing significant advantages in throughput and sensitivity. Using the recommended methods of annealing and ³H-radiolabeled water, the water uptake profiles of 24 polymers of the library of L-tyrosine-derived polyarylates are reported. This article addresses experimental concerns related to water uptake studies and may assist other researchers in improving the accuracy of their water uptake results. © 2011 Wiley Periodicals, Inc. *J Appl Polym Sci* 121: 1311–1320, 2011

Key words: water absorption; diffusion; annealing; hydrolytic degradation; polyester

INTRODUCTION

Water uptake is an important parameter in the characterization of biodegradable polymers.^{1,2} It affects degradation,^{3,4} swelling and induces changes in mechanical properties,^{5–9} the biological response,^{10–12} and drug release behavior.^{4,13–16} However, previous studies have reported very large variability in water uptake measurements. For example, Small et al.¹⁷ observed a variability up to 100% in the water uptake of polyacid-modified composite resins, Jeong et al.¹⁸ observed over 80% of variability in the water uptake of poly(D,L-lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) diblock polymer blend films, Bajpai et al.¹⁹ observed water uptake variability over 30%

for calcium alginate/chitosan bi-polymeric beads, and Lyu et al.²⁰ observed very high variability in the water uptake of poly(lactid acid) (PLA). In our laboratory, we observed that some polymers of the tyrosine-derived polyarylate library exhibited highly reproducible water uptake profiles, while others showed large variability, despite the fact that analyses were performed by the same operator using identical methods. Because of the importance of water uptake studies and the frequency at which such studies are performed in many different laboratories, an understanding of the high variability in water uptake measurements has been pursued in this work.

Water uptake by a polymer matrix is affected, by the polymer's free volume, which depends on the density, the physical state, and the glass transition temperature (T_g) of the polymer.²¹ Akbari et al.²² demonstrated that those properties were dependent on the fabrication technique. They showed that solvent-cast polyanhydride devices exhibited a less packed morphology and higher initial water uptake, while compression-molded devices had a more densely packed morphology and lower water uptake.

It was further shown that water uptake is influenced by polymer mobility and relaxation.^{23–25}

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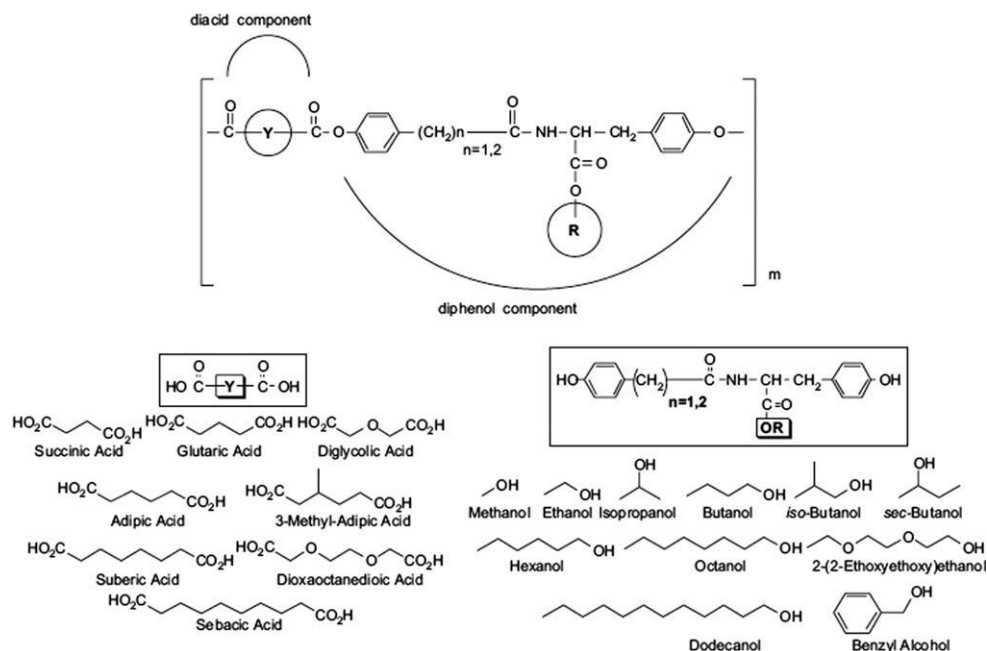


Figure 1 Combinatorial library of 112 polyarylates. Symbol Y represents one of eight diacids (left) and symbol R represents one of 14 tyrosine-derived diphenols (right). The number of methyl groups in the diphenol is also variable ($n = 1$ for HTR, $n = 2$ for DTR).

Therefore, it seems reasonable to speculate that the thermal history and the degree of physical aging experienced by the test specimen are additional fabrication-dependent parameters that may contribute to variability during water uptake studies. The published data does not offer consistent conclusions: While Akele et al.²⁶ showed that physical aging does not affect the water diffusion behavior into polycarbonate films, Surana et al.²⁷ demonstrated that physical aging decreases the rate and extent of water uptake by trehalose samples, and Loo et al.²⁸ observed that long annealing periods increase the water uptake of PLGA films.

The effect of a polymer's molecular weight (M_w) on water uptake studies is not fully understood. The few published studies examining the effect of M_w on water uptake indicate that the effect of M_w is unpredictable, i.e., reducing the M_w of the test polymer can result in either higher^{29,30} or lower water uptake.^{31,32} To investigate these topics, we evaluated the effects of sample annealing, and initial M_w on water uptake and degradation behavior.

A limited number of experimental methods have been used to measure water uptake, the most common being gravimetric analysis^{33,34} and thermogravimetric analysis (TGA).³⁵ In addition, the use of ^3H -radiolabeled water ($^3\text{H}_2\text{O}$) had been explored for both polymers^{17,36} and other materials.^{37,38} After incubation, the sample's degree of radioactivity indicates the sample's degree of hydration. This method is particularly suitable for measuring very small amounts of water uptake. Radioactive water has also

been used to determine the transport of vapor water through polymer films³⁹ and water permeation through a polymer using a Franz-diffusion cell.⁴⁰ Even though this method is generally described as straightforward, fast, and sensitive, it is not commonly used to characterize polymer systems. Hence, thermogravimetric analysis was used to validate the radioactive water method for water uptake investigations.

Among the tyrosine-derived polyarylates,⁴¹ earlier water uptake studies demonstrated that some polymers exhibited highly reproducible measurements, while other polymers consistently demonstrated highly variable water uptake data. This group of structurally-related polymers was selected for this investigation of water uptake methods because they displayed inconsistent levels of variance in water uptake and they have demonstrated potential use in medical applications such as bone pins,⁴² hernia repair devices,⁴³ and self-assembled nanoparticles for drug delivery.⁴⁴ The library of L-tyrosine-derived polyarylates consists of A-B-type copolymers having an alternating sequence of a diphenol and a diacid (Fig. 1).⁴⁵ This library was obtained by copolymerizing 14 tyrosine-derived diphenols with eight aliphatic diacids in all possible combinations resulting in 112 distinct polymers. Changes in polymer backbone or pendent chain length affect polymer properties such as T_g and surface hydrophobicity.⁴⁶

Suarez et al.^{47,48} studied the hydration of a series of polymers from this library by means of measuring thermally stimulated depolarization currents

showing that water is tightly bound to the amide carbonyl group and loosely bound to the ester carbonyl group in the pendent chain of the diphenol moiety. They observed that polymer packing was affected by hydration, with increased density associated with more hydrated states. Water fills in polymer-free volume and probably disrupts the inter-chain amide-hydrogen bond networks, enhancing polymer packing. The final motivation for this study is to build upon this prior work and to explore the structure–property relationships of a combinatorial library of polymers with respect to their water uptake behavior.

EXPERIMENTAL

Nomenclature

DTR, desaminotyrosyl-tyrosine alkyl ester: R = methyl (M), ethyl (E), isopropyl (iP), butyl (B), isobutyl (iB), *sec*-butyl (sB), hexyl (H), octyl (O), dodecyl (D), benzyl (Bn), 2-(2-ethoxyethoxy)ethyl (G).

HTR, hydroxyacetic acid-tyrosine alkyl ester: R = ethyl (E), hexyl (H), octyl (O).

Materials

L-tyrosine-derived polyarylates were synthesized as described previously by carbodiimide-mediated solution polycondensation of a diphenol and a diacid at room temperature.⁴¹ Poly(D,L lactic acid), 100 kDa, 0.84 dL/g, was obtained from Absorbable Polymer Technologies.

General methods

The following methods were used throughout:

Film processing

Polymer films of ~ 200 μm thickness were compression molded using a Carver Press (Fred S. Carver Inc.). Each sample was placed for 5 min prior to pressing at 50–70°C above the polymer's T_g . Optimal pressing temperature was defined individually by testing this range in 5° intervals. The temperature had to be high enough for the polymer to flow and form the film, and lower than a temperature where its low viscosity prevents the film formation, in addition to potential degradation.

After equilibration, pressure was then ramped from 0 to 15 kpsi over 1.5 min, held at 15 kpsi for 1 min, and ramped to 0 pressure over 1 min. Temperature was then ramped from the pressing temperature to room temperature ($\sim 20^\circ\text{C}$) in 2 min. After reaching room temperature, the film was removed from the mold and immediately used.

Molecular weight measurements

Samples of 7 mm in diameter were incubated at 37°C in individual vials with 10 mL of PBS. The buffer was replaced every 15 days. Samples were removed from the incubator every 30 days, blotted dry and frozen before molecular weight (M_w) measurement.

M_w was measured by a gel permeation chromatography (GPC) system consisting of two PL-gel columns (10^5 – 10^3 Å pore size and 30 cm in length, Polymer Laboratories LTD) connected to a Waters 717 autosampler and a Waters 2489 detector (Waters Corp., MA). The mobile phase was tetrahydrofuran (THF) at a flow rate of 1 mL/min. The M_w was calculated relative to a set of commercially available monodispersed polystyrene standards (Waters Corp., MA). The degree of polymerization (DP) was calculated by dividing the number average molecular weight (M_n) by the molecular mass of one repeating unit of each polymer.

Glass transition temperature measurements

The T_g was determined by differential scanning calorimeter (DSC 910, TA Instruments, Inc). The temperature profile was: ramp from -55 to 150°C at $10^\circ\text{C}/\text{min}$, isothermal for 2 min at 150°C , ramp from 150°C to -55°C at $10^\circ\text{C}/\text{min}$, isothermal for 1 min at -55°C , and -55 to 150°C at $10^\circ\text{C}/\text{min}$. The wet and dry T_g 's were determined from the first and second heating scan, respectively, by the half C_p extrapolated tangent method, as shown in Figure 2.

Water uptake by thermogravimetric analysis

Samples of 1 cm in diameter were immersed in different vials with 7 mL of water and stored at 37°C. After 1, 2, 3, and 4 weeks of incubation, the respective samples were removed from the vials, blotted dry, cut to squares of ~ 5 mm \times 5 mm, and placed into the thermogravimetric analyzer (TGA 2950, TA Instruments). The samples were equilibrated at 30°C and then ramped to 200°C at a rate of 7°C/min. As determined earlier by Brochini et al.,⁴⁹ all polymers from this library have a decomposition temperature above 300°C, and thus the polymer sample does not undergo decomposition during this technique. Measurements were taken in triplicate (three samples, each from a different film) at each time point.

Water content was measured using the following equation:

$$\text{WU}(\%) = 100 \cdot \frac{M_{\text{loss}}}{M_{\text{dry}}} - \text{WU}_0, \quad (1)$$

where M_{loss} is the change in mass of the sample between 30 and 140°C and M_{dry} is the (steady state)

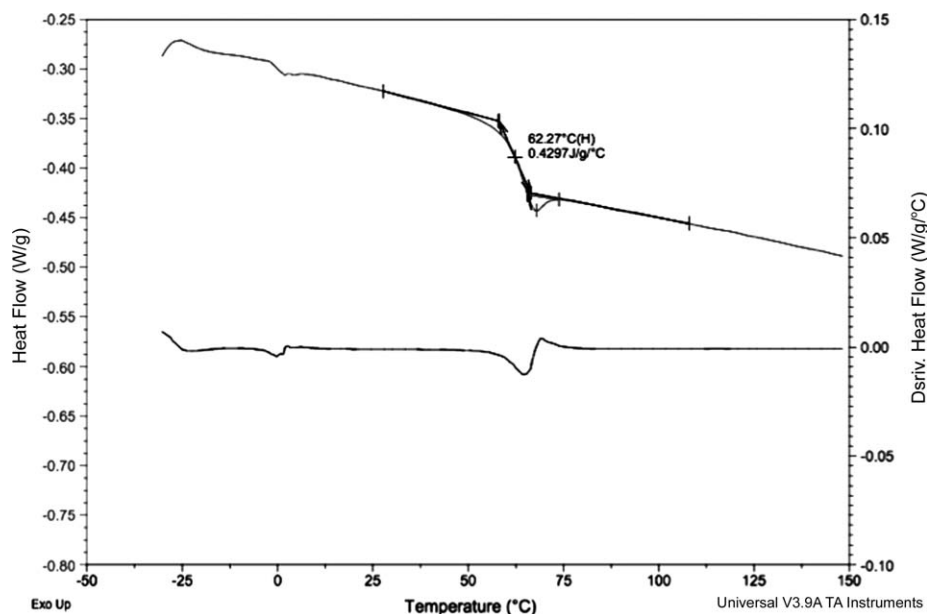


Figure 2 Example of DSC (second run) measurement for poly(DTB succinate) before incubation.

mass measured by the TGA at $> 140^{\circ}\text{C}$. Since polymer films contain some water from ambient humidity, baseline water content (WU_0), measured without incubation, was subtracted.

Water uptake by ^3H -radiolabeled water ($^3\text{H}_2\text{O}$)

^3H -radiolabeled water (Sigma-Aldrich) with an activity of 1 mCi/mL was diluted with HPLC grade non-radiolabeled (“cold”) water to a concentration of 0.2 $\mu\text{Ci/mL}$. Samples 1 cm in diameter were incubated in separated vials with 7 mL of $^3\text{H}_2\text{O}$ (0.2 $\mu\text{Ci/mL}$) and then stored at 37°C . After the same incubation times, the respective sample was removed from the vial, rinsed with distilled water, blotted dry and dissolved with 3 mL of THF (VWR) and 12 mL of liquid scintillation cocktail (LSC) (Ecolite). A control curve was constructed with 0, 0.5, 1, 2, 4, and 8 μL of 0.2 $\mu\text{Ci/mL}$ $^3\text{H}_2\text{O}$ (in triplicate), 3 mL of THF, and 12 mL of LSC (linear correlation, $R^2 > 0.998$). Radioactive counts were measured using a scintillation counter (Beckmann 6500), and water content ($M_{^3\text{H}_2\text{O}}$) was calculated using the calibration curve. Water uptake (WU) was calculated as the water content relative to the original dry weight (M_{sample}):

$$\text{WU}(\%) = 100 \cdot \frac{M_{^3\text{H}_2\text{O}}}{M_{\text{sample}}} \quad (2)$$

Experiments

Effect of annealing and quenching on water uptake

Films of three polymers from the library of tyrosine-derived polyarylates were used: poly(DTB succinate)

(145 ± 11 kDa), poly(DTE adipate) (127 ± 7 kDa), and poly(DTE glutarate) (80 ± 1 kDa). Also, poly(D,L lactic acid) (100 kDa) films were used as control experiments for an amorphous polymer used for similar applications. Films were pressed as described above and they were then either quenched by cooling to room temperature ($\sim 20^{\circ}\text{C}$) in 1 min or annealed at $5\text{--}10^{\circ}\text{C}$ above T_g for at least 20 h (Table I). Water uptake was measured using $^3\text{H}_2\text{O}$, after 3 or 5 days of incubation in $^3\text{H}_2\text{O}$ at 37°C . These early incubation times were selected to avoid mixing the effect of annealing with the onset of degradation. Before 5 days, there is no degradation of these polymers as shown in Figure 3. Water uptake measurements were performed using either water or labeled water instead of PBS, to avoid the effect of the ions present in the PBS and isolate the effect of polymer processing in water uptake.

A minimum of five samples was taken from different areas of the film. Plots of measured water uptake versus distance from the center of the film were used to evaluate film heterogeneity (Fig. 4), and the relative standard deviation of the average of all measurements on each film provided a further (quantitative) indication of the effect of sample preparation.

Effect of initial M_w on water uptake

The effect of the M_w was studied by measuring the water uptake profiles of two poly(DTiP adipate) films of different initial M_w 's. The M_w 's measured after annealing and prior incubation of these two polymer were 144 ± 2 kDa and 40 ± 1 kDa, respectively. Three films of each polymer were pressed and

TABLE I
Water Uptake After Incubation in Radioactive Water and 37°C

Polymer	T_g (°C) ^a	Pressing T (°C)	Annealing T (°C)	Days of incubation	n	Water uptake (%) ^b			
						Quenched film	rsd ^c	Annealed film	rsd ^c
poly(D,L lactic acid)	48	120	75	3	15	30.4 ± 5.2	17	35.0 ± 5.3	15
poly(DTB succinate)	67	140	67	3	15	5.8 ± 2.2	38	5.0 ± 0.8	16 ^d
poly(DTE adipate)	59	140	67	5	5	17.9 ± 1.1	6	14.3 ± 1.3 ^e	9
poly(DTE glutarate)	64	100	67	5	5	15.4 ± 1.0	6	15.1 ± 0.6	4

^a Glass transition temperatures are single measurements of polymer before pressing ±1°C.

^b Samples were taken along a film that was quenched or annealed. Each value is the mean value of n samples from the same film ± SD.

^c Relative standard deviation is the SD over the mean value.

^d Annealing significantly reduces variability on water uptake of poly(DTB succinate) at $P < 0.0001$.

^e Quenched and annealed for poly(DTE adipate) are different at $P < 0.0001$.

annealed at 63°C, 8°C above T_g for 20 h. Water uptake was measured using $^3\text{H}_2\text{O}$, after 6 h, 12 h, and 1, 2, 3, 4, 7, 14, 21, and 28 days of incubation in $^3\text{H}_2\text{O}$ at 37°C.

Comparison of methods to measure water uptake

Poly(D,L lactic acid) (100 kDa) films were used as control samples to validate and compare the two methods for water uptake, TGA ($n = 4$) and $^3\text{H}_2\text{O}$ ($n = 10$). An ANOVA statistical test was used to compare the uptake values obtained from the two methods, while the relative standard deviation was used to evaluate their reproducibility.

Water uptake measurements of tyrosine-derived polyarylates

Water uptake was measured for a subset of 24 polymers of the library of L-tyrosine-derived polyarylates

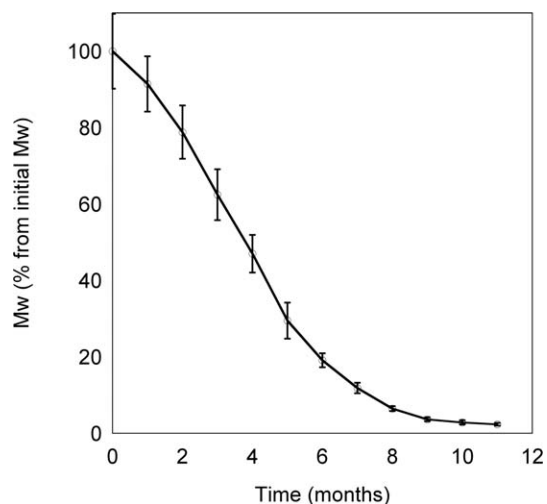


Figure 3 Degradation profile of poly(DTB succinate) incubated in phosphate buffer saline at 37°C. Each value is the mean value of three samples from three different films ± SD.

(Table II). Three films of each polymer were pressed using the previously described protocol and annealed for at least 20 h at 5 to 10°C above their T_g . Following the $^3\text{H}_2\text{O}$ method described before, water uptake was measured for 6 h, 12 h, and 1, 2, 3, 4, 7, 14, 21, and 28 days after incubation. Wet T_g was measured for the same times by DSC, as described earlier.

RESULTS AND DISCUSSION

Effect of annealing and quenching on water uptake

Results for the four polymers studied to evaluate the effect of sample annealing on water uptake are summarized in Table I. Quenched films of poly(DTB succinate) presented high variability (rsd of 38%), while the annealing poly(DTB succinate) films reduced the rsd to 16% ($P < 0.0001$). When plotting the water uptake versus the distance from the center of the film, Figure 5, it is clear that there is a spatial dependence of water uptake. Beyond 15 mm from the center of the film, the variance and mean of water uptake values increases. However, annealing for more than 20 h eliminates the spatial dependence of water uptake without changing the average water uptake value.

The other three polymers, poly(DTE glutarate), poly(DTE adipate), and poly(D,L lactic acid), did not demonstrate spatial variation in water uptake nor significant difference in rsd between the quenched and annealed films (Table I). Only poly(DTE adipate) films presented a difference in average water uptake values. Quenched films had 20% greater water uptake than the annealed films (P -value < 0.0001).

These results provide a possible explanation for the inconsistent results available in the literature, where explicit annealing protocols were not mentioned. In agreement with Hurrell and Cameron,⁵⁰

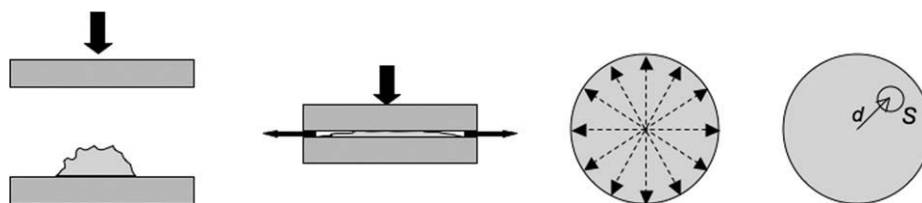


Figure 4 Pressing procedure to obtain polymer films. d is the distance of sample S from the center of the film.

our results show that including an annealing step before incubation in water can either improve or maintain the reproducibility of water uptake studies, keeping all other factors that may affect water uptake, constant. Processing all polymers in a similar way allows one to compare the results of a large polymer series isolating the effect of the polymer chemistry from its thermal history. We suggest that all test specimens should be annealed before incubation to avoid variable water uptake measurements that depend on the relative location of the sample on the polymer film.

Effect of initial M_w on water uptake

In an experiment performed using films of poly (DTiP adipate) having different M_w , the films with lower initial M_w had a higher equilibrium water content (Fig. 6) and a faster initial degradation (in a first-order kinetic model: $k = 0.4$ and 0.2 , respectively). We believe that the higher content of hydrophilic end groups in the lower M_w polymers provokes a higher driving force for water uptake, and a subsequently faster hydrolytic degradation, which will increase the hydrophilic end groups even more, in a positive feedback loop.

TABLE II
L-Tyrosine-Derived Polyarylates Used in This Study

Polymer ^a	T_g (°C) ^b	Pressing T (°C)	Annealing T (°C)	M_w (kDa) ^c	DP ^d	Water uptake equilibrium (%) ^e	Time of water equilibration
poly(HTH sebacate)	23	90	34	64 ± 5	65 ± 5	2.3 ± 0.4	1 days
poly(DTO sebacate)	16	86	37	123 ± 1	87 ± 7	2.7 ± 0.4	3 days
poly(DTO succinate)	43	160	53	84 ± 6	105 ± 19	3.5 ± 0.6	<6 h
poly(DTB succinate)	67	140	75	145 ± 11	208 ± 20	4.0 ± 0.3	4 days
poly(DTO adipate)	26	95	37	132 ± 2	111 ± 3	6.1 ± 0.3	28 days
poly(HTE adipate)	61	110	67	*	*	7.8 ± 1.1	7 days
poly(DTH suberate)	24	80	34	106 ± 2	85 ± 1	Not equilibrated	>42 days
poly(DTM sebacate)	45	115	55	126 ± 4	152 ± 8	12.3 ± 2.7	7 days
poly(DTM adipate)	67	137	77	99 ± 3	127 ± 3	14.5 ± 3.5	14 days
poly(DTB glutarate)	50	120	67	105 ± 1	89 ± 2	Not equilibrated	>42 days
poly(HTH adipate)	40	100	51	87 ± 2	93 ± 3	18.0 ± 2.1	21 days
poly(DTH adipate)	34	95	37	98 ± 1	102 ± 1	Not equilibrated	>42 days
poly(DTB adipate)	42	95	50	111 ± 3	108 ± 3	18.2 ± 1.2	21 days
poly(DTsB sebacate)	36	100	43	116 ± 3	124 ± 6	21.0 ± 1.2	21 days
poly(DTE glutarate)	64	100	72	80 ± 1	115 ± 5	29.6 ± 3.4	35 days
poly(DTiP adipate)	55	125	63	144 ± 2	193 ± 5	27.6 ± 1.0	28 days
poly(DTBn adipate)	48	125	57	69 ± 8	73 ± 8	32.2 ± 7.2	21 days
poly(DTBn methyladipate)	55	105	65	90 ± 1	56 ± 1	Not equilibrated	>42 days
poly(DTE adipate)	59	140	65	126 ± 7	169 ± 11	36.2 ± 3.2	28 days
poly(HTE succinate)	78	130	77	*	*	43.1 ± 10.6	14 days
poly(DTM (R)(+) methyladipate)	53	110	67	68 ± 1	75 ± 1	90.1 ± 8.8	7 days
poly(DTsB glutarate)	46	115	47	86 ± 3	85 ± 2	97.4 ± 4.1	21 days
poly(DTsB (R)(+) methyladipate)	45	95	45	79 ± 3	86 ± 16	136.5 ± 10.0	28 days
poly(DTB (R)(+) methyladipate)	35	85	45	61 ± 1	59 ± 4	Not equilibrated	>42 days

^a Polymers are ordered by water uptake after 28 days.

^b Glass transition temperatures are single measurements of polymer before pressing ±1°C.

^c Molecular weight: mean value of three different films ± SD. The "*" symbol indicates the polymers that did not dissolve in THF and thus, M_w could not be measured by THF-GPC.

^d Degree of polymerization: mean value of three different films ± SD.

^e Each value is the mean value of all samples after equilibration ± SD.

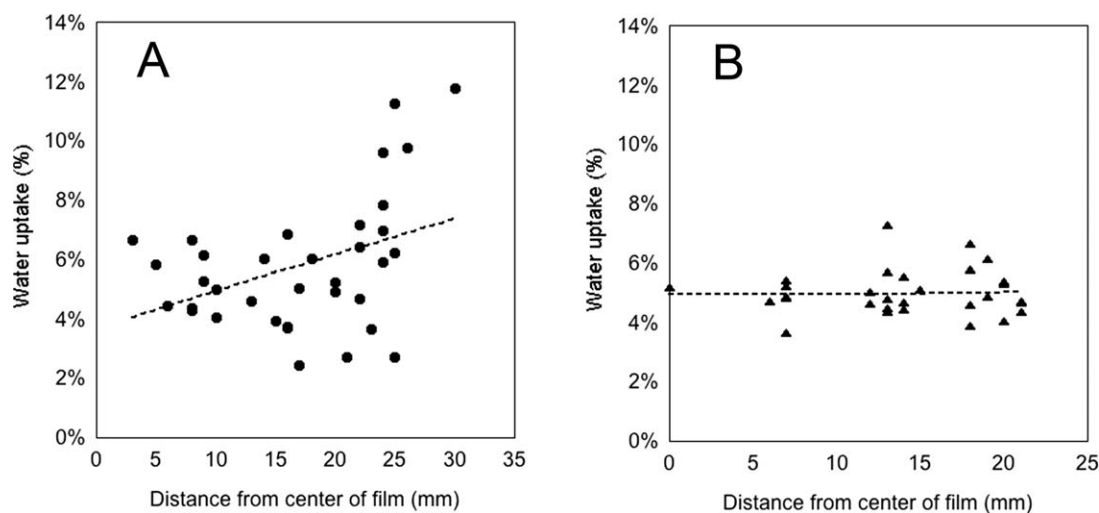


Figure 5 Water uptake after 3 days of incubation in radioactive water and 37°C of poly(DTB succinate). Samples were taken along a film that was (A) quenched (●) or (B) annealed (σ), showing reduction in water uptake variability after annealing. See also Table I.

This result was expected but not previously reported in this family of polymers. It is possible that previously reported high variability in water uptake is associated to different polymer M_w , provoking variability due to different degradation onsets. We suggest using high and comparable initial M_w polymers to study water uptake to be able to compare water uptake profiles of different polymers.

Comparison of methods to measure water uptake

For water uptake of poly(D,L lactic acid) films, the TGA and $^3\text{H}_2\text{O}$ methods were each internally reproducible, with relative standard deviation (rsd) less

than 11 and 6%, respectively. The ANOVA test showed no significant difference between the two methods (P -value: 0.75) (Table III). The advantages and disadvantages of the TGA and $^3\text{H}_2\text{O}$ methods are summarized on Table IV. The radioactive method was determined to be particularly suitable for high-throughput experimentation, since it was sensitive, simple, fast and allows for parallel measurements (30 samples per hour using a Beckman 6500 scintillation counter), while the TGA method requires serial measurements at a rate of about 1 sample per hour. This advantage is especially important when libraries of polymers are studied and many samples need to be evaluated at the same time. Thus, the $^3\text{H}_2\text{O}$ method was employed for the rest of this study.

We strongly recommend the use of the radioactive water method when studying water uptake for a large set in multiple time points and repetitions. This method is sensitive to low water content levels and it can be applied even when mass loss occurs over the sample because it is not based on final

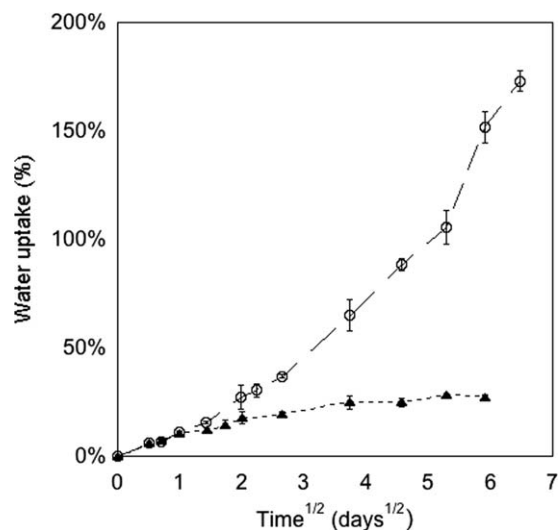


Figure 6 Water uptake profiles for poly(DTiP adipate) polymers with initial M_w of 40 kDa (○) and 144 kDa (σ). Each value is the mean value of three samples from three different films \pm SD.

TABLE III
Water Uptake for Poly(D,L lactic acid), Comparison of TGA and $^3\text{H}_2\text{O}$ Methods

Time (weeks)	Water uptake (%) by $^3\text{H}_2\text{O}$ ^{a,b}	Water uptake (%) by TGA ^{a,c}
1	67 \pm 4	57 \pm 6
2	60 \pm 4	57 \pm 6
3	53 \pm 2	50 \pm 1
4	48 \pm 2	51 \pm 2

^a Each value is the mean value \pm SD.

^b $n = 10$.

^c $n = 4$.

TABLE IV
Advantages and Disadvantages of Water Uptake
Methods: TGA and $^3\text{H}_2\text{O}$

Thermogravimetric analysis (TGA)	Radiolabeled water ($^3\text{H}_2\text{O}$)
Advantages No need to preweigh Little sample required (~ 10 mg)	Advantages Samples can be measured in parallel Only water uptake (and not initial water content) is measured Very accurate for low water uptake
Disadvantages Water content of film before incubation must be measured Samples must be immediately measured after incubation Samples must be measured sequentially (time consuming) Polymer must be thermo-stable up to 120°C	Disadvantages Administrative obstacles relating to the use of radioactive substances Controls must be run each time Generally may require larger sample size than TGA

weight but on final radioactivity content. This method is also suitable for polymers that are not stable at TGA temperatures.

Structure–property relationships for water uptake

Previous studies performed for this polymer library, showed a strong correlation between T_g and the hydrophobic nature of the polymer, where T_g increases as the number of carbon or oxygen atoms in the polymer backbone and pendent chain decreases.⁴⁵ Contrary to our initial expectations from the literature for different polymer systems,⁵¹ we

observed that water uptake (Table II) does not yield a simple correlation with the hydrophilicity of the polymer, as measured by the hydrophilic factor, as defined by Todeschini and Consonni⁵² and calculated by Smith et al.⁵³ The hydrophilic factor is a count descriptor defined as:

$$\text{Hy} = \frac{(1 + N_{\text{Hy}}) \cdot \log_2(1 + N_{\text{Hy}}) + N_{\text{C}} \cdot \left(\frac{1}{A} \log_2 \frac{1}{A}\right) + \sqrt{\frac{N_{\text{Hy}}}{A^2}}}{\log_2(1 + A)} \quad (3)$$

where N_{Hy} is the number of hydrophilic groups ($-\text{OH}$, $-\text{SH}$, $-\text{NH}$), N_{C} the number of carbon atoms, and A the number of atoms (hydrogen excluded). Overall, the trend does show that less hydrophobic polymers uptake more water, as expected, but there are significant divergences (Fig. 7). These are more pronounced at 28 days than at 1 day of incubation probably due to the presence of other factors such as the onset of degradation or conformation changes in presence of water during incubation.

Two polymers that do not follow this trend are poly(DTB succinate) and poly(HTE adipate). Their hydrophilic factors suggest higher water uptake levels than were observed. However, those polymers are in glassy state during incubation (i.e., their wet T_g remains above the incubation temperature of 37°C) (Fig. 8) and thus, their physical state prevented more water from penetrating into the polymer matrix.

Other polymers such as poly(DTM adipate) and poly(DTE glutarate) present lower water uptake than expected from their high hydrophilic factor and wet T_g below 37°C, while polymers like poly(DTM

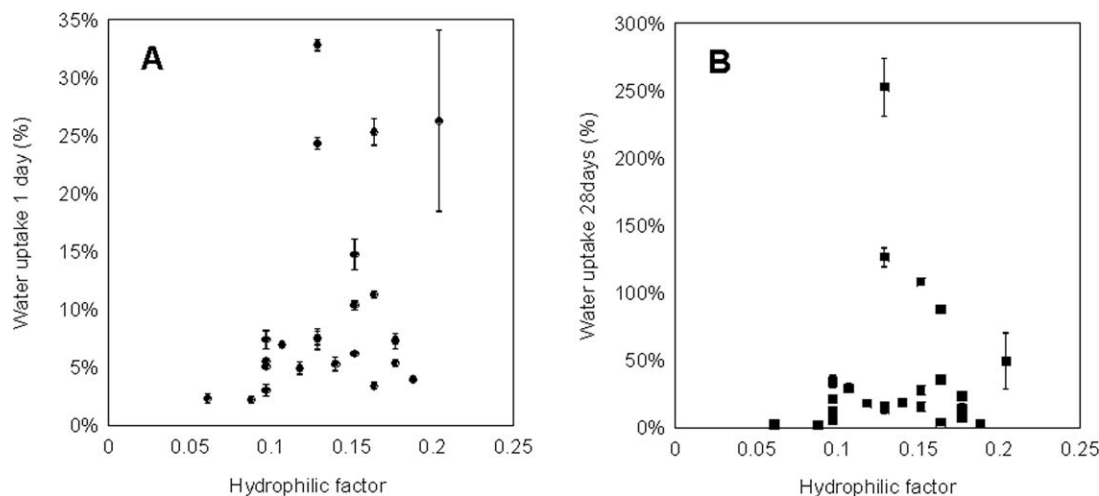


Figure 7 Water uptake after 1 day (A, ●) and 28 days (B, ■) of incubation, respectively, versus the hydrophilic factor as calculated by Smith et al.⁵² Each value is the mean value of three samples from three different films \pm SD.

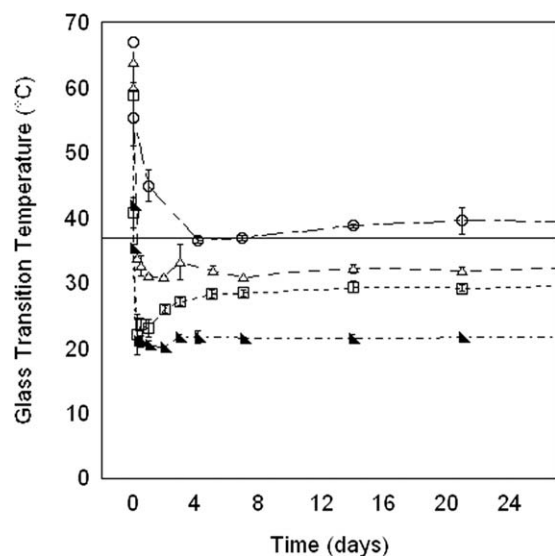


Figure 8 Glass transition temperature (T_g) for a subset of the library of tyrosine-derived polyarylates: poly(DTB succinate) (\circ), poly(DTE glutarate) (\triangle), poly(DTE adipate) (\square), and poly(DTB adipate) (\blacktriangle), in comparison with incubation temperature 37°C (—). Each value is the mean value of three samples from three different films \pm SD. Note that T_g of poly(DTB succinate) is at or above incubation temperature.

methyladipate) and poly(DTsB methyladipate) present very high water uptake with only intermediate values of hydrophilic factor. Those observations indicate the need of a more sophisticated model to understand the structure–property relationship of water uptake for this polymer library. A model built using decision tree analysis and artificial neural networks was able to accurately predict the water uptake using molecular descriptors obtained from relaxed three-dimensional polymeric structures obtained from molecular dynamic simulations of tetramers in vacuum and implicit water (manuscript submitted to Molecular Informatics).

CONCLUSIONS

The study of water uptake for a subset of L-tyrosine-derived polyarylates gave us interesting insights: polymer processing history and initial M_w , two commonly overlooked factors of a finished polymeric device, were found to be highly relevant to obtaining reproducible water uptake measurements for certain polymers. We believe that this oversight is responsible for part of the high variability observed in our previous results and other published studies. Initial polymer film characteristics affect both initial and late-stage water uptake behavior. Thus, the polymer processing techniques and the initial M_w must be controlled. In particular, an annealing step was found competent to reduce spatial variation in water

uptake in compression molded films and is therefore recommended prior to incubation to enable comparable measurements across sets of diverse polymers.

With proper attention to sample preparation, both TGA and $^3\text{H}_2\text{O}$ methods for measuring water uptake can produce satisfactory results. For investigations of large polymer sets, as in the study of combinatorial polymer libraries, the $^3\text{H}_2\text{O}$ method affords the important advantage of parallel processing, which becomes increasingly important when evaluating water uptake of 10 or more samples processed per day.

In the measurements of water uptake values for 24 polymers in the polyarylate library, it became evident that neither initial nor equilibration water uptake could be predicted by merely looking at the hydrophobic character and/or T_g of each polymer.

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