



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 non-crystalline 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 (1–2 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 the 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. The significance of such observations on the evolution of micrometer-size channels that form during hydrolytic erosion is discussed.

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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 the 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 in 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 [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 (D_2O) 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 mm³ 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 micrometer-sized inhomogeneities with water channels running between them [10].

This study investigates 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 (Fig. 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),

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