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Study of nanoscale structures in hydrated biomaterials using small-angle neutron scattering

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Abstract

Distribution of water in three classes of biomedically relevant and degradable polymers was investigated using small-angle neutron scattering. In semicrystalline polymers, such as poly(lactic acid) and poly(glycolic acid), water was found to diffuse preferentially into the noncrystalline regions. In amorphous polymers, such as poly(D,L-lactic acid) and poly(lactic-co-glycolic acid), the scattering after 7-days of incubation was attributed to water in microvoids that form following the hydrolytic degradation of the polymer. In amorphous copolymers containing hydrophobic segments (desaminotyrosyl-tyrosine ethyl ester) and hydrophilic blocks (poly(ethylene glycol) PEG), a sequence of distinct regimes of hydration were observed: homogeneous distribution (~ 10 Å length scales) at <13 wt% PEG (~ 1 water per EG), clusters of hydrated domains (~50 Å radius) separated at 24 wt% PEG (1 to 2 water per EG), uniformly distributed hydrated domains at 41 wt % PEG (~ 4 water per EG), and phase inversion at > 50 wt% PEG (> 6 water per EG). Increasing PEG content increased the number of these domains with only a small decrease in distance between the domains. These discrete domains appeared to coalesce to form submicron droplets at ~60 °C, above the melting temperature of crystalline PEG. Significance of such observations on the evolution of μm size channels that form during hydrolytic erosion is discussed.

Keywords

Hydration; PEG-containing copolymers; hydrated PEG domains; biodegradation; neutron scattering

1. Introduction

The *in vivo* performance of polymeric biomaterials is invariably affected by their interactions with water. For instance, associations between water and hydrophilic segments affect protein adsorption and cell attachment [1], plasticization by water reduces tensile strength and glass transition temperature (T_g) [2], and hydrolytic degradation affects drug release [3]. Comonomers are often introduced to control the distribution of water. Hydrophilic moieties, typically poly(ethylene glycol) (PEG), also called poly(ethylene

oxide) (PEO), are often incorporated into a polymer to increase the water uptake and accelerate degradation [3–4]. Incompatibility between hydrophobic and hydrophilic segments can lead to phase separation [5]. An understanding of the influence of phase behavior on the mechanical behavior, hydration rate and degradation is essential for designing polymers for biomedical applications.

Phase separation has been studied, for instance in block copolymers of PEG and poly(lactic acid) (PLA), by differential scanning calorimetry (DSC) and electron spin resonance spectroscopy (ESR) [6]. However, morphological changes that occur as a result of the phase separation cannot be inferred from such data. Microscopic techniques such as transmission electron microscopy (TEM) and atomic force microscopy (AFM) are powerful in directly imaging the phase behavior, but typically do not provide statistically averaged information. In contrast, small-angle neutron scattering (SANS) measurements, in which the samples are hydrated with deuterium oxide (D₂O) to provide contrast, is perhaps the only technique suitable for measuring the spatial distribution of nanometer-sized water domains in the bulk of the material averaged over ~100 nm³ volume in physiologically relevant environments [7–8]. X-ray and neutron scattering studies have been used to study the influence of PEG when it is copolymerized with poly(N-isopropyl acrylamide) [8], polyoxybutylene [9], PLA [10] and poly(ester amide)s [11]. A combination of small-angle X-ray scattering (SAXS) and SANS with confocal imaging in PLA-PEO-PLA polymers have revealed μm-sized inhomogeneities with water channels running between them [10].

In this study, we investigate the distribution of water at 10–100 nm length scales using SANS in a model hydrophobic-hydrophilic polymer, poly(desaminotyrosyl-tyrosine ethyl ester carbonate), abbreviated as poly(DTE carbonate), copolymerized with hydrophilic PEG (Figure 1). This distribution will be contrasted with those in semicrystalline and amorphous polymers. Two commonly used polymers, poly(L-lactic acid) (PLLA) and poly(glycolic acid) (PGA), served as models for semicrystalline polymers, and two other widely used polymers, poly(D,L-lactic acid) (PDLLA) and poly(lactic-co-glycolic acid) (PLGA), were used as models for amorphous polymers. Polymers based on poly(DTE carbonate) chemistry are promising materials for use in various biomedical applications such as bone implants [12] and cardiovascular stents [13]. More importantly, these polymers are a good model system because their versatile and flexible chemistry allows one to make controlled changes in composition in a large parameter space (PEG mol%, block size, iodination of tyrosine rings).

2. Experimental

2.1 Polymer synthesis and characterization

PLGA (Boehringer Ingelheim, lactic acid to glycolic acid ratio = 50:50), PLLA (NatureWorks), PGA (Sigma-Aldrich), and PDLLA (Sigma-Aldrich) were purchased and used as received. The tyrosine-derived polymers, poly(DTE-co-PEG carbonate)s and poly(I₂DTE-co-PEG carbonate)s listed in Table 1, were manually synthesized and their compositions verified using methods described previously [14–15]. A combinatorial library of poly(DTE-co-PEG carbonate) was also synthesized using an automated synthesizer (Chemspeed, Switzerland). DTE was polymerized with PEGs with six different molecular weights (100, 1,000, 2,000, 8,000, 20,000, and 35,000 Da) at three different weight percentages (20%, 30%, and 40%), giving a total of 18 unique polymers. Synthesis for each unique composition was repeated four times during the automated synthesis, for a total of 72 polymerization reactions. The combinatorial synthesis was performed using methods described previously [16]. All PEGs were purchased from Sigma Aldrich and vacuum dried for at least 24 hours before use. Compression molded films were pressed as described previously [17]. Glass transition temperature (T_g) was measured with a differential scanning

calorimeter (DSC, TA Instruments) using previously described methods [15]. Poly(DTE-*co*-PEG carbonate)s were scanned to 150 °C at a rate of 10 °C/min. Iodinated polymers with 0 and 8 wt% PEG_{1k} were scanned to 180 °C at 10 °C/min, while PLGA, PLLA, PGA, and PDLLA were scanned to 300 °C to obtain longer baselines for analysis and to identify crystalline melting features.

2.2 Water content

5 mm-diameter discs were punched from compression molded films. Two specimens of each polymer composition were measured after incubation at 37 °C in 5 mL phosphate buffered saline (PBS). PLLA, PGA, PLGA, and PDLLA were incubated for 1, 7, 14, 21, and 28 days to monitor changes in hydration properties as the polymers begin to degrade [18–19]. Poly(DTE-*co*-PEG carbonate)s, with and without iodine, that contained ≥ 25 wt% PEG were incubated in PBS for 3 and 6 h, and those with < 25 wt% PEG were incubated for 24 and 48 h to ensure that polymers were equilibrated. Surface water was dab-dried and films were heated to 350 °C in a thermal gravimetric analyzer (TGA, TA Instruments) to determine the water content. Water content is defined by the mass lost between 23 °C (room temperature) and 150 °C (where a good baseline is obtained indicating no further decrease in mass), and was calculated as a percentage using the equation:

$$(M_{wet} - M_{dry})/M_{wet} * 100\%, \quad (1)$$

where M_{wet} and M_{dry} are the masses of the polymer at 23 °C and 150 °C, respectively. Water content was also calculated as the number of water molecules per monomeric unit of ethylene glycol (EG), sometimes referred to as the hydration number.

2.3 SANS sample preparation

Powdered phosphate buffered saline (Sigma) was dissolved in deuterium oxide (Acros) to make 7.4 pH deuterated phosphate buffered saline (dPBS); PBS contains 0.138M NaCl and 0.0027M KCl. It was assumed that the interactions of the polymer with D₂O is similar to that with H₂O. Films of PLLA, PGA, PLGA, and PDLLA were incubated for 7, 14, 21, and 28 days. Poly(DTE-*co*-PEG carbonate) films with and without iodine that contained ≥ 25 wt % PEG were immersed in 10 mL dPBS for at least 6 h at ambient temperature, and those with < 25 wt% PEG were immersed for at least 48 h before testing. The films (~ 200 μm in thickness) were cut into 1 cm diameter circles, stacked 0.8–1 mm high, placed in custom-made sample holder with quartz windows, with a few drops of dPBS, and sealed with Teflon® tape to prevent water evaporation. The assembled cells were loaded into a sample changer on the variable temperature block. A temperature regulator was used to control the temperature for runs at non-ambient temperatures (37 and 60 °C).

2.4 SANS data collection and analysis

Three sets of SANS data were collected at three different sources, and these different data sets were processed such data they could be compared with each other. Data from poly(DTE-*co*-PEG carbonate)s in Table 1 were collected at the Argonne National Laboratory's spallation source using the small angle neutron diffractometer (SAND) instrument over a q range from 0.004 to 1 Å⁻¹ (q is the scattering vector; $q = 4\pi \sin(\theta/\lambda)$). Data from PLA, PGA and PLGA were collected on the SANS3 beam line ($\lambda = 6.09$ Å) at the Oak Ridge National Laboratories (ORNL) data using sample-to-detector distances of 6.5 m and 14.5 m so as to acquire data from $q = 0.006$ to 0.135 Å⁻¹ and $q = 0.003$ to 0.06 Å⁻¹, respectively. Data from poly(DTE-*co*-PEG carbonate)s with different PEG block sizes were collected on the Low-Q Diffractometer (LQD) over a q range of 0.003 Å⁻¹ to 0.5 Å⁻¹ at Los Alamos National Laboratory. Only one set of samples (used in Figure 5) were incubated and

run at 37 °C. All the other samples were incubated and run at room temperature (22–23 °C), unless otherwise indicated.

The isotropic 2D-data were reduced to 1D $I(q)$ vs. q plots, where $I(q)$ (expressed as $d\Sigma/d\Omega$ in all graphs) is the radially averaged intensity at each value of q . For PGA, the peak was fitted to a Gaussian with a linear base line. The distance between the scattering centers (D_2O rich interlamellar regions, hydrated domains) was calculated from the position of the peak maximum using Braggs law, and the integrated intensity was obtained from the area of the Gaussian peak. Data from PDLLA, PLLA and PLGA were plotted as $\log(q)$ vs. $\log(I(q))$ curves and interpreted in terms of fractals [20].

For poly(DTE-co-PEG carbonate)s, the observed intensity was least-squares fitted to a composite curve made of three components: a background, the interference peak and a central diffuse peak. The background intensity is due to incoherent scattering. The interference peaks were modeled using the Zernike-Prins approximation [21]:

$$I(q)=I_0\left\{\frac{(\sin(qR)-qR\cos(qR))}{(qR)^3}\right\}^2\left\{\frac{1-A^2}{1-2A\cos(qd)+A^2}\right\} \quad (2)$$

in which

$$A=\exp\left(-\frac{1}{20}\sigma^2q^2\right) \quad (3)$$

The scattering domains (hydrated domains) are assumed to be spherical. From this model, R , the radius of the scattering domains, d , the average distance between these domains, and σ , a measure of the deviation from the average value of d , i.e., the degree of nearest-neighbor correlation, were determined. A dimensionless parameter, fractional deviation (f_d), was calculated as the ratio σ/d , and was used as a measure of the degree of nearest-neighbor correlation. A small value of f_d indicates a narrow distribution of the distances between these domains.

In a few instances, an intense central diffuse scattering was present along with the interference peak. This could be fitted to a Guinier law from which size, the radius of gyration (R_g), of the scatterers (agglomerated hydrated domains) was estimated [22].

The changes in the intensity was followed by evaluating the invariant (Q) using the expression [23]:

$$Q=\int q^2 I(q) dq \quad (4)$$

3. Results and Discussion

Chemical structures of three of polymers, which are sufficient to describe the polymers used in this study, are given in Figure 1. Samples used in this study and some of their relevant properties are listed in Table 1. PGA and PLLA were both semicrystalline as confirmed by their respective melting peaks at 223 and 169 °C. PDLLA and PLGA were both amorphous.

Poly(DTE carbonate) and poly(I₂DTE carbonate) homopolymers were used as controls in evaluating the role of PEG, and these two families of polymers will be referred to as DTE and I₂DTE polymers, respectively. Polymers within these two classes of polymers will be further identified by the amount of PEG (wt%) and the size of the PEG block (nk , molecular

weight in kDa). For example, poly(DTE-co-41% PEG_{1k} carbonate) will be abbreviated as DTE-41% PEG_{1k}, and poly(I₂DTE-co-70% PEG_{2k}) will be abbreviated as I₂DTE-70%PEG_{2k}. In this study, wt% rather than mol% of PEG is used to identify the different polymers because wt% PEG is more meaningful in comparing the water uptake and the scattering intensities from samples with different PEG block sizes. PEG content in mol% is also listed in the Table. It should be noted that these are not diblock or random copolymers. Rather, these are random, multiblock copolymers in which PEG is inserted as a block of consecutive ethylene glycol units, and varying number DTE units occur between the PEG blocks.

In presenting and discussing the results, semicrystalline polymers will be discussed first, followed by amorphous homopolymers, and the amorphous, PEG-containing copolymers will be discussed last.

3.1 Water content

The water content measurements reported here refer to the water absorbed by the polymers while immersed in PBS. Because the objective was to determine the behavior of these polymers in a biological environment, saline is a more appropriate medium than water. dPBS was used for SANS measurements. We assumed that water uptake would be the same with H₂O and D₂O.

The water content values in PGA, PLLA, PDLLA, and PLGA at various time-points up to 28 days are given in Table 2. Water uptake in PLLA was minimal during the 28 day incubation period, consistent with previously reported results [24–25]. The water content in PGA, PDLLA, and PLGA increased by a large value after 14 days in PGA and PDLLA, and after 21 days in PLGA during incubation. The sudden jump in water content is indicative of the morphological changes that allow water to infiltrate the samples. In some samples, this time point corresponds to the onset of accelerated degradation [18, 26]. The amorphous PDLLA and PLGA also undergo significant degradation during 28 days of incubation [18].

The water contents in DTE and I₂DTE polymers are given in Table 1. An increase in the PEG wt% results in a polymer with lower T_g and higher water uptake [15]. At > 40 wt% PEG, polymers are increasingly soft and gel-like, and the high water content is reached quickly in less than 1 h [15]. At lower PEG concentrations, polymers are relatively strong and rigid, and the low water content prior to degradation is reached over a longer period of time [15]. We also noticed that use of PEG_{2k} instead of PEG_{1k} permits measurements to be made at higher PEG wt%: DTE-PEG_{1k} dissolves in water at about 60 wt% PEG, whereas DTE-PEG_{2k} is insoluble even at 70 wt% PEG.

An interesting point to note in the water uptake values is that at the same wt% PEG poly(DTE-co-PEG carbonate)s with smaller PEG blocks absorb less water than those with larger PEG blocks, as seen by comparing DTE-41wt% PEG_{1k} and DTE-41wt% PEG_{35k} in Table 1. The increase in the water content with larger PEG block from 42 wt% in PEG_{1k} to 56 wt% in PEG_{35k} could be because the connectivity in the longer PEG segments will be different than in the short ones. The short segments are isolated and more frequently surrounded by hydrophobic DTE segments, and thus take up less water. The longer PEG segments, on the other hand, are segregated into larger blocks (see section 3.4.1), interact less frequently with DTE segments, and are therefore able to absorb more water. Another explanation emerges when the water uptake in PEG₁₀₀ is considered. DTE-40% PEG₁₀₀ absorbed 17 wt% water (1.2 water per EG) compared to 42 wt% in DTE-41% PEG_{1k} (4.4 water per EG). This could be because the water uptake is determined by number of ether oxygens in the PEG segments, which is (n-1), where n is the number of repeat units in PEG. Thus, while PEG_{1k} (23 repeat units) has 22 ether oxygens, 10 units of PEG₁₀₀ have only 10

ether oxygens. The role of ether oxygen in determining the water absorption might be of consequence in protein adsorption studies.

3.2 PGA and PLLA

Scattering curves from dry PGA showed an interference peak at $q = 0.062 \text{ \AA}^{-1}$ ($d = 102 \text{ \AA}$, Figure 2) [27]. This peak arises from the inherent contrast between the amorphous and crystalline regions in the lamellar structure. As the amount of water absorbed by the polymer increases, the scattered intensity, both of the central diffuse scattering and the interference peak, first decreases, and then becomes more intense than in the dry sample. This sequence of changes is due to the preferential diffusion of water into the amorphous regions of this semicrystalline polymer. Water that diffuses into the amorphous regions outside the lamellar stack has no effect on the peak intensity, but water that diffuses into the amorphous regions between the lamellae contributes to the changes in the peak profile [7]. At water uptake between 3 and 20%, the peak intensity decreases (represented as a decrease in the invariant in Figure 2) as the D_2O diffusing into the interlamellar regions provides a contrast match between the hydrated amorphous regions and the crystalline regions. A further increase in water uptake increases the contrast between these two regions above that of the dry polymer, resulting in a higher peak intensity. The reduction in domain spacing at larger water content at longer times of immersion in water is likely due to hydrolytic degradation of the polymer. Multiple data points (squares) at similar water uptake values represent multiple samples taken at ~21% water content (14 days incubation). The points at ~28% water content correspond to 21- and 28-day time points indicating changes in the sample morphology with time while the water content remained unchanged.

Water uptake in PLLA was negligible. Correspondingly, the scattering was weak and was not analyzed. Although PLLA is semicrystalline like PGA, it is more hydrophobic, and therefore, unlike in PGA, even the less densely packed amorphous domains are impermeable to water.

3.3 PDLLA and PLGA

These two polymers showed no interference peaks in their scattering patterns. Unlike PGA, these polymers are amorphous and do not phase separate. Therefore, there are no regions in the polymer matrix that preferentially absorb water and give rise to the scattering contrast.

Figure 3a shows the scattering curve obtained from PDLLA at several time points. These data did not show any Guinier region. Therefore, the data were analyzed by plotting them as $\log I(q)$ vs. $\log(q)$ as shown in Figure 3b. These plots are linear over the entire observed q range. The slope of such a plot, the Porod exponent, is related to the fractal dimension of the scattering domains [20]. For a 3D object, a Porod exponent of 1 to 3 represents a mass fractal, 3 to 4 a surface fractal, and an exponent of 4 indicates a smooth interface between the phases. These characteristics refer to structure at length scales of 100 and 2000 $\text{\AA}$, the upper and lower limits of the data in Figure 3b. There was no scattered intensity in the dry sample. The Porod exponent in PDLLA was 3.6 at 7 days of hydration at room temperature and reached a plateau value of 4 after 14 days. At 67 $^{\circ}\text{C}$, this plateau value of 4 was observed as early as 7 days. The scattering observed in samples at > 7 days of incubation can be attributed to the surface scattering from microvoids created as the polymer erodes. We note that an increase in the Porod exponent is accompanied by a corresponding increase in SANS intensity (Figure 3a) consistent with the formation of microvoids. A fractal of 3.6 is indicative of the rough void surface. The increase in the Porod exponent to 4.0 with time suggests that as the polymer erodes the surfaces of these pores become smooth. A Porod constant was calculated from the plateau of the Porod low plot ($I q^4$ vs. q). This constant

almost doubled from the 7-day time point to the 28-day time point, consistent with the suggestion that new surfaces are formed due to microvoids formed during degradation.

PLGA shows a behavior similar to that of PDLLA. The Porod exponent increases from 3.5 to 3.9 during the initial stages (0 to 1 wt% water uptake), and then remains essentially unchanged up to ~ 33 wt% water uptake. It appears that the only signature of water uptake in these polymers is the formation microvoids that results from the hydrolytic degradation of the polymer that occurs within a few days, the actual duration depending on the thickness of the film.

3.4. Poly(DTE-co-PEG carbonate)s

Figure 4a shows the SANS scans from a series of non-iodinated polymers with different amounts of PEG. No interference peaks are seen in the 0 and 13 wt% PEG_{1k} polymers even after immersion in dPBS for several days. Since DTE is aromatic, its lower H:C ratio results in a higher neutron scattering length density than for dry PEG. Despite this contrast, no interference peak was observed in dry samples. Thus, consistent with the conclusion based on SAXS data [28], there is no phase separation in the dry samples. The absence of any scattering in the wet sample could be because at ~ 0.9 D₂O molecules per EG monomer hydrated PEG will match DTE in scattering contrast. However, absence of an interference peak in the SAXS data in a 12.5 wt% PEG (measured for the iodinated polymer in [28]), suggests that the absence of an interference peak in SANS is not due to a contrast-match between D₂O-PEG complex and DTE, but due to the homogeneous distribution of water throughout the bulk in low-PEG polymers. The scattering could be fitted to a random distribution domains of radius ~ 7 Å in the Zernike-Prins model. Fitting parameters are given in Table 3. The significance of this small radius is simply that water under these conditions is molecularly dispersed in the polymer matrix.

An interference peak (at $q \sim 0.03 \text{ \AA}^{-1}$) appears beginning with the DTE-24 wt% PEG_{1k} polymer. The inter-domain distances in the DTE-24% PEG_{1k}, DTE-41% PEG_{1k}, DTE-50% PEG_{2k}, DTE-71% PEG_{2k} polymers are 138, 148, 128 and 106 Å, respectively. The diameter of these domains, obtained by fitting the observed scattering to the Zernike-Prins model, is $49 \pm 3 \text{ \AA}$. Because these polymers are amorphous, the interference peak is not due to the presence of crystalline and amorphous domains as in PGA, but indicates the formation of hydrated domains with interdomain spacing of 110 – 150 Å. Since water associates preferentially with PEG, the conclusion is that the hydrated domains are the result of entrapment of water (D₂O) in the of hydration-induced microphase-separated PEG-rich regions [28]. As shown in Table 1, the number of water molecules per EG segments ranges from 1 to 19. The number of water molecules per EG unit, the hydration number, depends on the molecular weight of PEG, and ranges from 1.6 to 3.3 in a PEG homopolymer [29]. A hydration number of 1.5 has been reported for poly(propylene glycol) [30], and in general ranges from 3 to 7 per monomeric unit for a variety of anionic and cationic polymers [31]. Our results show that PEG-poor and PEG-rich domains begin to appear in hydrated samples at PEG concentration between 13 and 24 wt%, i.e., at hydration numbers between 1 and 1.5.

Assuming the volume of a 1kDa PEG to be ~ 1.5 nm³ (7 nm length and 0.5 nm diameter [32]), the distance between PEG blocks when PEG segregates into domains (13 wt% or 15 vol% PEG) can be calculated to be ~ 25 Å. This is about twice the diameter of a 1 kDa PEG block (~ 14 Å). Thus, after taking into account the swelling of the PEG domains upon hydration, it appears that as soon as the concentration is high enough for the adjacent PEG segments to touch each other, the PEG segments and associated water molecules form a hydrated PEG domain. Below this concentration, the hydrated PEG segments are most likely homogeneously distributed throughout the polymer.

Some of the polymers, e.g., DTE-24% PEG_{1k}, had intense central diffuse scattering (Figure 4a). This scattering can be explained by postulating that as water initially diffuses into the polymer matrix, it forms hydrated domains that agglomerate into clusters. The central diffuse scattering corresponds to the form factor of the cluster ($R_g \sim 300$ Å), and the discrete hydrated domains ($R \sim 50$ Å) within the cluster give rise to the interference peak. This is schematically illustrated in Figure 4c. At larger PEG contents, as these domains fill the entire sample volume, and the central diffuse scattering becomes weak. These discrete domains could be the precursors of the water channels that facilitate the erosion of the polymer. An AFM study of the morphology in a segmented block copolymer with PEG as one of the blocks in a chain of crystallizable tetra-amide segments showed that the polymer swells inhomogeneously and the surfaces have 10–50 nm high and 100 nm wide clusters [33]. In our study the PEG is incorporated into a noncrystallizable main-chain, and shows much smaller hydrated clusters.

3.4.1 Effect of PEG concentration and block size—As discussed in the previous paragraph, hydration induces PEG domains to phase-separate only above 13 wt% PEG_{1k}. PEG molecular weight (block size) also determines water uptake and phase behavior. No interference peak or excess scattering was observed with PEG₁₀₀ even up to 40 wt%. This indicates that even though PEG phase separates when the molecular weight is 1 kDa, at the same wt% PEG, 100 Da PEG segments do not form separate hydrated domains.

Data summarized in Figure 5 show that, as expected, the radii of the domains and the distances between the domains increase with an increase in PEG block molecular weight. This is further illustrated with the scattering data from one pair of these polymers with DTE-41 wt% PEG and block sizes of 1 and 35 kDa (Figure 4b). The data show that as the PEG molecular weight increases, the domains become larger, are spaced farther apart, and the distribution of these distances is also broader, i.e., a decrease in short range order. The untypically large value of 0.73 for DTE-41% PEG_{35k} is indicative of large distribution in the size and the interdomain distances of the hydrated domains, probably because of the large polydispersity in the chain-lengths when large PEG blocks from commercial sources are used. The changes with PEG content in the domain radius and inter-domain distance in PEG_{1k} and PEG_{2k} are quite similar, suggesting that their phase-separated microstructures are similar. In samples with PEG size > 2 kDa, however, the domains become smaller, and the inter-domain distance decreases with PEG content. The decrease in the inter-domain distance suggests that the number of domains increases as the PEG fraction is increased within a given volume. The decrease in the size with PEG fraction is however unexpected. The large decrease in domain size with larger PEG block reflect the constraints imposed by the DTE segments on phase separation.

3.4.2 Effect of temperature—Experiments were carried out at different temperatures to understand how the distribution of water is affected by changes in the mobility of the polymer chains and the interactions between water and the polymer chains. Scattering data obtained *in situ* during heating from three polymers DTE-13% PEG_{1k}, DTE-24 % PEG_{1k}, and DTE-41% PEG_{1k} (Figure 6) show the effect of temperature on the size and the spacing of the hydrated domains on the PEG content. The only scattering in DTE-13 % PEG_{1k} polymer was the very weak diffuse scattering that was barely above the background (Figure 6a). This again suggests that DTE-13 % PEG_{1k} to be the lower limit for phase separation, and is consistent with the SAXS results [28]. This weak diffuse scattering, could be fitted to a Zernike-Prins model with 7 Å-radius particles. This scattering was not observed when the sample was heated to 60 °C, suggesting reorganization of PEG and water interactions. This reorganization is more evident at higher PEG concentrations as discussed below.

In DTE-24 % PEG_{1k} (Figure 6b), the inter-domain distance increased from 138 to 142 Å (peak shifts to a smaller q) and the intensity increased when the sample was heated from room temperature to 37 °C. This could be due to coalescence of the neighboring domains. Larger domains increase the intensity while increasing the interdomain distances. The interference is replaced by monotonically decreasing central diffuse scattering at 60 °C. The scan obtained at room temperature, 4 h after cooling from 60 °C, shows partial recovery of the starting structure. In the 41 wt% PEG_{1k} polymer (Figure 6c), we also see that the domain spacing and the peak intensity increase with temperature from 148 Å at RT to 161 Å at 37 °C, and to 192 Å at 60 °C. In contrast to the DTE-24 % PEG_{1k} sample, complete recovery was observed in this polymer upon cooling to room temperature. The difference in the recovery behavior was also observed in SAXS, and was apparent in the differences in the DSC scans upon re-heating the low-PEG content samples as well [28]. This difference in reversibility could be due to the differences in the degree of dehydration of the PEG domains upon heating to 60 °C (melting point of PEG is 40 °C). Dehydration in DTE-24% PEG_{1k} with 1.5 moles of water per EG could be greater than in DTE-41 % PEG_{1k} with 4.4 moles of water per PEG. The observation that the DTE-24 % PEG_{1k} sample (Figure 6b) was cloudy when the scans at 60 °C and RT2 were obtained and became clear after 24 h, suggests that at 60 °C, the sample underwent macrophase separation with ~ μm size domains large enough to scatter light. Therefore, the differences in the reversibility could be attributed to the difference in the extent of the macrophase separation in the two samples

The macrophase separation is also indicated by the strong central diffuse scattering that appears at 60 °C, well above the T_g of the polymer. This is the only scattering at 60 °C in Figure 6b (DTE-24 % PEG_{1k}), and this scattering is seen along with the interference peak at 60 °C in Figure 6c (DTE-41 % PEG_{1k}). Both of these scattering have a Porod exponent of 3.1. A similar exponent was calculated for the scattering curves of dry samples at similar temperatures in SAXS reported in an earlier publication (e.g., Figure 3c in [28]), in which instance it was correlated with the melting of the PEG domains. Based on this observation, and the macrophase separation noted by the opacity of the sample in figure 6b, we attribute the central diffuse scattering in Figure 6 to the surface scattering from a network of coalesced hydrated PEG domains.

3.4.3. Effect of iodine—Iodination of these polymers has a profound effect on polymer properties. The wet modulus is higher than the dry modulus in iodinated polymers with 45 to 60 vol% PEG [34] and protein-repulsive effect of PEG is negated by the presence of iodine in these polymers [35]. The known effects of iodine (it makes the polymer hydrophobic and increases the T_g , Table 1) do not explain these observations. The effect of iodination on hydration behavior was therefore explored.

The scattering from iodinated and non-iodinated polymers are compared in Figure 7. Each pair of curves shows an iodinated and non-iodinated curve with the same mol% of PEG. Iodinated polymers with 0 and 8 wt% PEG_{1k}, like their non-iodinated counterparts, showed no significant interference peak. The intensities of the noniodinated and iodinated set in Figures 7a and 7b are consistent with the water uptake listed in Table 1, but not in Figure 7c at 71 wt% PEG. We attribute the lower intensity in the non-iodinated sample, despite the higher water content, to the changes in morphology associated with phase inversion in the non-iodinated sample as described in the next section.

Another difference is the large central diffuse scattering seen in the non-iodinated sample but not in the iodinated sample (e.g., Figure 7b). As indicated earlier (section 3.4), this central diffuse scattering in the non-iodinated polymers is due to the agglomeration of water domains into clusters at PEG contents with $R_g \sim 300$ Å at low PEG contents. Absence of such central diffuse scattering and the presence of an interference peak suggest that the PEG

domains are uniformly distributed throughout the iodinated polymer matrix at the PEG concentrations investigated here. The hydrated domains in the iodinated polymers are smaller (radius: 38 ± 3 vs. 49 ± 3 Å on the average) and are closer together (20 mol% PEG_{1K}: 106 vs. 148 Å; 20 mol% PEG_{2K}: 98.8 vs. 128 Å; the 30 mol% PEG_{2K}: 75.8 vs. 106 Å) than in the non-iodinated versions. These two observations show that PEG domains are distributed differently in the non-iodinated and iodinated polymer, and therefore the PEG molecules interact differently with the main chain when the DTE segments are iodinated. This difference in the distribution of PEG segments, rather than the differences in the hydrophobicity and the stiffness of the polymer, may account for the observed differences in mechanical behavior and protein adsorption in hydrated polymers.

3.4.4. Evolution of hydrated structures—The changes in the scattering curve with hydration and temperature were interpreted by calculating the invariant Q . Q is also the product of the total irradiated volume and the square of the difference in scattering-length density, and is independent of domain shape. The invariant was evaluated over a q range of 0.06 to 0.37 Å^{-1} in the neighborhood of the peak where the intensity was significantly above the background; the intensities were indistinguishable from the background at high q values. The expectation, based on the results from polymer-solvent systems [36], was that the invariant would be correlated with the water content. However, no such correlation was found in our samples. Figure 8 shows that as PEG increases from 24 to 41 wt%, corresponding to an increase in water content from 13 to 42 wt%, the SANS intensity increases as expected. But, a further increase in PEG from 50 to 71 wt%, corresponding to a water content increase from 63 and 85 wt% causes the scattered intensity to decrease.

The decrease in the intensity beyond about 45 wt% water uptake (Figures 4a and 8) could be due to inhomogeneous swelling at higher water contents. For instance, the variable temperature data (Figure 6c) shows that the intensity of the interference peak decreases at higher temperatures (60 °C). This decrease in peak intensity is accompanied by an increase in the intensity of the central diffuse scattering. It is possible that at elevated temperatures, a fraction of the hydrated domains coalesce to form submicron size droplets and contribute to the central diffuse scattering at $q = 0 \text{ Å}^{-1}$, while the contribution of the clusters of smaller domains to the interference peak decreases.

A similar explanation does not account for the decrease in the intensity of the interference peak at higher PEG contents in Figure 4a because there is no significant change in the central diffuse scattering. A more likely explanation, illustrated in Figure 4c, is that phase inversion occurs at ~ 50 wt% PEG [37]. Below 50 wt% PEG, discrete water domains exist in a continuous DTE matrix, and an increase in PEG or water content increases the peak intensity. Above 50 wt% PEG, DTE domains are embedded in a continuous PEG/water matrix, and an increase in PEG content is accompanied by a decrease in the number of DTE domains, which decreases the scattered intensity. It is possible that transformation from hydrated PEG domains embedded in the hydrophobic DTE matrix into domains of DTE segment in hydrated PEG matrix passes through a bicontinuous phase. This interpretation was explored by calculating the invariants for various models using the expression [23]:

$$Q = 2\pi^2 \varphi (1 - \varphi) (\Delta\rho)^2 \quad (5)$$

where φ is the volume fraction of hydrated PEG, and $\Delta\rho$ is the scattering length density (SLD) contrast. If $\Delta\rho$ remains unchanged with degree of hydration, a reasonable assumption given the increase in volume, it is apparent that Q reaches a maximum at $\varphi = 0.5$, and decreases symmetrically on either side of 0.5. To consider the effect of changing $\Delta\rho$, the SLDs were calculated using the standard expressions [38] with the densities of 1.324, 1.952, and 1.122 g cm^{-3} for DTE, I₂DTE polymers and PEG, respectively [7, 39]. The observed

invariant values in Figure 8 were reproduced by assuming that water is partitioned between PEG and DTE domains, and that some PEG segments are present in the DTE domains. Thus, the phase separation is incomplete, especially in the non-iodinated samples.

3.4.5. Consequences of phase separation—The hydrated PEG domains suggested by the SANS data explains many of the bulk and surface properties of these polymers. At low PEG concentration (<13 wt%), water makes the polymer soft, and at significantly higher PEG contents (>40 wt%), the hydrated material behaves like a gel [15]. Between these two extremes, water has been shown to increase the modulus of the polymer [34]. SANS data show between water content of 13 to 24 wt %, PEG segments phase separate to form hydrated domains. Under this condition, it is possible that the applied load is transferred from one DTE domain to another, bypassing the PEG domains. The phase-separated PEG segments in the hydrated state no longer reduce the modulus of the DTE as they would in the dry state where PEG segments are integral part of the chain and hence lower the bulk modulus [40]. This is possible when the PEG domains are uniformly distributed over the entire sample, as it does in the iodinated polymers, but not when PEG domains form clusters as it does in the non-iodinated polymers.

The rate of erosion in a degradable polymer increases with increases in both water content and temperature. Based on TEM analysis of a 20 wt% PEG_{1k} non-iodinated polymer (8 mol % PEG_{1k}), Sousa et al. found that at 2 days, water and PEG are effectively homogeneously distributed at a resolution of ~ 100 Å [41]. At 12 months, erosion of PEG-rich fragments results in interconnected network of high diffusivity channels with characteristic length scales of 500–1000 Å. SANS data show that in DTE-24% PEG_{1k} polymer, the closest in our set to the DTE-20 % PEG_{1k} polymer used for TEM, the distribution of water is not homogeneous at a length scale of 100 Å even after a few hours of hydration. Instead, domains of water 50 Å in radius appear to be separated by about 150 Å. Our results suggest that water is uniformly distributed at low water contents. As the PEG wt% increases, water content also increases, which results in the nucleation of hydrated domains. Initially, these domains form clusters, and as their number increases with increase in PEG content, the domains fill the entire volume. These ~10nm size domains could be the precursors of μm-size channels that form during erosion, such as those observed by Sousa et al. [41].

These results show that SANS can be used to determine the distribution of water in the bulk of the polymer. It can be used to monitor how chemical modifications alter the penetration of water into the material such as the development of water droplets that can compromise the strength of adhesives made of hydrophobic-hydrophilic monomers [42]. Insights obtained by SANS data can advance the design of biomaterials for such applications.

Conclusions

The data presented here show that SANS is a powerful technique for characterizing and understanding the different types of distribution of hydrated domains in different polymers. Careful interpretation is required in the interpretation of the data. While the interference peak in semicrystalline polymers (PGA) is due to the selective diffusion of water into the amorphous regions between crystalline lamellae, a similar peak in random copolymers containing hydrophilic domains such as PEG (poly(DTE-*co*-PEG carbonate)s) is due to the hydration-induced phase separation of the PEG segments. The central diffuse scattering in amorphous polymers (PDLLA and PLGA) after 7-days of incubation is due to microvoids resulting from erosion of the polymer. A similar scattering in PEG-containing copolymers is attributed to the clusters of hydrated domains even in the absence of erosion. An intense central diffuse scattering at elevated temperature is due to the coalescence of the water

domains. These structures could be the precursors of the hydration channels that facilitate erosion.

In random segmented block copolymers, such as poly(DTE-*co*-PEG carbonate)s, above a critical fraction of > 15 vol% PEG, water uptake resulted in the formation of randomly distributed hydrated PEG domains separated by 100 – 150 Å. With increasing PEG content, these domains evolve into clusters, eventually filling the entire sample volume. Increase in PEG content increases the water uptake, and the hydrated PEG segments, instead of being randomly distributed domains embedded in the hydrophobic matrix, become the matrix for the hydrophobic domains.

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Figure 1.

Chemical structure of (a) $\text{poly}(\text{I}_2 \text{ DTE-co-PEG carbonate})$ s, (b) PGA, and (c) PLLA. In Figure (a), y is the mole fraction of PEG, given in Table 1 for the various polymers used in this paper. The mean total number of DTE monomers in the polymer chain was 200, as low as 52 in one sample, and as high as 482 in another sample. The nominal values of n for PEG are: 2 for PEG₁₀₀, 23 for PEG_{1k}, 45 for PEG_{2k}, 182 for PEG_{8k}, and 795 for PEG_{35k}. In Figures (b) and (c), the number of monomers (n) in PGA and PLA, are typically 600 and 800.

Figure 2. Plots of the inter-domain distance and the invariant of the scattering peak vs. water uptake for PGA. Insets: q vs. $I(q)$ graphs at selected points.

Figure 3.

(a) Scattering curves for PDLLA for different incubation times. (b) An example of a fractal plot of PDLLA (28 days of incubation) showing the fitted linear portion in the $\log(I(q))$ vs. $\log(q)$ curve,

Figure 4.

SANS data of polymers with (a) different PEG compositions and (b) different PEG block sizes. (c) Schematic illustration of the distribution of hydrated PEG domains (blue in color and dark in gray scale), and the DTE segments (pink in color and light in gray scale). Three of the curves shown in Figure 4a can be seen more clearly in Figure 7. In the scattering curves shown in this and the following figures, filled symbols are the observed data, and the solid colored lines are the corresponding fits for each data set. The error bars in all the scattering curves discussed in this paper are similar to the ones shown in this figure, which are large close to $q = 0$ and negligible at higher q values.

Figure 5.

Changes in (a) domain radius and (b) inter-domain distance for poly(DTE-co-PEG carbonates)s containing different PEG molecular weights and weight percentages. Polymers with PEG₁₀₀, which had no interference peak, are not shown in the Figure.

Figure 6.

SANS data from (a) DTE-13 % PEG_{1k}, (b) DTE-24 % PEG_{1k}, and (c) DTE-41 % PEG_{1k} at different temperatures. Labels RT1 and RT2 refer to the experiments at room temperature before and after heating, respectively. In (a), for clarity, a fit (blue line) is only provided for RT2. In (b) fit is omitted for 60 °C sample that shows macrophase separation..

Figure 7.

Comparisons in SANS interference peaks between pairs of DTE and I₂DTE polymers containing (a) 20 mol % PEG_{1k}, (b) 15 mol % PEG_{2k}, and (c) 30 mol % PEG_{2k}. Weight % of PEG for each polymer pair is indicated in the figure legends.

Figure 8.

Plots of the changes in invariant and the d-spacing of the interference peak in the non-iodinated series as a function of the wt% PEG in DTE-24% PEG_{1k}, DTE-41% PEG_{1k}, DTE-50% PEG_{2k}, and DTE-71% PEG_{2k}. The scattering curves are given in Figure 4a. Phase inversion that occurs in the sample is illustrated in the two inset figures, going from lower water content (left) to higher water content (right). Black lines in the inset figures represent hydrophobic segments, and the white lines represent the hydrophilic segments.

Glass transition temperature (T_g), melting point (T_m), and water content values for the polymers used in this study. The samples will be identified in the text by their PEG wt% (rounded to the nearest integer; calculated for the dry polymer) with their block size (in Da) shown in subscript.

Table 1

Sample composition with Weight % PEG	Mol % PEG	Vol % PEG From [27]	T_g (°C)	Water uptake (wt. %)	Water per EG(mole ratio)
Poly(DTE-co- y% PEG _{nk} carbonate)					
0 % PEG	0	0.0	96	3.0	n/a
DTE-13% PEG _{1k}	5	14.7	63	5.3	1.1
DTE-24% PEG _{1k}	10	26.7	39	13	1.5
DTE-41% PEG _{1k}	20	45.0	4.3	42	4.4
DTE-50% PEG _{2k}	15	53.6	-18	63	8.5
DTE-71% PEG _{2k}	30	73.7	-46	85	19.3
DTE-41% PEG _{35k}	0.71	45.0	-5.7	56	7.5
Poly(I ₂ DTE-co- y% PEG _{nk} carbonate)					
I ₂ DTE carbonate	0	0.0	136	1.5	n/a
I ₂ DTE-8% PEG _{1k}	5	15.9	81	2.7	0.9
I ₂ DTE-29% PEG _{1k}	20	47.4	8.9	19	1.7
I ₂ DTE-37% PEG _{2k}	15	50.4	4.2	29	2.8
I ₂ DTE-58% PEG _{2k}	30	71.0	-31	62	6.9
poly(glycolic acid)	n/a	n/a	46, 223	27	n/a
poly(lactic acid)*	n/a	n/a	57, 169	n/d	n/a
poly(D, L-lactic acid)	n/a	n/a	42	43	n/a
poly(lactic-co-glycolic acid)	n/a	n/a	44	33	n/a

* - Purchased as PLA. However, based on the large melting endotherm observed in the DSC scan, and the T_g and T_m values, it appears that it contains only about 1.2 mol% of D isomer, and hence will be labeled as PLLA. n/a – not applicable. n/d – not detected.

Table 2

Water uptake (wt%) in PGA, PLLA, PDLLA, and PLGA as a function of incubation time.

Sample	7 day	14 day	21 day	28 day
poly(glycolic acid), PGA	3.30	21.2	27.7	27.2
poly(L-lactic acid), PLLA	n/d	n/d	n/d	n/d
poly(D,L-lactic acid), PDLLA	1.87	35.5	39.9	43.3
poly(lactic-co-glycolic acid), PLGA (50:50)	0.81	1.04	29.9	32.8

n/d – not detected

Table 3

Zernike-Prins fitting parameters for poly(DTE-co-PEG carbonate)s and poly(I2-DTE-co-PEG carbonate)s

Sample with wt% PEG	Inter-domain distance (Å)*	Fractional Deviation	Zernike-Prins radius (Å)
DTE			7
DTE13% PEG _{1k}			7
DTE-24% PEG _{1k}	134	0.39	50
DTE-41% PEG _{1k}	146	0.26	54
DTE-50% PEG _{2k}	125	0.30	56
DTE-71% PEG _{2k}	107	0.43	46
DTE-41% PEG _{35k}	304	0.73	101
DTE-24% PEG _{1k} 23° C initial	144	0.37	42
DTE-24% PEG _{1k} 37° C	152	0.46	52
DTE-24% PEG _{1k} 60° C			
DTE-24% PEG _{1k} 23° C final			
DTE-41% PEG _{1k} 23° C initial	146	0.26	54
DTE-41% PEG _{1k} 37° C	155	0.40	64
DTE-41% PEG _{1k} 60° C	178	0.47	74
DTE-41% PEG _{1k} 23° C final	144	0.31	47
I ₂ DTE			6
I ₂ DTE-8% PEG _{1k}			7
I ₂ DTE-29% PEG _{1k}	107	0.33	45
I ₂ DTE-37% PEG _{2k}	100	0.33	35
I ₂ DTE-58% PEG _{2k}	79	0.32	42

* These distance are the values obtained by fitting the data to the Zernike-Prins model. These are in general lower than that obtained from the position of the peak-maximum ($q_{\max}$) using $2\pi/q_{\max}$.