Construction of a blood-compatible interface based on surface segregation in a polymer blend

Toyoaki Hirata^a, Hisao Matsuno^{a,*}, Daisuke Kawaguchi^b, Norifumi L. Yamada^c, Masaru Tanaka^d, and Keiji Tanaka^{a,e,*}

^a Department of Applied Chemistry, Kyushu University, Fukuoka 819-0395, Japan

^b Education Center for Global Leaders in Molecular Systems for Devices, Kyushu University, Fukuoka 819-0395, Japan

^c Neutron Science Laboratory, High Energy Accelerator Research Organization, Ibaraki 305-0801, Japan

^d Department of Biochemical Engineering, Yamagata University, Yamagata 992-8510, Japan
(Present Address, Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka 819-0395, Japan)

^e International Institute for Carbon-Neutral Energy Research (WPI-I2CNER), Kyushu University, Fukuoka 819-0395, Japan

*To whom correspondence should be addressed

FAX: +81-92-802-2880 TEL: +81-92-802-2879 (HM) and +81-92-802-2878 (KT)

E-mail: h-matsuno@cstf.kyushu-u.ac.jp (HM) and k-tanaka@cstf.kyushu-u.ac.jp (KT)

ABSTRACT

The technique of surface segregation was applied to prepare a bio-inert polymer interface. A small amount, 10 wt%, of poly(2-methoxyethyl acrylate) (PMEA), which exhibits excellent bio-inertness properties, fed into a matrix polymer was able to suppress platelet adhesion sufficiently to be of practical use. PMEA was effective because it was preferentially segregated at the outermost region of the polymer blend. Combining interfacial-sensitivity analyses such as the air bubble contact angle and neutron reflectivity measurements and sum-frequency generation spectroscopy with the platelet adhesion test gives a better understanding of how the bio-inert property is expressed at the water interface.

1. Introduction

Surface functionalization is of growing interest for many industrial and medical applications to enhance the value of the materials used in these fields. Thus, various chemical and physical methods to optimize surface properties have been proposed [1-16]. Blending different kinds of polymers is one such technology [4-12]. When a polymer “A” with a lower surface free energy is mixed into a different polymer “B”, “A” is preferentially partitioned into the surface. This phenomenon is called surface segregation [4-12]. Thus, if polymer “A” possesses a special function, the surface property of polymer “B” is consequently modified. This method of surface modification is quite simple and does not need special apparatus unlike other methods such as chemical reaction [1-3,13,14], corona [15,16] and plasma treatment [17,18]. The most intriguing advantage of this method is that the surface so modified is more robust because the surface segregation is driven by thermodynamics. In addition, this technique can be applied to a valuable polymer because even though a small amount of the polymer is fed into a matrix polymer, it should all be concentrated at the surface.

Previously, we applied this method to prepare a thin film, in which the outermost region was fully covered with poly(2-methoxyethyl acrylate) (PMEA) [19], a typical bioinert polymer [20-22]. Although PMEA is in a rubbery state under physiological conditions due to its low glass transition temperature (T_g), a sufficiently stable and flat PMEA surface could be constructed by adding a polymer known to be glassy, poly(methyl methacrylate) (PMMA) [19]. The enrichment of PMEA even took place at the interface with water. Using various techniques to measure interfacial-sensitivity, we have succeeded in gaining a better understanding of aggregation states and interfacial dynamics of PMEA at the water interface and learning more about the effects of the aggregation states on the bio-inert properties of PMEA [23,24]. In previous studies, the blend ratio of PMEA to PMMA was set at 50/50 (wt/wt) to ensure perfect coverage with PMEA at the outermost water interface [19,23,24]. Here, we show that a small amount of PMEA, 10 wt%, fed into PMMA was sufficient to exhibit bio-inertness at a level of practical use to enable platelet adhesion.

2. Experimental section

2.1 Materials

Polydisperse PMEA at a quality level that can be produced at the industrial scale for use in medical applications was synthesized by free-radical polymerization [19]. Commercially-available monodisperse PMMA and deuterated PMMA (dPMMA) synthesized by living anionic polymerization were used. Characteristics of the polymers determined by gel permeation chromatography (GPC) and differential scanning calorimetry (DSC) are summarized in Table 1.

Table 1. Characteristics of polymers used in this study.

Polymer	M_n^a	PDI ^b	T_g^c / K
PMEA	26k	3.23	240
PMMA	85k	1.09	401
dPMMA	93k	1.07	403

^a M_n ; The number-average molecular weight determined by GPC calibrated using PMMA standards.

^bPDI; polydispersity index determined by GPC.

^c T_g ; The bulk glass-transition temperature determined by DSC.

2.2 Film preparation

Thin PMEA/PMMA and PMEA/dPMMA blend films with a thickness of approximately 60 nm were prepared onto SiO_x substrates. The blend ratio of PMEA/(d)PMMA was adjusted to a weight ratio of 10/90 (wt/wt). These films were dried in a vacuum oven at room temperature for 24 h and subsequently annealed for 6 h at 413 K which was above the T_g of 375 (377) K calculated based on the Fox equation [25] and below the phase separation temperature of 457 (456) K calculated based on the Flory-Huggins equation [26] for PMEA/(d)PMMA blends. Phase separation did not occur for these blend films containing 10 wt%-PMEA at the temperatures employed. That is, the system was always miscible as previously reported [19].

2.3 Atomic force microscopic (AFM) observations

The surface morphology of the blend films was examined by AFM (Agilent Technologies 5500 Scanning Probe Microscope, Agilent Technologies, Inc., Santa Clara, CA, US) using an intermittent contact mode at room temperature in water. The cantilever tip used for the measurement was microfabricated from Si, and its spring constant and resonance frequency in air were $2.8 \text{ N}\cdot\text{m}^{-1}$ and 75 kHz, respectively. The tip radius was approximately 5 nm. The drive frequency used in water was 30 kHz, which was on the lower frequency side of the resonance. To avoid possible deformations of the sample surface during the observation, the ratio of the set point to the free amplitude of the cantilever was maintained at approximately 0.9 (10% damping of the amplitude of oscillation).

2.4 Contact angle measurements

The blend films were characterized at the water interface by static contact angle (θ) measurements at room temperature using an air bubble as a probe. The θ value was recorded as a function of the immersion time in water using a Drop Master 500 (Kyowa Interface Science Co. Ltd., Niiza, Japan). The first θ value was obtained immediately after film immersion into water, and the time interval between measurements was set to be 30 min up to 24 h.

2.5 Neutron reflectivity (NR) measurements

The density profile of the blend films along the depth direction was examined by NR with a SOFIA reflectometer at the Materials and Life Science Experimental Facility, Japan Proton Accelerator Research Complex (J-PARC) [27,28]. A Teflon-made reservoir filled with D_2O was mounted onto the film. The measurements were conducted in air, and then, in D_2O after pre-immersion for 24 h at room temperature, which enables the film structure to reach a *quasi*-equilibrium state. A beam of neutrons with a wavelength (λ) that ranged from 0.25 to 0.88 nm at a resolution of 3% was guided into the specimen from the quartz side. Details of our experimental setup are described elsewhere [29,30]. The

reflectivity was calculated on the basis of the model (b/V) profile along the depth direction by means of Parratt32 software, a freeware program from the Hahn-Meitner Institute (HMI). The (b/V) values of PMEA, PMMA, dPMMA, SiO₂, and D₂O used for the calculation were 1.15×10^{-4} , 1.04×10^{-4} , 7.02×10^{-4} , 3.48×10^{-4} , and $6.38 \times 10^{-4} \text{ nm}^{-2}$, respectively.

2.6 Sum-frequency generation (SFG) spectroscopy

The aggregation states of polymers and water at the interface were examined by SFG measurements [31-35]. SFG spectra were collected with visible light with a λ of 532 nm and tunable infrared (IR) beams traveling through the prism and overlapping at the interface between film and air or H₂O. The measurements were carried out at room temperature using one type of polarization combination, namely *ssp* (SF output, visible input, and infrared input). Details of our experimental setup are described elsewhere [34].

2.7 Platelet adhesion tests

Blood was drawn from healthy volunteers and mixed with sodium citrate. The platelet-rich plasma was then obtained by centrifugation [20,21]. The platelet concentration was determined by an automated hematology analyzer. Before the tests, the films were immersed in water for a predetermined time. Then, the platelet suspension was placed on each film surface at room temperature for 1 h. After washing the platelets with phosphate buffered saline (PBS), the adhered platelets were fixed by immersing the films in glutaraldehyde in PBS. Samples were freeze-dried prior to scanning electron microscopy.

3. Results and discussion

Panels (a, b) of Fig. 1 show AFM height and phase images, respectively, of the PMEA/PMMA (10/90) blend film immersed in water for 24 h. Both images were featureless, meaning that the blend

film was miscible and structurally stable without any collapse from conditions like dewetting and dissolution, even in water. Panel (c) of Fig. 1 is a sectional view along the line in panel (a). Solid circles in panel (d) of Fig. 1 show a root-mean-square surface roughness (R_{rms}) for the blend film as a function of immersion time in water. The R_{rms} values were approximately 0.31 nm and remained unchanged for 24 h, indicating that the flatness of the blend film at the outermost region could be kept at the nanometer-level, even in water.

Fig. 1. AFM (a) height and (b) phase images for the PME/PMMA blend film. (c) A sectional view along a line in (a). (d) Solid circles denote the time-dependence of R_{rms} values determined by AFM height images. Open circles denote the θ values determined by contact angle measurements using an air bubble as a probe.

While the interfacial roughening of the blend film did not occur in water, the bubble contact angle (θ) on the blend film measured in water clearly changed with increasing immersion time, as shown by open circles in Fig. 1(d). The initial θ value of $127.5 \pm 0.7^\circ$ right after water immersion slightly increased to $130.6 \pm 0.2^\circ$ after 12 h, meaning that the structural reorganization of the blend, or PME, occurred at the water interface. After 12.5 h, an air bubble could not be attached to the blend film; therefore, further measurements were truncated. The same phenomenon was observed for the PME/PMMA (50/50)

blend [24]. However, the final θ value was lower for the PMEA/PMMA (10/90) blend than for the PMEA/PMMA (50/50) blend by approximately 4° . In addition, the time before an air bubble could not attach to the blend film was later for the PMEA/PMMA (10/90) blend than for the PMEA/PMMA (50/50) blend by approximately 3 h. These differences imply that, rather than the PMEA/PMMA (50/50) blend film being fully covered with PMEA, PMMA somehow exists at the outermost region of the PMEA/PMMA (10/90) film in water after some time has passed.

To clarify this phenomenon, the density profile in the blend films along the direction normal to the surface was examined by specular NR measurements in air and D_2O . Panel (a) of Fig. 2 shows the scattering vector (q_z) dependence of NR for the PMEA/dPMMA (10/90) film in air and D_2O . The data for D_2O was offset by two decades for sake of clarity. The solid curves in panel (a) were calculated based on model (b/V) profile shown in panel (b), representing the best fit to the experimental data, shown by open circles. To simplify the fitting model, the film was divided into three layers with a Gaussian roughness at each interface, σ_i , as shown in panel (e) of Fig. 2. The layers 1 and 3 correspond to the segregation layers. Table 2 summarizes the parameters used for fitting, where t and ξ represent the total film thickness and the decay length for the preferential segregation of D_2O at the substrate interface. In general, according to the mean field approximation, the composition profile of a miscible polymer mixture in the surface region is expressed by a simple exponential decay function [36]. However, the experimental NR data obtained here did not fit well with such a function. Thus, the following (b/V) profile was adopted:

$$(b/V)(z) = \sum_{i=1}^N \frac{(b/V)_i - (b/V)_{i+1}}{2} \left\{ 1 + \operatorname{erf} \left(\frac{z - z_i}{\sqrt{2}\sigma_i} \right) \right\} \quad (1)$$

where N and z are the number of layers and the depth, respectively. The fit was judged based on the χ^2 correlation. Assuming the incompressibility of the polymer chains, the average (b/V) value for the PMEA/dPMMA blend with 9/91 (v/v) in air was calculated to be $6.49 \times 10^{-4} \text{ nm}^{-2}$. While the $(b/V)_1$ of $2.78 \times 10^{-4} \text{ nm}^{-2}$ and $(b/V)_3$ of $2.69 \times 10^{-4} \text{ nm}^{-2}$ values were much smaller than the average (b/V) value,

the $(b/V)_2$ value of $6.90 \times 10^{-4} \text{ nm}^{-2}$ was slightly larger than average. This means that the PME A component with a lower (b/V) value was enriched at both the air and substrate interfaces. As a result, the volume fraction of PME A at the air interface was estimated to be 62%, which was in good accordance with the data (61%) obtained by angular-dependent X-ray photoelectron spectroscopy [19].

Fig. 2. NR curves for (a) PME A/dPMMA and (c) PME A/PMMA blend films in air and D₂O. Open symbols denote the experimental data and solid and dotted curves are the calculated reflectivity based on model (b/V) profiles in panels (b and d) for (a and c), respectively. (e) A schematic illustration of the model used for fitting. (f) Enlarged depth dependence of $\phi_{\text{PME A}}$ and $\phi_{\text{D}_2\text{O}}$ in the blend film near the D₂O interface. The x-axis denotes the depth from the D₂O/polymer interface.

The periodicity of Kiessig fringes for the PME A/dPMMA film in D₂O became smaller than that obtained in air, indicating that the film became thicker in D₂O (Fig. 2(a)). The original thickness of 55.8 nm increased to 59.9 nm in D₂O, as shown by the t value in Table 2. This observation makes it clear that the blend film was definitely swollen by D₂O. The obtained (b/V) values for the layers 1, 2 and 3 in

D₂O were 2.79×10^{-4} , 6.89×10^{-4} and $2.63 \times 10^{-4} \text{ nm}^{-2}$, respectively (Table 2). These values can be understood by taking into account D₂O penetration into the film in addition to the interfacial segregation of PMEA. The σ_1 value at the D₂O interface was 1.4 nm and larger than the value at the air interface (0.7 nm). This means that the outermost interface became more diffused in contact with D₂O.

Table 2. Parameters used to fit experimental reflectivity curves

Blend film	Medium	$(b/V)_i / 10^{-4} \text{ nm}^{-2}$			t / nm	σ_i / nm				ξ / nm	χ^2
		$(b/V)_1$	$(b/V)_2$	$(b/V)_3$		σ_1	σ_2	σ_3	σ_4		
PMEA/dPMMA	air	2.78	6.90	2.69	55.8	0.7	1.2	2.3	0.5	-	8.0×10^{-3}
PMEA/dPMMA	D ₂ O	2.79	6.89	2.63	59.9	1.4	1.4	2.8	0.5	2.0	5.9×10^{-3}
PMEA/PMMA	air	1.05	-	-	56.9	0.6	-	-	0.4	-	5.1×10^{-3}
PMEA/PMMA	D ₂ O	1.76	1.20	1.56	61.4	1.4	1.4	2.8	0.4	2.0	4.2×10^{-3}

The NR measurement was also applied to a PMEA/PMMA film with a very similar thickness to address the depth profile of the composition in this blend film under an aqueous environment. The data are shown in panels (c and d) of Fig. 2, and the parameters used to fit the curve to the reflectivity results are collected in Table 2. Panel (f) of Fig. 2 shows the depth dependence of the volume fraction of PMEA (ϕ_{PMEA}) and D₂O ($\phi_{\text{D}_2\text{O}}$) in the blend film in close proximity to the D₂O interface by combining NR data for the PMEA/dPMMA and PMEA/PMMA blend films in D₂O.

The number computed as one minus the sum of the fractions of PMEA and D₂O corresponds to the dPMMA fraction at a certain depth. Table 3 summarizes the volume fraction of each component at the outermost interface (*i.e.* $d = 0$). The $\phi_{\text{PMEA}}(0)$, $\phi_{\text{dPMMA}}(0)$, and $\phi_{\text{D}_2\text{O}}(0)$ values were 35.6, 12.5 and 51.9 vol%, respectively, for the PMEA/dPMMA (10/90) blend film. If D₂O is not counted, $\phi_{\text{PMEA}}(0)$ is approximately 74 vol%, which was larger than the value obtained in air (62 vol%). That is, the segregation of PMEA to the outermost region in the film was enhanced due to contact with D₂O. However, unlike the PMEA/dPMMA (50/50) blend, in which the outermost region was completely covered with PMEA, 12.5 vol%-PMMA existed at the outermost region in the PMEA/dPMMA (10/90) blend film. This is consistent with the results of the air bubble contact angle measurements described

above.

Table 3. The volume fraction of each component at $d = 0$ in D_2O .

Blend ratio (wt/wt)	$\phi_{PMEA}(0)$ / vol%	$\phi_{dPMMA}(0)$ / vol%	$\phi_{D_2O}(0)$ / vol%
10/90	35.6	12.5	51.9
50/50	44.5 ^a	0 ^a	55.5 ^a

^a The data are reported in a previous study [21].

Fig. 3 shows the SFG spectra representing local conformation of the PMEA/PMMA blend films at the air and H_2O interfacial regions obtained with the *ssp* polarization combination, representing the information along the direction normal to the interface [24,31-35]. While a strong peak in the range of $2800-2900\text{ cm}^{-1}$ attributed to the stretching vibration of the C-H bonds in the PMEA and PMMA chains was observed at the air interface, this signal became weaker as the immersion time in water increased, implying that the polymer chains of the blend film at the interface were not very ordered in water.

Fig. 3. SFG spectra for the PMEA/PMMA blend film at the air and H_2O interfaces with the *ssp* polarization combination. For the H_2O interfaces, spectra were obtained immediately and at 24 h after water immersion.

Signals observed in the range $3000-3800\text{ cm}^{-1}$, which were attributed to the stretching vibration of O-H bonds reflecting the state of water molecules under our experimental conditions, strongly depended on the surrounding environment [31,32]. At the air interface, a very broad and weak peak, which might be derived from the adsorbed water from the atmospheric environment, was observed. However,

unfortunately, further discussion about the water structure based on this spectrum would be difficult due to the low intensity of the signal. On the other hand, a clear peak around 3200 cm^{-1} , which was attributed to ordered water (relatively highly coordinated water) was immediately observed after water immersion [24,37,38]. When the polymer blend was immersed in water for 24 h, the intensity of such a broad peak became weaker, and other peaks appeared at higher wavenumber regions in the range of $3600\text{--}3800\text{ cm}^{-1}$, which corresponds to a disturbed-network structure of water manifesting as dangling O-H ($\sim 3600\text{ cm}^{-1}$) and free O-H ($\sim 3740\text{ cm}^{-1}$), for example [31,32,39]. As previously reported, these lower coordinated or free waters are key to suppressing platelet adhesion on the polymer interface [23,24]. Although the $\phi_{\text{PMEA}}(0)$ value was lower for the PMEA/PMMA (10/90) blend than for the PMEA/PMMA (50/50) blend by approximately 9 vol%, water molecules at the interface were effectively disturbed.

Fig. 4. Number of platelets (N_{PLT}) adhered to the various films with different water pre-immersion times. Bars show the average counts with standard deviation ($n = 3$). *, $P < 0.1$ (Student's t -test).

Finally, we come to the platelet adhesion behavior, often used as an indicator of the blood-compatibility of materials, for the PMEA/PMMA (10/90) blend film in water [18,21,23,24]. Fig. 4 shows the number of platelets (N_{PLT}) adhered on the PMEA/PMMA (10/90) blend film at the water interface as a function of the pre-immersion time in water before the platelet adhesion tests. Interestingly, while a relatively large number of platelets adhered for the blend film without pre-immersion in water, the N_{PLT} values clearly decreased with increasing water immersion time. That is, the suppressibility of platelet adhesion increased with immersion time. The level of suppression was

comparable to that for a homogeneous PMEA film as previously reported [24]. Thus, these results showed that only 10 wt% PMEA in the blend film was sufficient to express excellent blood-compatibility at the water interface.

4. Conclusions

We demonstrated that a small amount of PMEA (10 wt%) blended in a PMMA film was segregated to the water interface and showed excellent blood-compatibility comparable to that of a homogeneous PMEA film. These results convince us that this simple surface modification method based on thermodynamically-driven segregation will contribute to the development of an increasing number biomedical devices requiring highly advanced functionalization.

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