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**Surface Pressure–Area Mechanics of Water-Spread
Poly(ethylene glycol)-Based Block Copolymer Micelle
Monolayers at the Air–Water Interface: Effect of
Hydrophobic Block Chemistry**

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1 Surface Pressure–Area Mechanics of Water-Spread Poly(ethylene
2 glycol)-Based Block Copolymer Micelle Monolayers at the Air–Water
3 Interface: Effect of Hydrophobic Block Chemistry

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Abstract

Amphiphilic block copolymer micelles can mimic the ability of natural lung surfactant to reduce the air–water interfacial tension down close to zero and prevent the Laplace pressure-induced alveolar collapse. In this work, we investigated the air–water interfacial behaviors of polymer micelles derived from eight different poly(ethylene glycol)(PEG)-based block copolymers having different hydrophobic block chemistries to elucidate the effect of the core block chemistry on the surface mechanics of the block copolymer micelles. Aqueous micelles of about 30 nm in hydrodynamic diameter were prepared from the PEG-based block copolymers via equilibrium nanoprecipitation and spread on water surface using water as the spreading medium. Surface pressure–area isotherm and quantitative Brewster angle microscopy measurements were performed to investigate how the micelle/monolayer structures change during lateral compression of the monolayer; widely varying structural behaviors were observed, including wrinkling/collapse of micelle monolayers, and deformation and/or desorption of individual micelles. By bivariate correlation regression analysis of surface pressure–area isotherm data, it was found that the rigidity and hydrophobicity of the hydrophobic core domain, which are quantified by glass transition temperature (T_g) and water contact angle (θ) measurements, respectively, are coupled factors that need to be taken into account concurrently in order to control the surface mechanical properties of polymer micelle monolayers; micelles having rigid and strongly hydrophobic cores exhibited high surface pressure and high compressibility modulus under high compression. High surface pressure and high compressibility modulus were also found to be correlated with the formation of wrinkles in the micelle monolayer (visualized by Brewster angle microscopy). From this study, we conclude that polymer micelles based on hydrophobic block materials having higher T_g and θ are more

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1 suitable for surfactant replacement therapy applications which require the therapeutic surfactant to
2 produce high surface pressure and modulus at the alveolar air–water interface.

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4 **Keywords:** block copolymer micelles, surface mechanical properties, Brewster angle
5 microscopy, water contact angle, glass transition temperature

6

1 Introduction

Nature uses mixtures of lipids having different hydrophobic tails (acyl chains of varying unsaturation and length) to construct molecular membranes that perform specific desired functions. For instance, most of the fatty acids that constitute the plasma membranes of cells are mono- or polyunsaturated fatty acids so that they can impart fluidity to the lipid membrane.¹ On the other hand, a saturated lipid, dipalmitoylphosphatidylcholine (DPPC), is enriched up to 40% of the total lipid content in the alveoli in order to be able to reduce the surface tension of the alveolar lipid monolayer down close to zero at end expiration.^{2,3} Similarly, Langmuir monolayers of synthetic homopolymers^{4–6} and block copolymers^{7,8} have been shown to exhibit a wide range of surface mechanical behavior depending on the relaxation dynamics of the polymer molecules. However, using synthetic polymers to control the surface mechanical properties of physiological air–water interfaces for therapeutic purposes is challenging, because it is difficult to molecularly spread polymers on water surface without using an organic spreading solvent.^{9,10} Recently, our group has demonstrated that water-spread monolayers of amphiphilic block copolymer micelles can have surface mechanical characteristics that closely mimic those of natural lung surfactant monolayers; aqueous micelles formed with poly(styrene-*block*-ethylene glycol) (PS-PEG) block copolymers spontaneously spread on water surface (without undergoing any change in micellar morphology) and form an insoluble micelle monolayer that is capable of producing near-zero surface tension under high compression.^{9,11} This micelle monolayer system bears resemblance to polymer-brushed nanoparticle monolayers and differs from the conventionally studied block copolymer films. The latter are typically prepared by spreading the polymer from a state of singly dispersed chains using co-solvents, forming a continuous asymmetric monolayer or “surface micelles”.^{7,8} For clinical and therapeutic applications, it is imperative that polymers are administered in aqueous suspension,

precluding the use of organic solvents. This necessity drives the hydrophilic modification of the polymer, typically achieved through PEGylation. PEG-based amphiphilic block copolymers exhibit the propensity to assemble into micellar nanostructures within aqueous environments. Further, unlike lipid-based lung surfactant compositions (such as the calf-derived Infasurf[®]), this Polymer Lung Surfactant (PLS) composed of PS-PEG micelles exhibits the advantage of evading the detrimental impact of biological inhibitors like serum proteins and phospholipases in Acute Respiratory Distress Syndrome (ARDS) conditions. Serum proteins are known to competitively adsorb at the air–water interface within alveoli, functioning as inhibitors for lipid-based lung surfactants, whether natural or synthetic, during lung injury situations (as depicted in Figure 1).^{5,12–14} Our previous research has demonstrated that PLS maintains its capability to lower surface tension (increase surface pressure (Π)), even in the presence of albumin, a model serum protein.^{9,10} Moreover, PLS naturally remains unaffected by enzymatic degradation by phospholipases, which are activated under inflammation.² Given its commendable physiological behavior and economical feasibility for production scale-up, PLS holds substantial promise as an alternative to current lipid-based lung surfactants for treating conditions like ARDS and related ailments.⁹

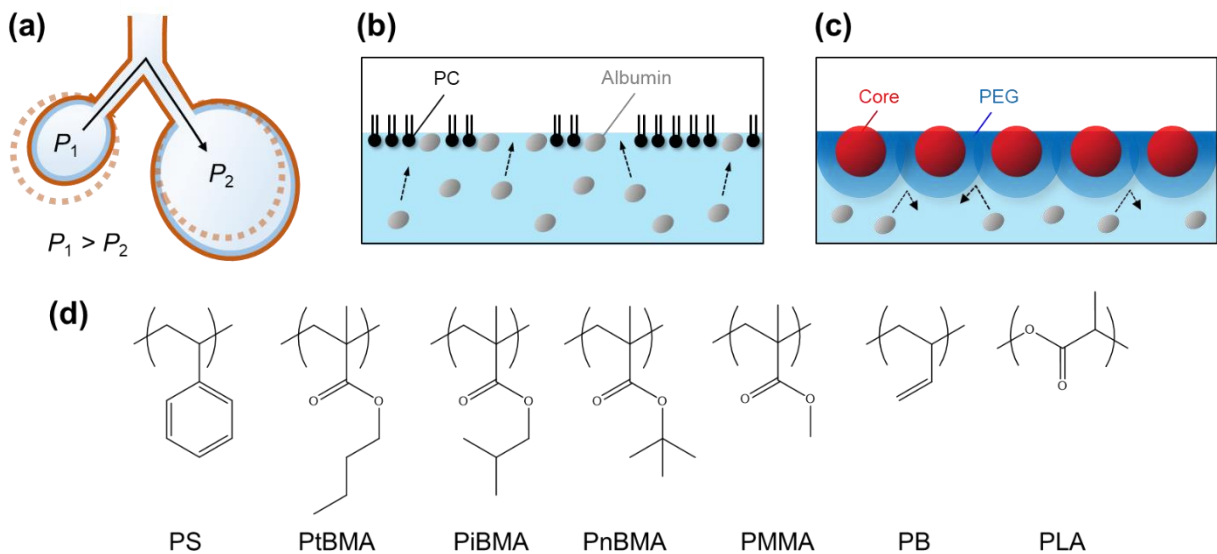


Figure 1. (a) Lung surfactant dysfunction causes the collapse of small alveoli due to an imbalance in Laplace pressure. The displacement of the alveolar walls from the dotted to solid lines depicts the gradual collapse of the alveolar structure of the lung. **(b)** Replacement of lung surfactant lipids (such as phosphatidylcholine (PC)) with serum proteins (such as albumin) at the alveolar air–water interface is a cause of surfactant dysfunction in injured lungs. **(c)** Block copolymer micelles form stable monolayers on the surface of alveolar lining fluid that are resistant against protein adsorption. **(d)** The hydrophobic block chemistries examined in this study: poly(styrene) (PS), poly(*t*-butyl methacrylate) (PtBMA), poly(isobutyl methacrylate) (PiBMA), poly(*n*-butyl methacrylate) (PnBMA), poly(methyl methacrylate) (PMMA), poly(1,2-butadiene) (PB), and poly(*D,L*-lactic acid) (PLA).

Previously, we have shown that changing the overall size of PS-PEG (while holding the PEG block size constant) significantly influences the surface mechanical properties of PS-PEG micelles⁹ and also that differently sized micelles prepared using an identical PS-PEG material behave differently with one another at the air–water interface.^{9,11} Herein we extend these previous studies into other PEG-based block copolymers. Specifically, the present study aims to investigate the effect of hydrophobic block chemistry on the surface mechanics of PEG-based copolymer micelles. The ultimate goal of these efforts is to establish design principles for block copolymer micelle-based PLS formulations for use as a surfactant replacement therapy for respiratory distress syndrome (including ARDS). To be suitable for this application, block copolymer micelles must be able to: (i) reduce the air–water interfacial tension (γ) down close to zero at maximum compression (in order to minimize the work associated with expanding the alveolar surface area (A) at the onset of and during inhalation) and (ii) enhance the area compressibility modulus, E ($= A(\partial\gamma/\partial A) = -A(\partial\Pi/\partial A)$), of the alveolar air–water interface so that the alveolar tissues are stabilized against collapse due to a gradient in the Laplace pressure (Figure 1(a)).^{13,15} In analogy to the fact that the hydrophilic–lipophilic balance and the fluidity of the hydrophobic tail group control the interfacial mechanics of lipids,¹⁶ it is reasonable to expect that the surface mechanical properties of block copolymer micelles are also controlled by the hydrophobicity and the mechanical

1 rigidity/deformability of the micelle core material. Similar observations have also been reported
2 for colloidal particles at air–water and oil–water interfaces.^{17,18}

3 In this study, eight different PEG-based diblock copolymers having comparable molecular
4 weights but different hydrophobic block chemistries (Figure 1(d)) were used. The water contact
5 angle (θ) and glass transition temperature (T_g) properties of the hydrophobic block materials were
6 characterized to quantitate, respectively, the thermodynamic affinity for the air–water interface
7 and the compliance of the polymer micelles under lateral compression. Spherical micelles having
8 comparable size characteristics were prepared from these copolymers by equilibrium
9 nanoprecipitation.^{9,11} Aqueous micelle suspensions were spread onto clean water subphases in a
10 Langmuir trough to form micelle monolayers. Simultaneous surface pressure-area isotherm and
11 Brewster angle microscopy (BAM) imaging/reflectivity measurements were performed on these
12 water-spread micelle monolayers at varying surface areas in order to understand how the
13 monolayer's structure and mechanical properties evolve during compression and also how the
14 structural and mechanical attributes are interrelated to each other. From these data, structural
15 behaviors responsible for diverse mechanical responses of the micelle monolayers under
16 compression could be deduced, including deformation and even coalescence of the micelle cores,
17 desorption of the micelles from the interface, and wrinkling/collapse of the monolayer. We also
18 found strong correlations between the surface pressure-area isotherm pattern of the monolayer and
19 the θ and T_g properties of the hydrophobic block polymer by multivariate correlation analysis.
20 Based on these results, guiding principles for searching for and designing candidate PLS
21 therapeutics for ARDS that can benefit millions of patients worldwide.^{19,20}

22 23 **Results and Discussion**

Preparation and Characterization of Block Copolymers and Block Copolymer

Micelles. Table 1 lists the molecular characteristics of poly(ethylene glycol)(PEG)-based amphiphilic block copolymers used in this study. Diblock copolymers with low polydispersity indices ($M_w/M_n = 1.1\text{--}1.5$ where M_w and M_n denote the weight and number-average overall molecular weights of the block copolymer, respectively) were prepared by controlled polymerization techniques (Figures S1–S6 of the Supporting Information (SI)). Since the surface mechanical properties of block copolymer micelles depend on the molecular weight of the block copolymer,⁹ we tried to keep the molecular weights of the diblock copolymers within a relatively narrow range (8.7–13.8 kDa); the target molecular weight was 5 kDa for both the hydrophilic (PEG) and hydrophobic blocks. Hereafter, all block copolymers are named using the notation P(X)-PEG in which P(X) is the abbreviation for the hydrophobic block polymer as listed in Figure 1(d). Except for the PS-PEG-OH and PB-PEG-OH copolymers that have a hydroxyl group (–OH) at the end of the PEG block, all the other block copolymers used have methoxy(–OCH₃)-ended PEG blocks.

Table 1. Molecular characteristics of the block copolymers studied. $M_{n,core}$ is the number-average molecular weight of the hydrophobic micelle core-forming block (determined by ¹H NMR). $M_{n,PEG}$ is the number-average molecular weight of the hydrophilic micelle corona-forming PEG block (determined by ¹H NMR). M_w is the overall weight-average molecular weight of the block copolymer. M_n is the overall number-average molecular weight of the block copolymer. M_w/M_n is the overall molecular weight polydispersity index (determined by GPC). θ is the water advancing contact angle of the hydrophobic block (measured using spin-cast films of hydrophobic homopolymers having the same respective molecular weights as the hydrophobic blocks of the block copolymers); ^(a) measurements were performed in the present study; ^(b) values were taken from the literature. T_g is the glass transition temperature of the hydrophobic block (values estimated for the corresponding hydrophobic homopolymers in the bulk state at the respective specific molecular weights using the Flory–Fox relation and our own DSC and literature T_g data).

Polymer	PEG End Group	$M_{n,core}$	$M_{n,PEG}$	M_w/M_n	θ (°)	T_g (°C)
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		(g/mol)	(g/mol)			
PS-PEG	−OCH ₃	5,152	5,000	1.23	88.8 ^(a)	85
PS-PEG-OH	−OH	5,200	5,500	1.11	88.8 ^(a)	86
PtBMA-PEG	−OCH ₃	6,079	5,000	1.19	85.8 ^(a)	94
PiBMA-PEG	−OCH ₃	5,481	5,000	1.23	87.8 ^(a)	51
PnBMA-PEG	−OCH ₃	7,192	5,000	1.11	83.2 ^(a)	16
PMMA-PEG	−OCH ₃	3,739	5,000	1.22	68.2 ^(a)	87
PB-PEG-OH	−OH	5,000	4,500	1.12	96.0 ^{(b),21}	−3
PLA-PEG	−OCH ₃	3,693	5,000	1.47	79.8 ^{(b),22}	35

Our hypothesis for this study is that the hydrophobicity and mechanical rigidity of the micelle core domain significantly influence the surface mechanical properties of polymer micelles. The hydrophobicity and rigidity can be measured, respectively, in terms of the wettability at the air–water interface and the bulk-state glass transition temperature (T_g) of the hydrophobic block polymer. The wettability (w) is defined as $w \equiv \gamma_{PW} - \gamma_{PA}$, where γ_{PW} and γ_{PA} are the polymer–water and polymer–air interfacial tensions, respectively, and is a measure of the thermodynamic tendency of the micelle core material to wet (i.e., anchor to) the air–water interface. The wettability can be measured by measuring the contact angle (θ) of a water droplet on a polymer substrate at the three-phase (air–water–polymer) contact line; note according to the Young’s equation, $\gamma_{PA} = \gamma_{PW} + \gamma_{AW} \cos(\theta)$ where γ_{AW} is the air–water interfacial tension ($= 72 \text{ mN/m}$ at 25°C),²³ $w (\equiv \gamma_{PW} - \gamma_{PA}) = -\gamma_{AW} \cos(\theta) \propto -\cos(\theta)$. For accurate experimental determination of the θ (and T_g) properties of the hydrophobic blocks of the block copolymers studied, the corresponding homopolymers (having comparable molecular weights (6.6–8.2 kDa) were prepared; the molecular characteristics of the homopolymers used are summarized in Table S1.

Water contact angle (θ) and differential scanning calorimetry (DSC) measurements were performed on these homopolymers; the results are presented in Table 1, Table S1, and Figures S16–S17 of the SI. In terms of their mechanical rigidity, the 7 different hydrophobic block polymers studied can be divided into two groups: rigid polymers with $T_g > 60$ °C (PS, PtBMA, and PMMA in the bulk state) vs. soft polymers with $T_g < 60$ °C (PB, PiBMA, PnBMA, and PLA in the bulk state). Note the use of 60 °C as the boundary for defining rigid vs. soft polymers is arbitrary and for convenience. Also, the actual T_g of a polymer in the micelle form can be different from when it is in the bulk state because the glass transition behavior can be influenced by the (micellar) nanoconfinement,²⁴ the plasticizing effect of water,²⁵ and the localization of the block junction points.²⁶ A study is currently in progress in our laboratory to accurately determine the T_g properties of polymer micelles using such techniques as transverse proton NMR relaxation and molecular-rotor optical viscometry measurements. In the present study, using the bulk T_g values was sufficient for the purpose of testing for a correlation between the glass transition vs. surface mechanical properties of block copolymer micelles. In terms of their degrees of hydrophobicity/wettability, the hydrophobic block polymers can be divided into two groups: more hydrophobic materials having $\theta > 80^\circ$ (PS, PtBMA, PiBMA, PnBMA, and PB) vs. less hydrophobic materials having $\theta < 80^\circ$ (PMMA and PLA).

Micelles were prepared from the 8 different block copolymers in water using the two-step equilibrium nanoprecipitation (ENP) method,¹¹ and characterized by TEM and dynamic light scattering (DLS) (Table 2). All micelles were spherical in shape, and their sizes were comparable within a narrow range across different block copolymers; i.e., D_c (core diameter determined by TEM) = 18 ± 2 nm (Figure S18), and D_h (micelle hydrodynamic diameter by DLS) = 30 ± 4 nm. The micelle structures were stabilized by dense PEG coronas which produce steric repulsion

between the micelles and thus prevent them from aggregation and/or coalescence.²⁷ As presented in Table 2, the dimensionless PEG grafting density values were much greater than one in all cases ($\sigma_{\text{PEG}} = 6\text{--}13$); here, the dimensionless grafting density (σ_{PEG}) is defined as $\sigma_{\text{PEG}} \equiv pR_{\text{g,PEG}}^2/D_c^2$, that is, as the ratio of the projected cross-sectional area of a PEG chain in its unperturbed conformation ($\pi R_{\text{g,PEG}}^2$) relative to the area per PEG corona chain at the micelle core surface ($\pi D_c^2/p$); here, $R_{\text{g,PEG}}$ is the radius of gyration of the PEG block in the Gaussian state, $p (= (\pi D_c^3/6)(M_{\text{n,core}}/N_A\rho_{\text{core}})^{-1})$ is the aggregation number of the micelles, $M_{\text{n,core}}$ is the number-average molecular weight of the hydrophobic (core-forming) block, N_A is the Avogadro number, and ρ_{core} is the mass density of the micelle core.

Table 2. Structural and surface mechanical properties of the block copolymer micelles. $\phi_{\text{w,ENP}}$ is the volume fraction of water in the water/organic cosolvent (acetone) mixture in which equilibrium block copolymer micelles were initially formed during the equilibrium nanoprecipitation (ENP) formulation process. D_c is the mean diameter of the hydrophobic core domains of the block copolymer micelles (determined by dry-state EM). D_h is the mean hydrodynamic diameter of the block copolymer micelles measured at a concentration of 0.05 wt.% in Milli-Q water (determined by DLS/cumulant analysis). PDI_{DLS} is the micelle size polydispersity index (determined by DLS/cumulant analysis). σ_{PEG} is the dimensionless PEG corona chain grafting density. E_{max} is the maximum compressibility modulus of the water-spread block copolymer micelle monolayer. Π at E_{max} denotes the micelle monolayer surface pressure at maximum compressibility modulus. Π_{max} is the maximum surface pressure, which, in most cases, is equal the surface pressure at monolayer collapse. ^(a) Core-crosslinked PB-PEG-OH micelles were used for dry-state TEM analysis.

Polymer	$\phi_{\text{w,ENP}}$	D_c (nm)	D_h (nm)	PDI_{DLS}	σ_{PEG}	E_{max} (mN/m)	Π at E_{max} (mN/m)	Π_{max} (mN/m)
PS-PEG	0.1	19.0	31.4	0.157	9.71	184.7	40.8	63.5
PS-PEG-OH	0.5	16.5	31.2	0.082	9.37	99.8	62.1	69.4
PtBMA-PEG	0.3	17.1	27.5	0.082	7.21	133.1	55.1	67.7
PiBMA-PEG	0.1	17.1	28.6	0.018	8.19	117.4	50.7	64.2
PnBMA-PEG	0.3	16.9	26.1	0.012	6.26	60.5	53.0	60.7
PMMA-PEG	0.5	15.6	30.7	0.072	12.38	56.8	37.7	37.7

PB-PEG-OH	0.1	19.5 ^(a)	34.5	0.142	8.00	34.5	15.8	30.1
PLA-PEG	0.2	15.6	26.6	0.190	13.14	7.6	17.0	18.1

Surface Mechanics of Water-Spread Block Copolymer Micelles. Surface pressure–area

(Π – A) isotherms were determined for the block copolymer micelles after spreading them in the form of an aqueous solution onto the air–water interface within a Langmuir trough filled with Milli-Q water through compression of the surface at a rate of 4.5 cm²/min (equivalent to a linear speed of 3 mm/min); here, the surface pressure (Π) is defined as the difference between the surface tension of the clean air–water interface (γ_0) and that of the micelle-laden air–water interface (γ), that is, $\Pi \equiv \gamma_0 - \gamma$. The surface area per micelle (a_m) was calculated as $a_m = A/N$, where A is the total surface area, $N (= cVN_A/pM_n)$ is the total number of micelles spread, $c (= 5 \text{ mg/mL})$ is the concentration of the polymer (micelles) in the spreading solution, and V is the volume of the micelle solution spread. Because the surface area of the trough can only be changed by a factor of 11 (782 cm² $\leftrightarrow$ 71 cm²) in an experiment, for each sample, Π – a_m isotherm measurements were performed twice using two different spreading volumes ($V = 10$ and 100 μL) in order to cover a sufficient range of a_m . In all cases, when 10 μL of the spreading solution was spread, the initial surface pressure of the micelles ($\Pi = 0$ –5 mN/m) was much lower than the equilibrium spreading pressure of PEG ($\Pi_e \cong 10 \text{ mN/m}$). In this low surface concentration limit, it is reasonable to assume that the micelles spontaneously spread (due to the Marangoni effect) with negligible loss to the subphase (due to the strong affinity of PEG chains to the air–water interface ^{28,29}). However, if the surface is already saturated with polymer micelles, the surplus amount of micelles would be submerged into the subphase during the spreading process; in this case, the true value of N is unknown but is expected to be much smaller than that estimated based on stoichiometry.

For this reason, each Π - a_m isotherm curve obtained at $V = 100 \mu\text{L}$ was horizontally shifted to match the reference Π - a_m isotherm obtained at $V = 10 \mu\text{L}$ by multiplying the a_m values by a constant shift factor (Figure S19). This superposition is justifiable based on two underlying assumptions: (i) that the equilibrium surface pressure (Π_{eq}) is a unique function of the surface area, and (ii) that the recorded Π values from area scans equate to Π_{eq} ; this equivalence was validated through our observation, wherein Π exhibited minimal variation, not exceeding 0.1 mN/m within a 40-minute timeframe when the area was maintained under the condition of $\Pi = 10 - 20 \text{ mN/m}$ (a range commonly associated with the superposition process). The combined (superposed) isotherms were further transformed into the final forms presented in Figures 2(a) and 3(a) by normalizing a_m by the hydrodynamic cross-sectional area of the micelles ($a_h = \pi D_h^2/4$); during compression, the neighboring micelles start experiencing steric repulsive forces when $a_m/a_h \approx 1$. Additionally, Π - a_m isotherms capturing the full compression and expansion cycle were acquired at an accelerated rate of $45 \text{ cm}^2/\text{min}$ (equivalent to a linear speed of 30 mm/min), concurrent with the BAM experiment (displayed in Figure S20). Significant hysteresis was observable across a majority of the samples, with particularly notable instances in monolayers consisting of PS-PEG-OH, PtBMA-PEG, and PiBMA-PEG micelles. These specific monolayers have been compressed beyond their respective collapse pressures. As such, the underlying cause of this phenomenon is linked to the desorption of micelles from the interface. This desorption encompasses monolayer collapse, folding, and/or potentially irreversible micelle loss to the subphase, all transpiring at the collapse pressure threshold. The gradual kinetics associated with the re-spreading of collapsed monolayers and/or the re-adsorption of desorbed micelles during the expansion process contributes to this behavior. A comprehensive analysis of these effects can be found in our earlier study pertaining to PS-PEG micelles of varying sizes.¹¹

Micelles with Rigid (Glassy) Cores.

Figure 2(a) displays the Π - a_m/a_h isotherms for block copolymer micelles with rigid (glassy) cores at room temperature (with $T_g > 60$ °C in the bulk state); $T_g \cong 85 - 86$ °C and $\theta \cong 89^\circ$ for bulk PS, and $T_g \cong 94$ °C and $\theta \cong 86^\circ$ for bulk PtBMA. The polymer micelles in this category showed a common pattern of surface pressure behavior. As schematically depicted in Figure 2(e), in the dilute micelle surface concentration limit, each isolated individual micelle is nearly fully immersed in water, while, at the same time, it is strongly anchored to the air–water interface (data supporting this are presented/discussed throughout this subsection) because a significant number of the PEG corona chains are adsorbed and assume a two-dimensional (2D) flattened coil structure at the air–water interface; this PEG surface layer (“pancake”) formation is driven by the strong affinity of PEG to the air–water interface.²⁸ As shown in Figure 2(a), when a_m/a_h reaches a value of about 10 during compression, the PEG pancakes (i.e., the adsorbed PEG chains) from different micelles start sterically interacting with each other, forming a 2D semi-dilute PEG solution, and as a result, Π starts rising faster than the ideal gas-like law predicts ($\Pi \sim A^{-1}$). In this 2D semi-dilute PEG surface concentration regime (i.e., at $5 < a_m/a_h < 10$), we found that Π actually scales with A to the power of approximately -4.9 (Figure S21). The de Gennes scaling theory predicts that in the semi-dilute concentration regime, the osmotic pressure of a polymer solution (Π_{osm}) scales with the mass concentration of the polymer (c), i.e., $\Pi_{\text{osm}} \sim c^\nu$, and the scaling exponent, ν , is related to the so-called Flory exponent, ν , by the equation, $\nu = d\nu/(d\nu - 1)$ where d is the dimensionality.³⁰ Applying this relation to our 2D situation (that is, $\Pi = \Pi_{\text{osm}}$, $d = 2$, and $c \sim A^{-1}$) gives $\Pi \sim A^{-\gamma}$ where $\gamma = 2\nu/(2\nu - 1)$.^{4,5,31} Therefore, the 2D Flory exponent for the adsorbed PEG corona chains is estimated to be $\nu \cong 0.63$, which suggests that the air–water interface provides a “good solvent” environment for the PEG chains,³²

and thus the adsorbed PEG chains are expected to assume extended conformations in the 2D space.³³ Note, however, that this 2D Flory exponent of the micellar PEG chains is lower than that previously reported for free PEG chains at the air–water interface ($\nu \cong 0.77$).³²

Further compression leads to a plateau in Π at $a_m/a_h \cong 5$. The plateau surface pressure coincides with the equilibrium spreading pressure of PEG ($\Pi_{e,PEG} \cong 10$ mN/m),³⁴ which suggests that at the plateau transition, the air–water interface becomes fully saturated with the adsorbed PEG chains. Within the plateau region ($1 < a_m/a_h < 5$), continued compression causes gradual desorption of the adsorbed PEG segments into the subphase, while the water surface remains saturated with the remaining adsorbed PEG segments, which causes the surface pressure to remain constant.

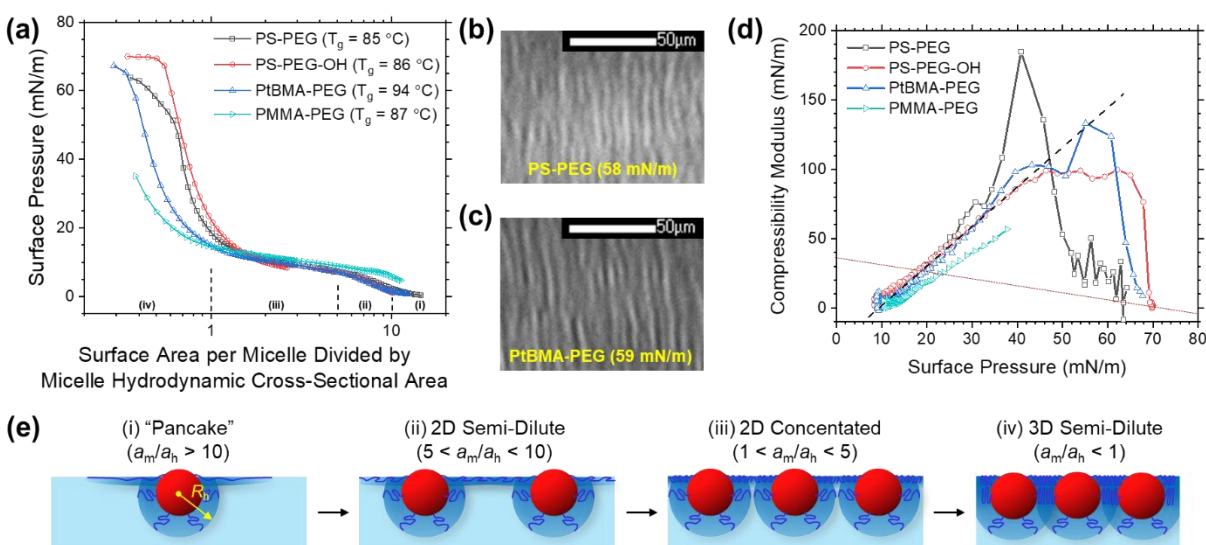


Figure 2. Surface mechanical behaviors of rigid core micelles ($T_g > 60$ °C). **(a)** Surface pressure (Π) vs. surface area per micelle (a_m) divided by micelle hydrodynamic cross-sectional area ($a_h = \pi R_h^2$) isotherms. Each isotherm curve represents a superposition of two data sets obtained by spreading 10 and 100 μ L of a 5 mg/mL block copolymer micelle solution in water onto a clean water surface at an initial surface area of 782 cm^2 , respectively, and then by compressing the monolayer at a speed of 3 mm/min to a final area of 71 cm^2 . The phase regions, as numbered in **(e)**, have been indicated to correspond to various states of surface coverage. **(b,c)** Representative

BAM images of PS-PEG and PtBMA-PEG micelle monolayers at high compression. The surface pressure (Π) values at which the BAM images were taken are given in parentheses. **(d)** Compressibility moduli (E) as functions of Π . The blue dashed line is a linear fit to the data, and the slope of this line (γ) is estimated to be 2.85. The red dotted line shows the limit of Laplace stability for the alveoli ($2E - \gamma > 0$). **(e)** Conformational changes in adsorbed PS-PEG micelles during compression.

When the micelle monolayer is compressed beyond $a_m/a_h \approx 1$, as depicted in Figure 2(e), the non-adsorbed PEG corona chains in the subphase overlap with each other between neighboring micelles, which leads to an even faster rise in Π with compression. As further discussed below (with reference to Figure 2(b)), this surface pressure rise is, again, believed to be due to a build-up of the semi-dilute PEG osmotic pressure (Π_{osm}); in this case, the osmotic pressure is built up, not within the PEG pancake layer but, in the subphase region. Previously, on the basis of the analysis of Brewster angle microscopy (BAM) images, we have estimated that in PS-PEG micelle monolayers, the compressive stress applied to the monolayer during compression is stored within a layer of about 1 nm thickness.¹¹ This “mechanical” thickness (t_m) was estimated using a model adapted from lipid fluid membranes: $t_m = (\beta B/E)^{1/2}$, where B is the bending stiffness of the monolayer, derived as $B = (\Delta\rho)g\lambda^4/(16\pi^4)$, incorporating parameters such as the wrinkle wavelength (λ), the density difference between air and water ($\Delta\rho$), the gravitational constant (g), and the compressibility modulus (E). This stress-bearing layer exhibited a thinner profile compared to the overall thickness of micelle monolayers. This phenomenon can be attributed to the high curvature of the micelle core surface, as the area of corona overlap between adjacent micelles remains relatively diminutive (~ 5 nm in cross-sectional diameter at maximum overlap, as depicted in Figure 2(e)). In this semi-dilute PEG subphase concentration regime (i.e., at $a_m/a_h < 1$), the unrelaxed osmotic pressure produced by compression causes the micelle monolayer to form wrinkles and eventually to collapse and fold, as can be seen in BAM images of Figures 2(b) and

2(c). In all cases involving micelles with rigid and strongly hydrophobic cores (i.e., PS-PEG, PS-PEG-OH and PtBMA-PEG micelles), wrinkles appeared in the micelle monolayers when the compression exceeded their respective maximum compressibility modulus values ($E_{\max}$). Detailed characteristics of the wrinkled structures have been discussed in our previous publication.¹¹ In each of these three cases, the maximum surface pressure, $\Pi_{\max}$, was approximately 70 mN/m (the surface tension was nearly zero at maximum compression) (Table 2). These results suggest that these PS-PEG, PS-PEG-OH and PtBMA-PEG micelles have an extremely strong affinity for the air–water interface due to the strong hydrophobic character of the core-forming blocks, and as a result, the micelle monolayers were able to withstand the lateral compression without losing material to the subphase. To the contrary, as shown in Figure 2(a), micelles with (rigid but) less hydrophobic cores (i.e., PMMA-PEG micelles) failed to resist the compression, and were unable to produce sufficiently high surface pressure; no wrinkles were observed in this system.

The lower area portions of the Π – a_m/a_h isotherms shown in Figure 2(a) were further converted to plots of E vs. Π (Figure 2(d)). As shown in Figure 2(d), in the intermediate- Π regime (i.e., at $\Pi \cong 10$ –30 mN/m), the E – Π curves for PS-PEG, PS-PEG-OH and PtBMA-PEG micelles were found to superimpose into a single straight line, which is consistent with the prediction of the semi-dilute scaling theory; as discussed earlier, since $\Pi - \Pi_{e,\text{PEG}} = \Pi_{\text{osm}} \sim c^y \sim A^{-y}$ (where $y = dv/(dv - 1)$), $E (\equiv -A(\partial\Pi/\partial A) = -A(\partial\Pi_{\text{osm}}/\partial A)) = y\Pi_{\text{osm}} = y\Pi - y\Pi_{e,\text{PEG}} (\text{const.})$. The slope of the E – Π lines was estimated to be $y = 2.85 \pm 0.05$; the exact same behavior ($y = 2.8$ –2.9) has previously been observed for PS-PEG micelles having different core diameters ($D_c = 14$ –27 nm) (see Figure 4(C) of Ref. 11). As discussed above, in this regime, Π increases during compression due to an overlap of the subphase PEG corona layers between adjacent micelles; therefore, $d = 3$ (i.e., the overlap occurs in 3D space). From the value of the slope ($y = 2.85$), therefore, the value of the 3D Flory

exponent for the PEG corona chains could be determined ($\nu \cong 0.51$). We note that this ν value is lower than that reported for free PEG chains in water ($\nu \cong 0.58$),³⁵ but this result is consistent with our previous observation that PEG chains experience a closer-to-poor solvent environment when they exist in the end-grafted (brush) state.^{36,37}

At higher surface pressures ($\Pi > 30$ mN/m), the compressibility moduli (E) for the PS-PEG, PS-PEG-OH and PtBMA-PEG micelle monolayers exhibited a maximum ($E_{\max}$) followed by a rapid decline (Figure 2(d)). As demonstrated in Figures 2(c) and 2(b), further compression past the point of $E_{\max}$ caused wrinkling and eventual collapse of the monolayers; the onset of wrinkling typically coincided with the location of $E_{\max}$. In this high Π regime, the PEG concentration vs. surface area relationship ($c \sim A^{-1}$) is no longer valid, and thus E - Π curve shows a negative deviation from the linear relationship ($E = \gamma\Pi - \text{const.}$); E eventually decreases down close to zero at $\Pi = \Pi_{\max}$.

Interestingly, as shown in Figure 2(d), in the case of PMMA-PEG micelles ($T_g \cong 87$ °C and $\theta \cong 68^\circ$ for bulk PMPMA), the slope (γ) of the E vs. Π graph was equal to 2.85 only within a narrow range of Π (= 15–20 mN/m), but it decreased to a lower value ($\gamma = 1.49$) at $\Pi > 20$ mN/m due to continuous desorption of the micelles from the air–water interface; the desorption of PMMA-PEG micelles is thought to be due to the relatively less hydrophobic nature of PMMA, and is further supported by quantitative Brewster angle microscopy (QBAM) analysis (discussed later).

Micelles with Soft Cores. As shown in Figure 3(a), the Π - a_m/a_h isotherms for soft core micelles ($T_g < 60$ °C) did not follow the general overall trends observed with the rigid core micelles. The monolayers of PiBMA-PEG and PnBMA-PEG micelles (having soft and strongly

hydrophobic cores) exhibited the PEG desorption plateau ($\Pi_{e,PEG}$) at higher surface areas ($a_m/a_h = 4-10$) than those for the rigid core micelles ($a_m/a_h = 2-5$); note $T_g \cong 51\text{ }^\circ\text{C}$ and $\theta \cong 89^\circ$ for bulk PiBMA, and $T_g \cong 16\text{ }^\circ\text{C}$ and $\theta \cong 83^\circ$ for bulk PnBMA. Further compression caused a rapid upturn in Π followed by a second plateau. The onset of the upturn (corona overlap between micelles) occurred at $a_m/a_h > 1$, which indicates that the soft core micelles had a flattened (oblate) shape at the air–water interface (further supported by QBAM analysis (discussed later)) in order to maximize the contact between the hydrophobic core and the air (Figure 3(e)); a similar behavior has been reported for soft microgels.^{38,39} The second plateau, we believe, is due to the deformation (vertical elongation) of the core domains (also supported by QBAM (discussed later)); micelle fusion, however, did not seem to occur because further compression caused an increase in Π beyond 60 mN/m. At $a_m/a_h < 1$, these micelles produced reasonably high surface pressures ($\Pi_{max} > 60\text{ mN/m}$) and showed indications of monolayer collapse (the high-pressure plateau) similarly to the micelles having rigid and strongly hydrophobic cores (such as PS-PEG micelles). However, no wrinkles were observed at all surface areas examined (Figures 3(b) and 3(c)), which suggests that the compressive stress was relaxed by core deformation in this case (rather than by formation of wrinkles). Hence, the occurrence or absence of wrinkling under high compression provides a discriminative criterion between “rigid monolayers”, characterized by micelles like PS-PEG and PtBMA-PEG, and “soft monolayers”, encompassing micelles like PiBMA-PEG and PnBMA-PEG. Notably, the rigid monolayers exhibit a more pronounced increase in Π along surface pressure–area isotherms and generally higher values of E_{max} . We note that the T_g of the micelle core is in general much lower than the T_g of the polymer in the bulk state (bulk T_g data presented in Table 1).²⁴ On the basis of the surface mechanical behavior of the PiBMA-PEG micelles, for instance, it is reasonable to expect that the T_g of the PiBMA core is lower than room temperature.

Unfortunately, however, precise experimental determination of the micelle core T_g remains a difficult task.^{40,41}

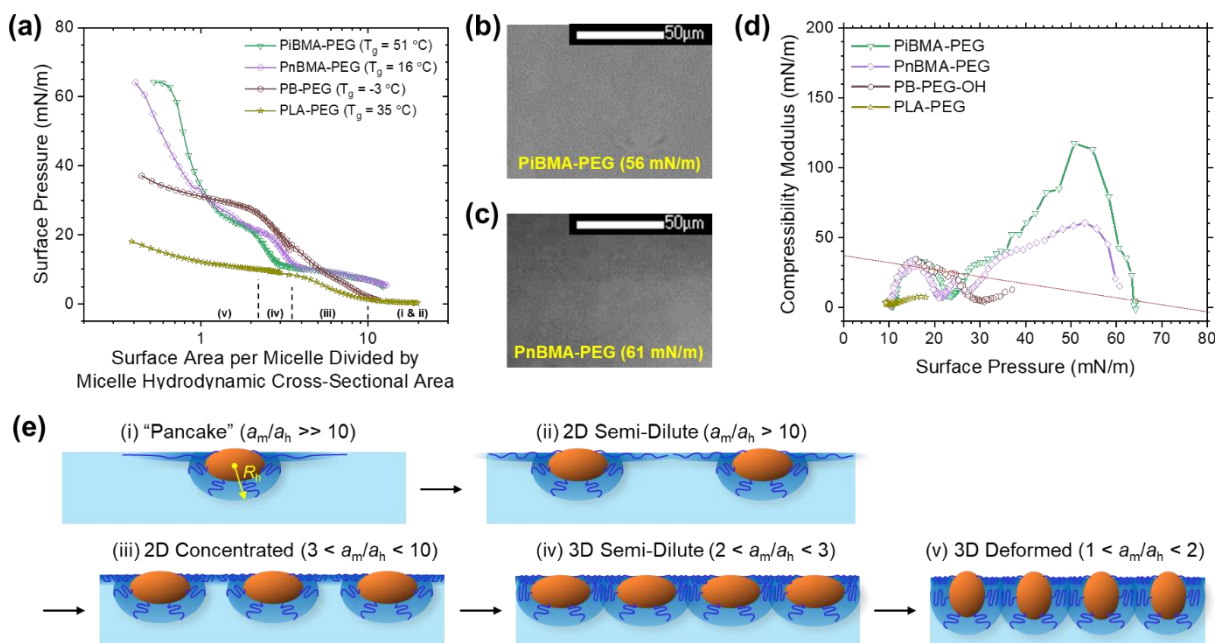


Figure 3. Surface mechanical behaviors of soft core micelles ($T_g < 60^\circ\text{C}$). **(a)** Surface pressure (Π) vs. surface area per micelle (a_m) divided by micelle hydrodynamic cross-sectional area ($a_h = \pi R_h^2$) isotherms. Each isotherm curve represents a superposition of two data sets obtained by spreading 10 and 100 μL of a 5 mg/mL block copolymer micelle solution in water onto a clean water surface at an initial surface area of 782 cm^2 , respectively, and then by compressing the monolayer at a speed of 3 mm/min to a final area of 71 cm^2 . The phase regions, as numbered in **(e)**, have been indicated to correspond to various states of surface coverage. **(b,c)** Representative BAM images of PiBMA-PEG and PnBMA-PEG micelle monolayers at high compression. The surface pressure (Π) values at which the BAM images were taken are given in parentheses. **(d)** Compressibility moduli (E) as functions of Π . The blue dashed line is a linear fit to the data, and the slope of this line (γ) is estimated to be 2.85. The red dotted line shows the limit of Laplace stability for the alveoli ($2E - \gamma > 0$). **(e)** Conformational changes in adsorbed PiBMA-PEG micelles during compression.

PB-PEG-OH micelles have a strongly hydrophobic but liquid-like core ($\theta \cong 96^\circ$ and $T_g \cong -3^\circ\text{C}$ for bulk PB). The surface pressure-area isotherm of water-spread PB-PEG-OH micelles was

identical to that reported for a chloroform-spread PB-PEG-OH monolayer.⁴² As shown in Figure 3(a), in this PB-PEG-OH case, the PEG plateau ($\Pi_{e,PEG}$) almost did not occur; there was only a slight shoulder in the isotherm curve at $a_m/a_h \cong 7$. Instead, Π steadily increased until it reached a plateau at $\Pi \cong 30$ mN/m ($> \Pi_{e,PEG}$) at $a_m/a_h \cong 2$. This plateauing indicates that PB-PEG-OH micelles merged into a continuous layer, which was enabled due to the liquid-like nature of the PB domain and also the strong tendency of PB to wet the air–water interface;⁴³ the spreading coefficient of PB ($s \equiv \gamma_{AW} - \gamma_{PA} - \gamma_{PW}$) = 14 mN/m) is positive at room temperature.^{44,45} Further compression caused a gradual slight increase in Π (at $a_m/a_h < \sim 2$), which is likely due to a viscoelastic effect.

PLA-PEG micelles having soft and less hydrophobic cores exhibited a plateau at $\Pi_{e,PEG}$ (Figure 3(a)); note $T_g \cong 35$ °C and $\theta \cong 80^\circ$ for bulk PLA. However, for this group, further compression caused only a slight increase in Π . Similar to the PMMA-PEG micelles (having a rigid but less hydrophobic core), Π did not become saturated even at maximum compression (at $a_m/a_h \cong 0.4$). These results suggest that, at $\Pi > \Pi_{e,PEG}$, the polymer micelles continuously desorbed from the air–water interface during compression, which prohibited a buildup of osmotic pressure. A similar behavior has also been reported for poly(lactic acid-*co*-glycolic acid)-*b*-PEG (PLGA-PEG) micelles.⁸

As shown in Figure 3(d), the E vs. Π curves were more complicated for the polymer micelles having softer cores because of the occurrence of an intermediate plateau at $\Pi > \Pi_{e,PEG}$. There was a clear trend in the E_{max} data for the micelles having soft and strongly hydrophobic cores; E_{max} decreased with decreasing T_g (i.e., PiBMA-PEG > PnBMA-PEG > PB-PEG-OH), which indicates that the micelle core rigidity controls the E of the micelle monolayer. The PiBMA-PEG and PnBMA-PEG micelles (having highly hydrophobic cores) were still able to produce $\Pi_{max} > 60$ mN/m, which suggests that these micelles did not become desorbed from the air–water interface

even under high lateral compression, nor did they merge and transform into a continuous film (because of the metastability of the micelle structure although both these polymers have positive spreading coefficients, i.e., $s \cong 13$ mN/m for PiBMA,²¹ and $s \cong 18$ mN/m for PnBMA²¹). The PLA-PEG micelles (having less hydrophobic cores) were characterized by relatively very small values of $E_{\max}$ (< 10 mN/m) because of the micelle desorption. The values of $E_{\max}$, Π at $E_{\max}$ (Π_{peak}) and $\Pi_{\max}$ for all polymers tested are summarized in Table 2.

Bivariate Correlation Regression Analysis. The results presented in the previous subsections establish that the core rigidity and hydrophobicity (measured in terms of T_g and θ , respectively) determine the surface mechanics of the micelle monolayer. Previously, using PS-PEG micelles of systematically varying sizes (derived from an identical PS-PEG material), we have shown that the micelle core diameter (D_c) (which scales with the PEG corona chain grafting density (σ_{PEG})) is also an important factor that determines the surface mechanical properties of the micelles.¹¹ In the present work, we performed univariate and bivariate correlation regression analyses with measures of monolayer surface mechanics ($E_{\max}$, Π_{peak} and $\Pi_{\max}$) as dependent variables and micelle physicochemical characteristics (T_g and θ) as independent variables. Table 3 summarizes the values of the coefficients of determination (R^2) obtained from these analyses. As shown in the table, the R^2 's from the univariate analysis were generally lower than those from the bivariate analysis, which suggests that the surface mechanical properties of polymer micelles are not controlled by a single parameter. Figure 4 displays 2D color maps of $E_{\max}$, Π_{peak} and $\Pi_{\max}$ as functions of $\{T_g, \theta\}$, which graphically illustrate that $E_{\max}$ and $\Pi_{\max}$ show bivariate correlations with T_g and θ ; the values of $E_{\max}$, Π_{peak} and $\Pi_{\max}$ were highest at the upper right corner of the T_g –

θ plane (i.e., when both T_g and θ are greatest). These results support that the micelle core T_g and θ are coupled parameters that simultaneously influence the micelle surface mechanics.

Table 3. The coefficients of determination (R^2) for the one and two-dimensional linear regression of the surface mechanical properties of the block copolymer micelles ($E_{\max}$, Π_{peak} , $\Pi_{\max}$) as functions of their physicochemical characteristics (T_g , θ).

Variable 1	Variable 2	R^2		
		Maximum Compressibility Modulus ($E_{\max}$)	Surface Pressure (Π) at $E_{\max}$ (Π_{peak})	Maximum Surface Pressure ($\Pi_{\max}$)
T_g	—	0.415	0.312	0.256
θ	—	0.079	0.000	0.077
T_g	θ	0.707	0.356	0.492

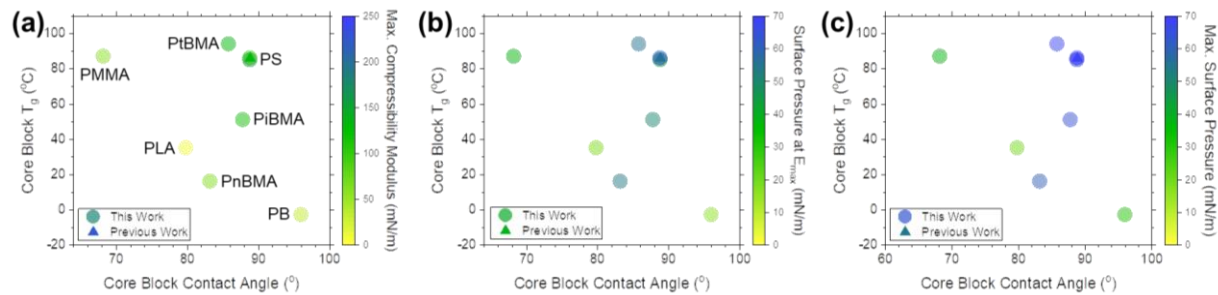


Figure 4. Two-dimensional plots of the (a) maximum compressibility modulus ($E_{\max}$), (b) surface pressure at $E_{\max}$ (Π_{peak}) and (c) maximum surface pressure ($\Pi_{\max}$) as functions of the glass transition temperature (T_g) and contact angle (θ) of the core-forming block. $E_{\max}$, Π_{peak} and $\Pi_{\max}$ data obtained in our previous study using PS-PEG-OH micelles are also displayed (triangles).¹¹

Quantitative Brewster Angle Microscopy (Reflectivity) Analysis. Quantitative

Brewster angle microscopy (QBAM) analysis was performed to investigate how the structures of the micelle monolayers change during compression and how the core T_g and θ influence the monolayer structure under compression. In QBAM experiments, the reflectivity of p -polarized light from the micelle-laden water surface at the Brewster angle of water ($= 53.1^\circ$) was measured as a function of monolayer surface area. For a homogeneous film of thickness t and refractive index n_f on water surface, the reflectivity (R) at the Brewster angle is given as

$$R = \left(\frac{\pi t}{\lambda} \right)^2 \left[\frac{n_f^2 - n_w^2 - 1 + (n_w^2/n_f^2)}{1 + n_w^2} \right]^2 \quad (1)$$

where λ is the wavelength of the light, and n_w is the refractive index of water.⁴⁶ The refractive index of the film, n_f , can be estimated using

$$n_f \cong n_w + \frac{dn}{dc} \frac{M}{At} \quad (2)$$

where dn/dc is the specific refractive index increment, which can be estimated as $w_{\text{core}}(dn/dc)_{\text{core}} + w_{\text{corona}}(dn/dc)_{\text{corona}}$ (here, w_i and $(dn/dc)_i$ are, respectively, the weight fraction and specific refractive index increment of species i), M is the total mass of the micelles at the air–water interface, and A is the total area of the micelle monolayer. For insoluble (non-desorbing) monolayers formed by micelles having rigid (non-deformable) cores, it is expected that M and t are constant (unchanged) during compression. The values of R were computed from video recordings of BAM images. Representative BAM images and R vs. A plots for all block copolymer micelles tested are presented in Figures S22–S30 of the SI.

Figure 5(a) shows both II vs. A and $R^{1/2}$ vs. A plots (stacked on a shared x -axis) for PS-PEG-OH micelles. The high- A (i.e., non-collapsed monolayer) portion of the $R^{1/2}$ vs. A curve was first fit to Eq. (1) above by using M and t as adjustable parameters; the actual amount of polymer

micelles at the air-water interface (M) is not known because of possible initial loss of micelles to the subphase during the spreading process. As shown with a dashed line in Figure 5(a), the reflectivity profile was well fit with a thickness value of $t = 8$ nm at high to intermediate surface areas ($A \cong 233\text{--}777$ cm²), i.e., until Π reached Π_{max} during compression, which supports that PS-PEG-OH micelles are indeed non-desorbing even at reasonably high Π and the PS core does not deform under compression due to its high T_g . At high compression ($A < \sim 200$ cm²), the constant- t model was no longer able to fit the data because of the formation of wrinkles and collapsed structures. We note that the best-fit thickness value ($t = 8$ nm) is smaller than the micelle core diameter ($D_c = 16.5$ nm) because the micelle monolayer is not a solid film; it contains interstitial regions between micelle cores which are filled with water and PEG corona chains (Figure 2(e)). An alternative analysis was also performed in which t was calculated from measured R using Eq. (1) at constant M (determined by fitting as described above). As shown in Figure 5(a) (green triangles), t was found to be nearly constant over a wide range of surface areas ($A \cong 230 - 550$ cm²). At $A > 550$ cm² (during the initial period of compression), t was overestimated likely because of a small bias error in reflectivity calibration, of which the effect became negligible as the reflectivity signal was increased at higher compression. Compression past ~ 200 cm² caused a continuous increase in the estimated value of t because of the wrinkling and collapse of the monolayer. As shown in Figures S22 and S24, PS-PEG and PtBMA-PEG micelles (having rigid and strongly hydrophobic cores) also exhibited similar reflectivity behaviors to PS-PEG-OH micelles (Figures 5(a) and S23); the $R^{1/2}$ vs. A profiles of PS-PEG and PtBMA-PEG micelles could also be reasonably modeled with Eq. (1) using a constant value of t over a wide range of A , again supporting the non-deformable and non-desorbing nature of these micelles.

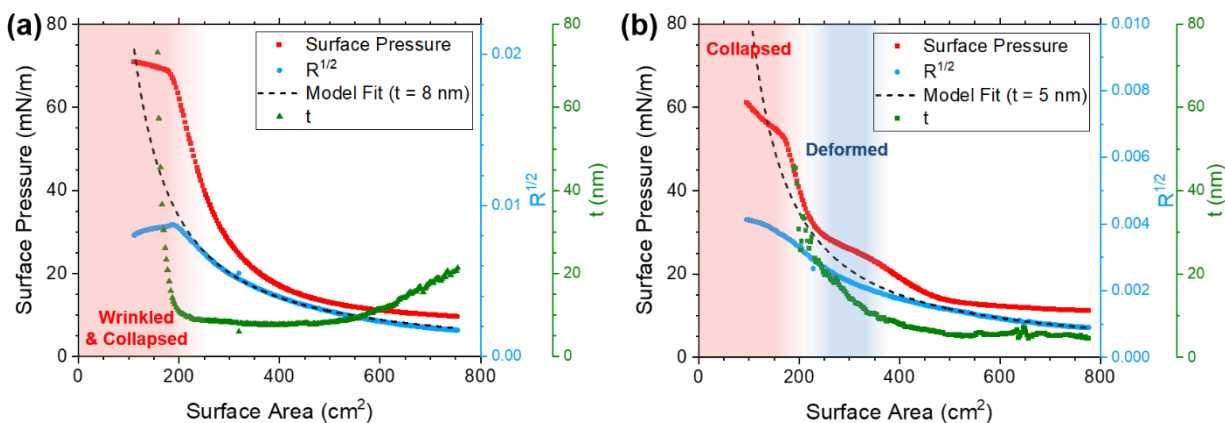


Figure 5. Surface pressure (Π , red squares) and square-root of reflectivity at the Brewster angle ($R^{1/2}$, blue circles) measured as functions of surface area (A) during compression at a barrier speed of 30 mm/min after spreading 100 μ L of a 5 mg/mL block copolymer micelle solution in water onto a clean water surface at an initial surface area of 777 cm². The $R^{1/2}$ data were fit to Eq. (1) at a constant optical thickness (t) (dashed line). Alternatively, the values of t (green triangles) were also estimated from the $R^{1/2}$ data using Eq. (1). **(a)** The PS-PEG-OH micelle monolayer became wrinkled and collapsed at $\Pi > 68$ mN/m, which caused the deviation of the experimental R data from the prediction of Eq. (1) at constant t . The values of t calculated from the measured values of R using Eq. (1) were constant at $A = 233 - 513$ cm². **(b)** The PiBMA-PEG micelle monolayer showed a secondary plateau at $\Pi = 25 - 30$ mN/m. The onset of the secondary plateau coincided with the onset of deviation of the experimental R from the model fit with constant t and also with the onset of the increase in t estimated from R .

Figures 5(b) and S25 displays Π vs. A and $R^{1/2}$ vs. A plots for PiBMA-PEG micelles (having soft and strongly hydrophobic cores). The high- A portion of the $R^{1/2}$ vs. A curve was fit to Eq. (1) by using M and t as adjustable parameters. A good fit was obtained at $A > 420$ cm², i.e., before reaching the intermediate plateau at $\Pi \cong 27$ mN/m, with a thickness value of $t = 5$ nm. This t value is again significantly smaller than the core size ($D_c = 17.1$ nm). This thickness is also smaller than that determined for PS-PEG-OH micelles ($t = 8$ nm), which supports that, as discussed in Section 2.2.2 above, individual isolated PiBMA-PEG micelles had a flattened (oblate) core geometry (Figure 3(e)). Since PiBMA is more deformable ($T_g \cong 51$ °C in bulk), in the PiBMA-PEG case, it is reasonable to calculate t from measured R using Eq. (1) at constant M . As shown in Figure 5(b),

t was found to increase from 5 to 20 nm during compression across the intermediate plateau ($A \cong 260 - 420 \text{ cm}^2$), which is in contrast to the constant t behavior seen in the cases of PS-PEG-OH and other rigid-core micelles in the same surface area range, and suggests that the intermediate plateau occurred due to the deformation of the micelle core. As Π approached Π_{max} , t was seen to increase more rapidly with compression because of the collapse of the monolayer. We note that the constant M assumption used in the above analysis is reasonable because PiBMA-PEG micelles are not expected to easily desorb from the air-water interface. PnBMA-PEG and PB-PEG-OH micelles (having soft and strongly hydrophobic cores) also exhibited qualitatively similar reflectivity behaviors (Figures S26 and S28).

The $R^{1/2}$ vs. A profiles of PMMA-PEG and PLA-PEG micelles having weakly hydrophobic cores could not be modeled using Eq. (1) under the assumption of constant M because the high compression caused desorption of the micelles from the air-water interphase (Figures S27 and S29). Alternatively, for PLA-PEG micelles, for instance, M was calculated from measure R using Eq. (1) at constant t (Figure 6). As shown in the figure, M was found to decrease linearly with decreasing A , which indicates that the PLA-PEG micelles were indeed continuously lost to the subphase during compression. The polymer micelles in this subgroup (having non-strongly hydrophobic cores) did not have sufficient affinity to the air-water interface to withstand the compressive stress beyond $\Pi \cong 10 \text{ mN/m}$. The core-crosslinked PB-PEG-OH micelles readily desorbed from the air-water interface even under moderate compression, as evidenced by near constant reflectivity (R) and also by the very low maximum surface pressure (Π) (Figure S30). This is understandable because after the crosslinking treatment, anionic sulfonate ($-\text{SO}_4^-$) and sulfite ($-\text{SO}_3^-$) moieties (from redox initiating agents) become incorporated to the surfaces of the PB core domains, and as a result, the micelles overall become more hydrophilic.

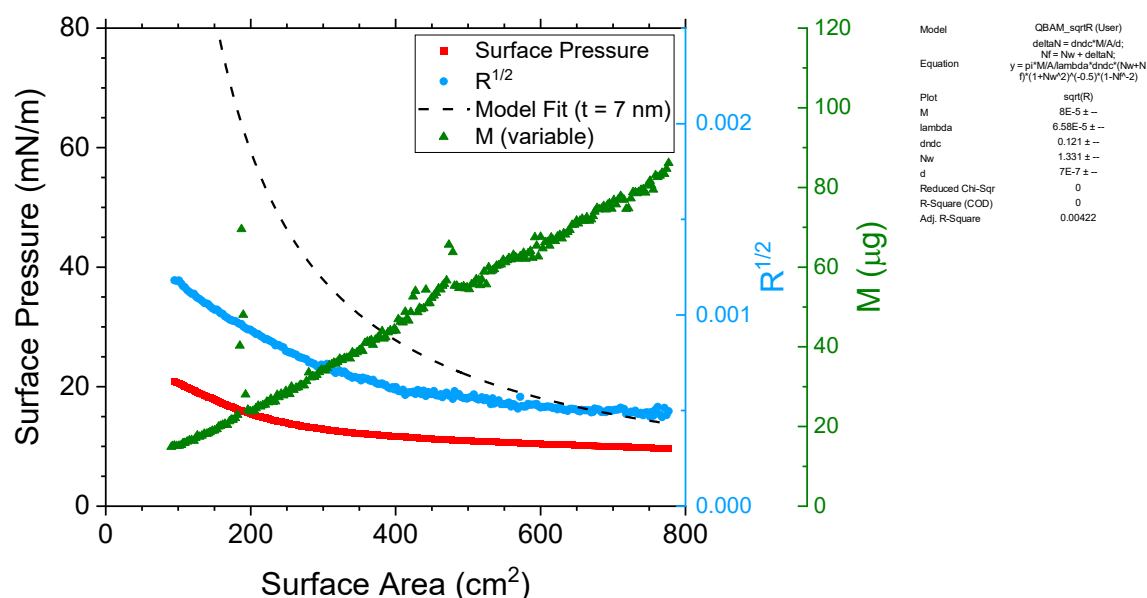


Figure 6. Surface pressure (Π , red squares) and square-root of reflectivity at the Brewster angle ($R^{1/2}$, blue circles) measured as functions of surface area (A) during compression at a barrier speed of 30 mm/min after spreading 100 μL of a 5 mg/mL PLA-PEG micelle solution in water onto a clean water surface at an initial surface area of 777 cm^2 . The dashed line represents values of $R^{1/2}$ computed using Eq. (1) at a constant optical thickness (t). The mass of PLA-PEG micelles adsorbed to the air–water interface (M , green triangles) was estimated from the $R^{1/2}$ data using Eq. (1). The linear decrease of M with decreasing A indicates a steady desorption of the micelles from the air–water interface during compression.

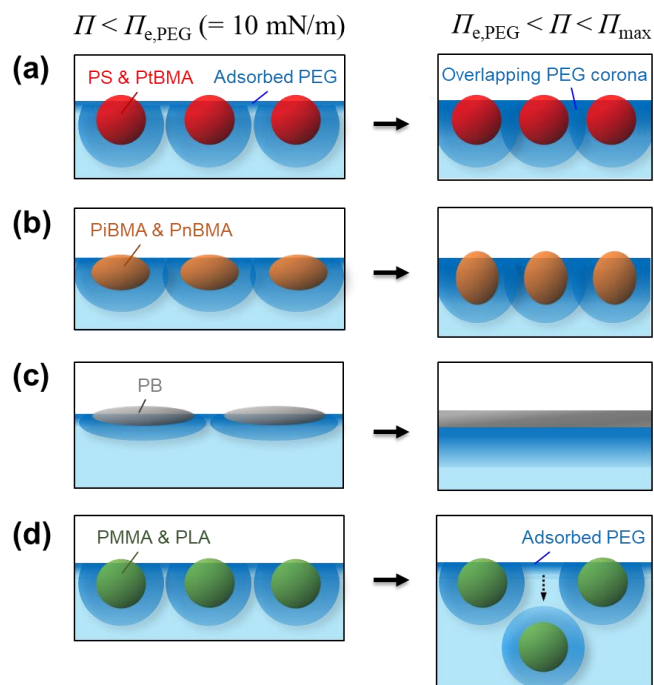


Figure 7. Schematic illustration of what happens to water-spread PEG-based block copolymer (BCP) micelles at the air–water interface under high compression. **(a)** BCP micelles with very hydrophobic, rigid non-deformable cores. **(b)** BCP micelles with very hydrophobic, soft deformable cores. **(c)** BCP micelles with very hydrophobic, liquid-like cores. **(d)** BCP micelles with less hydrophobic cores.

Discussion. Figure 7 schematically summarizes our findings from this work. Figure 7(a) shows the responses of polymer micelles having rigid ($T_g > 60\text{ }^\circ\text{C}$) and strongly hydrophobic ($\theta > 80^\circ$) cores against lateral compression at the air–water interface; their behavior is similar to what has been reported for polymer brush-coated solid nanoparticles at the air–water interface.^{47,48} During compression, the saturation of the air–water interface by adsorbed PEG chains produced a plateau in Π at $\Pi_{e,\text{PEG}} (\cong 10\text{ mN/m})$ (at $a_m/a_h \cong 1 - 5$). Further compression beyond $a_m/a_h \approx 1$ caused an overlap in the subphase PEG corona between adjacent micelles. The corresponding build-up of the osmotic pressure ($\Pi_{\text{osm}} \sim c^v$) caused a rapid rise in $\Pi (= \Pi_{e,\text{PEG}} + \Pi_{\text{osm}})$ and eventually the wrinkling and collapse of the monolayer at $a_m/a_h < 1$.

Figure 7(b) depicts the structural behavior of polymer micelles having soft ($0\text{ }^{\circ}\text{C} < T_g$ (in bulk) $< 60\text{ }^{\circ}\text{C}$) and strongly hydrophobic ($\theta > 80^{\circ}$) cores at the air–water interface. There are two sets of data that suggest that these micelles assumed a flattened (oblate) shape after spreading on the water surface; the upturn in Π from the $\Pi_{e,\text{PEG}}$ plateau in the Π vs. a_m/a_h plot occurred at a much higher surface area (i.e., at $a_m/a_h \cong 3$ for PiBMA-PEG and 4 for PnBMA-PEG) than that observed for spherical PS-PEG(-OH) and PtBMA-PEG micelles ($a_m/a_h \cong 1$); the thicknesses of these soft-core micelle monolayers ($t \cong 4\text{--}5\text{ nm}$) estimated by QBAM measurements were much smaller than those obtained for rigid-core PS-PEG(-OH)/PtBMA-PEG micelles with comparable core diameters ($t \cong 8\text{--}11\text{ nm}$). Also, in these soft-core cases, an additional, intermediate- Π plateau was observed (at $\Pi \approx 27\text{ mN/m}$ for PiBMA-PEG and 23 mN/m for PnBMA-PEG), likely because of the transformation of the shape of the micelle cores from oblates to spheres (even to prolates) during compression. However, PiBMA-PEG and PnBMA-PEG micelles did not seem to coalesce even at very high Π ($> 60\text{ mN/m}$). Instead, the PiBMA-PEG and PnBMA-PEG micelle monolayers became collapsed under high compression. In contrast, PB-PEG-OH micelles having liquid-like cores ($T_g \cong -3\text{ }^{\circ}\text{C}$ in bulk, $\theta \cong 96^{\circ}$) turned into a continuous film at $a_m/a_h < 2$ because of the strong tendency of PB to wet the water surface (Figure 7(c)). PMMA-PEG and PLA-PEG micelles having weakly hydrophobic ($\theta < 80^{\circ}$) cores were found to desorb from the air–water interface at $\Pi \geq \Pi_{e,\text{PEG}}$ (Figure 7(d)), which prevented them from producing high Π . We wish to highlight, as evident in Figure 6, that the desorption of micelles with less hydrophobic cores initiates at relatively lower surface micelle concentrations, notably within the 2D PEG “mushroom-to-pancake” transition region (at $\Pi \cong \Pi_{e,\text{PEG}} \cong 10\text{ mN/m}$). This observation has been incorporated into the visualization presented in the right-hand cartoon of Figure 7(d), where adjacent micelles are

depicted as somewhat spaced apart, and the 2D “pancake” layer of PEG consistently blankets the water surface, irrespective of the desorption of micelles.

Lastly, let us discuss which of the tested block copolymers are in fact suitable for use as a surfactant replacement therapy for treating respiratory distress syndrome (such as ARDS). A successful Polymer Lung Surfactant (PLS) candidate should be able to produce high surface pressure (> 60 mN/m) at high compression in order to help reduce respiratory work (especially at end-expiration).^{12,49} As summarized in Table 2, PS-PEG(-OH), PtBMA-PEG, PiBMA-PEG and PnBMA-PEG micelles (i.e., polymer micelles having rigid (or, at least, only slightly soft) and strongly hydrophobic cores) were found to satisfy this high surface pressure requirement. Additionally, a PLS candidate should be able to stabilize alveoli against collapse/over-distention (that occurs due to an imbalance in Laplace pressure (ΔP) among different sized alveoli) by appropriately varying the alveolar air–water interfacial tension (γ) (Figure 1(a)).⁹ Recently, it has been proposed that the mechanical stability of alveolar tissue is ensured when ΔP is regulated such that $d(\Delta P)/dr < 0$ (where r is the radius of the alveolus) at all times during the breathing cycle; it can be shown that, in the small and slow deformation limit with negligible bending stress, substitution of the Young-Laplace equation ($\Delta P = 2\gamma/r$) into the above stability criterion yields an alternative expression, $2E > \gamma$ (where $E = A(\partial\gamma/\partial A)$).¹⁵ Assuming that our measured surface tension values (obtained using a Wilhelmy plate in a Langmuir trough) represent equilibrium surface tension values, our surface pressure-area isotherm data can further be analyzed against this alveolar stability criterion. In the E vs. Π plots shown in Figures 2(d) and 3(d), the limits of alveolar stability ($2E = \gamma$, that is, $2E = \gamma_0 - \Pi$) are shown using dotted lines; in the region above this line, the polymer micelles satisfy the Laplace stability requirement. As shown in Figure 2(d), in the cases for micelles having rigid and strongly hydrophobic cores (PS-PEG(-OH) and PtBMA-PEG micelles),

the $2E - \gamma$ values were positive over most of the range of II because of the continuous increase of E with II ; these micelles would be able to mechanically stabilize the alveoli. On the other hand, in the cases of micelles having soft and strongly hydrophobic cores (PiBMA-PEG and PnBMA-PEG micelles), the region of positive $2E - \gamma$ became significantly reduced because of the existence of the intermediate- II plateau (Figure 3(d)). PLA-PEG micelles having weakly hydrophobic cores and also PB-PEG-OH micelles having liquid-like cores were unable to produce positive $2E - \gamma$ values at all conditions because their $E_{\max}$ values were too low. Taken together, PS-PEG(-OH) and PtBMA-PEG micelles (having rigid and strongly hydrophobic cores) appear to be most appropriate for use as a lung surfactant.

Conclusions

Micelles derived from amphiphilic block copolymers are promising materials for surfactant replacement therapy applications. In surfactant replacement therapy, the surface tension-regulating ability of a surfactant is key to producing therapeutic effects. In order to better understand factors controlling the surface tension behavior of water-spread block copolymer micelles at the air–water interface, we prepared eight different PEG-based block copolymers having a comparable overall molecular weight and hydrophilic/hydrophobic block composition but having different hydrophobic block chemistries (PS-PEG, PS-PEG-OH, PtBMA-PEG, PiBMA-PEG, PnBMA-PEG, PMMA-PEG, PLA-PEG, and PB-PEG-OH) and investigated their micellar surface mechanical and monolayer morphological properties by surface tension-area isotherm and quantitative Brewster angle microscopy measurements. We found that the rigidity (glass transition temperature (T_g)) and degree of hydrophobicity (water contact angle (θ)) of the micelle core domain are two key factors that predominantly determine the surface mechanical behavior of the micelle monolayer through their influence on the interfacial affinity and deformability of the micelle structure under lateral compression. PS-PEG(-OH) and PtBMA-PEG micelles having rigid (high T_g) and strongly hydrophobic (high θ) cores produced high surface pressure (Π) and high compressibility modulus (E) under high compression, because these micelles have a strong affinity for the air–water interface, while at the same time their core domains are mechanically rigid, and as a result, these micelles are able to sustain a build-up of PEG osmotic pressure during compression. Also, for the same reason, PS-PEG(-OH)/PtBMA-PEG micelle monolayers became wrinkled/collapsed when further compressed beyond a certain limit. PiBMA-PEG and PnBMA-PEG micelles having soft (lower T_g) and strongly hydrophobic (high θ) cores were also able to produce reasonably high surface pressure, but, on the other hand, these micelles were found to

undergo deformation (vertical elongation) under compression, which was manifested as an intermediate plateau in *II*. PB-PEG-OH micelles having liquid-like (very low T_g) and strongly hydrophobic (high θ) cores became merged into a continuous film under compression because PB has a strong tendency to wet the air–water interface; for this reason, high surface pressure was not achievable with this material. PMMA-PEG and PLA-PEG micelles having weakly hydrophobic (lower θ) cores did not have enough affinity for the air–water interface and were prone to desorption under compression and thus unable to produce high surface pressure. Taken together, block copolymer micelles with rigid and strongly hydrophobic cores appear to be good candidates for use as lung surfactants.

1 Experimental Section

2 Synthesis and Characterization of Polymers Tested. PS-PEG-OH and PB-PEG-OH were

3 purchased from PolymerSource; according to the vendor, these polymers were synthesized by
4 living anionic polymerization, and the PEG blocks of these block copolymers have hydroxyl end
5 groups. All other block copolymers used in this study were synthesized in our laboratory using a
6 commercial monomethoxy/monohydroxy-terminated PEG (5.0 kDa, Sigma Aldrich) as a
7 precursor. PS-PEG and poly(alkyl methacrylate)-PEG block copolymers were synthesized by
8 Reversible Addition–Fragmentation (Chain) Transfer Polymerization (RAFT) using procedures
9 described in Ref. ⁵⁰. PLA-PEG was synthesized by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-
10 catalyzed ring-opening polymerization.⁵¹ PS and poly(alkyl methacrylate) homopolymers were
11 also synthesized similarly by RAFT using 4-cyano-4-
12 [(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (CDSP) as the RAFT agent.

13 The molecular weights (M_n 's) of the polymers were determined by ¹H NMR (Figures S1 – S6 of
14 the Supporting Information (SI) for block copolymers, and Figures S9 – S13 for homopolymers).
15 The polydispersity indices of the polymers ($D = M_w/M_n$) were determined by gel permeation
16 chromatography (GPC) (Figure S14 for diblock copolymers, and Figure S15 for homopolymers).
17 The glass transition temperatures (T_g) of the homopolymers were determined by differential
18 scanning calorimetry (DSC) (Figure S16). The advancing water contact angles (θ) were measured
19 on spin-coated homopolymer films by the sessile drop technique (Figure S17). The molecular
20 characteristics of all block copolymers and homopolymers used are summarized in Table S1 of the
21 SI. The exact chemical structures of the polymers used are also shown in Figures S1 – S6 (block
22 copolymers) and Figures S9 – S13 (homopolymers). Detailed procedures for polymer synthesis
23 and characterization are described in Section S1 of the SI. We note that in the GPC measurements

for some of the block copolymers (i.e., PiBMA-PEG, and PMMA-PEG) the presence of lower molecular weight shoulders was observed (Figure S14(B)). As shown in Figure S7, the CDSP end functionality of the PEG-CDSP macro-RAFT agent was close to 100%. Therefore, the lower molecular weight shoulders are thought to be the result of dead polymer chains formed during the RAFT polymerization process (rather than unreacted PEG chains). Regardless of the nature of these lower molecular weight fractions, they should not have influenced the surface mechanical behavior of the block copolymer micelles. Any hydrophobic homopolymers would have been incorporated into the core domains of the micelles. As demonstrated in Figure S8, the coexistence of PEG homopolymer chains was also confirmed not to affect the structural as well as surface mechanical properties of copolymer micelles.

Formulation of Block Copolymer Micelles. Block copolymer micelles were prepared using the Equilibrium Nano Precipitation (ENP) procedure.¹¹ Briefly, micellization was initially induced by adding water to a block copolymer solution in acetone. This micelle solution was equilibrated at room temperature for 24 h. The solvent composition was adjusted to minimize the size polydispersity of the micelles; as shown in Table 2, the optimal solvent composition ($\phi_{w,ENP}$) varied from block copolymer to block copolymer. After the equilibration step, acetone was removed from the micelle solution via dialysis against pure water. The block copolymer micelles thus prepared were confirmed to be stable in water at least for 3 weeks when stored at 4 °C. The core diameters of polymer micelles (D_c) were measured by transmission electron microscopy (TEM) (Figure S18); TEM measurements were done using dried micelle specimens collected on carbon-coated TEM grids. In the case of PB-PEG-OH micelles, TEM was performed after the PB core was chemically crosslinked using the literature procedure.⁵² The hydrodynamic diameters (D_h)

and polydispersity indices ($PDI = 2\mu/\Gamma^2$ where Γ and μ are the first and second cumulants of the DLS autocorrelation function) of the polymer micelles were measured by dynamic light scattering (DLS). Detailed procedures for micelle formulation and characterization are described in Section S2 of the SI.

Surface Pressure-Area Isotherm and Brewster Angle Microscopy Measurements.

Surface pressure–area (Π – A) isotherms for block copolymer micelles were obtained using a KSV 5000 Langmuir trough with two symmetric Delrin barriers (Biolin Scientific). The trough temperature was controlled using a circulating water bath. All measurements were performed at 25 °C. The trough and barriers were initially cleaned with ethanol and Milli-Q water. Then, the trough was filled with 1.4 L of water, and the barriers were mounted. The surface tension was measured using a filter paper Wilhelmy plate facing the direction of the compression. The water surface was aspirated to remove contaminants until the surface pressure increase during a blank compression ($A = 782 \rightarrow 71 \text{ cm}^2$) did not exceed 0.2 mN/m. Afterwards, 10 or 100 μL of a polymer micelle solution was spread to a surface area of water of $A = 782 \text{ cm}^2$ using a 50- μL Hamilton syringe. A $\sim 2 \text{ }\mu\text{L}$ drop of a micelle solution (5.0 mg/mL) formed at the tip of the syringe needle was carefully contacted to water to spread polymer micelles on water surface. After 10-minute equilibration, the Π – A isotherm measurement was conducted during compression at a barrier speed of 3 mm/min. The Π readings were recalibrated to account for the swelling of the filter paper in water, i.e., to correct for the true perimeter of the water-swollen filter paper, as described in our previous publication.¹¹ The original Π – A isotherms were converted to Π – a_m isotherms; note a_m (surface area per micelle) = A/N where N (number of micelles spread) = cVN_A/pM_n . For each block copolymer, the two Π – a_m isotherm curves (obtained using the two different amounts of spreading

solution, i.e., 10 vs. 100 μL) were superposed by shifting the isotherm obtained with 100- μL spreading along the a_m axis to make it overlap with the isotherm obtained with 10- μL spreading.

Brewster angle microscopy (BAM) measurements were performed using a UltraBAM instrument (Accurion) hosted on a KSV NIMA two-barrier Langmuir trough platform (Biolin Scientific). The general trough operating procedures were similar to the above. The spreading volume was 100 μL . After equilibration for 10 minutes, the micelle monolayer was compressed from $A = 777 \text{ cm}^2$ to $A = 90 \text{ cm}^2$ at a barrier speed of 30 mm/min, and during the compression, the surface pressure values and BAM images were simultaneously recorded every 1 second. BAM images were collected at a lateral resolution of 2 μm in a field of view (FOV) of $800 \times 430 \mu\text{m}^2$, and a region of interest (ROI) of $100 \times 100 \mu\text{m}^2$ located at the center of the FOV was analyzed for the determination of the reflectivity of the micelle-laden air–water interface. The intensity of the reflected p -polarized light ($\lambda = 658 \text{ nm}$) from the micelle-laden water surface at the Brewster angle of water ($= 53.1^\circ$) was measured and converted to an absolute reflectivity scale using a calibration procedure which utilizes the null-surface (pure water) reflectivity data obtained at a series of angles in the range $53.1 \pm 0.5^\circ$.

Supporting Information

The Supporting Information is accessible at no cost on the ACS Publications website: Molecular characteristics of the homopolymers (Table S1, Figures S9–S13, and Figures S15–S16) and block copolymers (Figures S1–S7 and Figure S14); supplementary surface pressure–area isotherms (Figures S8, S19–S21); water contact angle measurements (Figure S17); TEM characterization of the micelles (Figure S18); and quantitative BAM analysis (Figures S22–S30).

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