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Can Polymersomes Form Colloidosomes?

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Supporting Information

ABSTRACT: Hydroxy-functionalized polymersomes (or block copolymer vesicles) were prepared via a facile one-pot RAFT aqueous dispersion polymerization protocol and evaluated as Pickering emulsifiers for the stabilization of emulsions of *n*-dodecane emulsion droplets in water. Linear polymersomes produced polydisperse oil droplets with diameters of ~50 μm regardless of the polymersome concentration in the aqueous phase. Introducing an oil-soluble polymeric diisocyanate cross-linker into the oil phase prior to homogenization led to block copolymer microcapsules, as expected. However, TEM inspection of these microcapsules after an alcohol challenge revealed no evidence for polymersomes, suggesting these delicate nanostructures do not survive the high-shear emulsification process. Thus the emulsion droplets are stabilized by individual diblock copolymer chains, rather than polymersomes. Cross-linked polymersomes (prepared by the addition of ethylene glycol dimethacrylate as a third comonomer) also formed stable *n*-dodecane-in-water Pickering emulsions, as judged by optical and fluorescence microscopy. However, in this case the droplet diameter varied from 50 to 250 μm depending on the aqueous polymersome concentration. Moreover, diisocyanate cross-linking at the oil/water interface led to the formation of well-defined colloidosomes, as judged by TEM studies. Thus polymersomes can indeed stabilize colloidosomes, provided that they are sufficiently cross-linked to survive emulsification.

It is well-known that amphiphilic block copolymers self-assemble in solution to form a wide range of "nano-objects" such as spherical micelles,[1] wormlike micelles,[2,3] and polymersomes (or block copolymer vesicles).[1,4−6] Usually, self-assembly is achieved via post-polymerization processing in dilute solution by utilizing a solvent switch,[1] a pH switch[7] or thin film rehydration.[8] Recent advances in polymerization-induced self-assembly via reversible addition−fragmentation chain transfer (RAFT) chemistry[9,10] have enabled diblock copolymer spheres, worms or vesicles to be prepared directly in water at 10−25% solids.[11]

Colloidosomes comprise colloidal particles self-assembled around oil (or water) droplets that have been subjected to further stabilization.[12] They have received much attention in recent years because of their potential application for the controlled release of actives. A wide range of colloidosomes have been prepared using silica particles,[13] clays,[16] polymer latexes,[15] and microgel particles[16] utilizing various stabilization strategies. Adsorbed particles have been locked together by thermal annealing,[15] gel trapping,[17] polyelectrolyte complexation,[18] or covalent crosslinking.[16] As an example of the latter approach, we have recently synthesized a series of poly(glycerol monomethacrylate)-stabilized polystyrene (PGMA-PS) latexes.[19] These particles acted as unusually efficient oil-in-water Pickering emulsifiers for a range of model oils. Furthermore, well-defined colloidosomes were readily produced via covalent cross-linking of the hydroxyl groups on the PGMA stabilizer chains at the oil/water interface. To avoid inter-colloidosome fusion, cross-linking was confined within the droplet phase using a commercial oil-soluble polymeric diisocyanate, tolylene-2,4-diisocyanate-terminated poly(propylene glycol) (PPG-TDI).[19]

Herein, we prepare polymersomes at 10% solids using polymerization-induced self-assembly, evaluate these particles as Pickering emulsifiers, and explore strategies for the production of covalently cross-linked colloidosomes. *As far as we are aware, there are no previous reports of the use of polymersomes to stabilize either Pickering emulsions or colloidosomes.* Potential advantages of using polymersome-based emulsifiers are (i) the encapsulation of both oil-soluble actives and water-soluble actives simultaneously, (ii) the relatively low density of polymersomes, which may act as a buoyancy aid, and (iii) the scalability of the synthetic polymer chemistry described herein.

The polymersomes used in this work were prepared as outlined in Figure 1, and the chemical structures and typical transmission electron microscopy (TEM) images of the linear and cross-linked polymersomes are shown in Figure 2. First, a

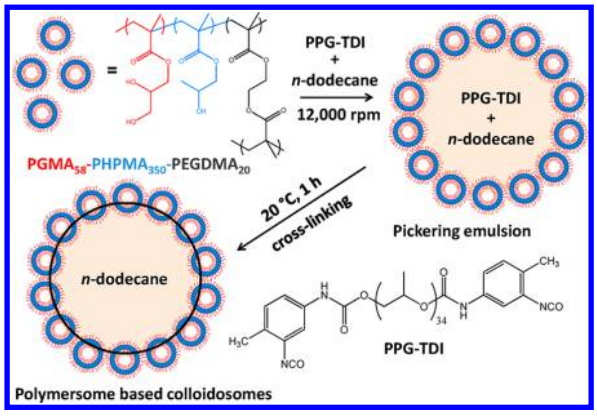

Figure 1. Schematic representation of the preparation of covalently cross-linked colloidosomes using cross-linked polymersomes, *n*-dodecane as the internal oil phase and an oil-soluble polymeric cross-linker (PPG-TDI).

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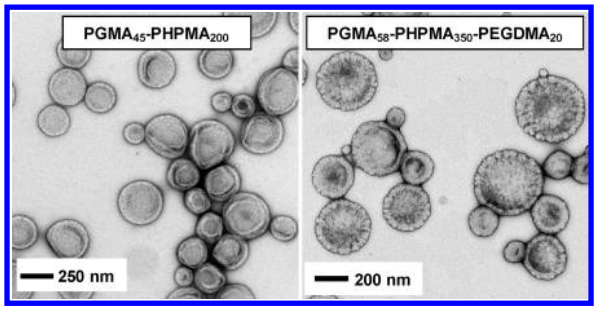

Figure 2. TEM images obtained for linear $PGMA_{45}$-$PHPMA_{200}$ and cross-linked $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ polymersomes.

water-soluble PGMA chain-transfer agent (CTA) was synthesized using RAFT chemistry in ethanol. This CTA was then chain-extended using 2-hydroxypropyl methacrylate (HPMA) to produce a PHPMA block under RAFT aqueous dispersion polymerization conditions. Hence, as the PHPMA chain grew, it gradually became water-insoluble, driving in situ self-assembly. Initially, spherical micelles were formed, but when a sufficiently long PHPMA block was targeted, the diblock copolymer morphology evolved to form worms, jellyfish, and finally polydisperse polymersomes.[11] Such linear polymersomes were readily transformed into cross-linked polymersomes simply by addition of a dimethacrylate cross-linker [e.g., ethylene glycol dimethacrylate (EGDMA)] at the end of the HPMA polymerization.[20] The targeted diblock and triblock compositions in this work were $PGMA_{45}$-$PHPMA_{200}$ and $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$, respectively [see Figure 2 for TEM images and Figure S1 in the Supporting Information (SI) for gel permeation chromatography curves for the resulting polymersomes]. Thus cross-linked polymersomes were prepared by the addition of 20 units of EGDMA cross-linker per diblock copolymer chain.

These polymersomes were prepared at ~10 wt % solids in water and used without further purification; the various concentrations required for the Pickering emulsion and colloidosome studies were obtained by dilution with deionized water. As shown in Figure 1, aqueous polymersome dispersions were homogenized with an equal volume of *n*-dodecane at 12 000 rpm for 2 min at 20 °C to produce Pickering emulsions (see the SI for further details). Colloidosomes were prepared in the same manner simply by dissolving a known amount of PPG-TDI cross-linker in the oil phase prior to homogenization.

Figure 3a shows an optical microscopy (OM) image of spherical *n*-dodecane Pickering emulsion droplets prepared using a 2.3 wt % aqueous dispersion of $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ cross-linked polymersomes. Fluorescence microscopy studies of the equivalent Pickering emulsion prepared using

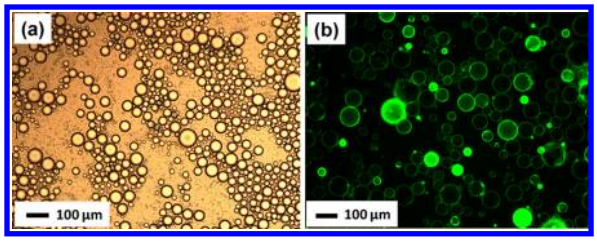

Figure 3. (a) OM image obtained for an *n*-dodecane-in-water Pickering emulsion prepared using $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ cross-linked polymersomes. (b) Fluorescence microscopy image of the corresponding Pickering emulsion prepared using the equivalent fluorescein-labeled $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ polymersomes.

a fluorescein-labeled PHPMA block confirmed that these polymersomes were indeed located at the oil droplet surface, as expected (Figure 3b). Such Pickering emulsions were highly stable: no demulsification was observed after storage for several weeks at 20 °C.

Figure 4 shows the effect of varying the aqueous polymersome concentration on the mean droplet diameter of the resulting

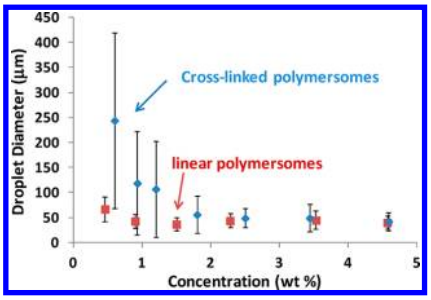

Figure 4. Plots of mean droplet diameter (obtained by laser diffraction) vs aqueous polymersome concentration for both linear $PGMA_{45}$-$PHPMA_{200}$ and cross-linked $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ polymersomes. The error bars represent the standard deviations of the mean volume-average droplet diameters rather than experimental errors.

Pickering emulsions, as determined by laser diffraction studies. Increasing the concentration of the cross-linked $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ polymersomes led to a monotonic reduction in the mean droplet diameter until a limiting value of ~ 50 μm was attained at ~ 2.0 wt %.

This behavior has been observed previously for spherical particles adsorbed at various oil/water interfaces.[19,21] Higher polymersome concentrations are required for stabilization of smaller oil droplets because of the concomitant increase in surface area. Moreover, the curvature observed at lower concentrations scales as r^2, where r is the mean droplet radius (Figure S2). Thus, this provides good evidence that the cross-linked polymersomes behave like other spherical particles, such as latexes.[19,21] These polymersome-based Pickering emulsions were highly stable toward coalescence, but they did exhibit creaming of the less dense oil droplet phase on standing for several hours at 20 °C. This allowed the aqueous phase of the emulsion to be visually inspected. The turbidity of this lower phase indicated that the polymersomes were not fully adsorbed at the oil/water interface, at least at the polymersome concentrations investigated herein. This is in contrast to the PGMA-PS latex-stabilized Pickering emulsions reported previously, in which there was no evidence of any excess particles in solution up to a certain limiting concentration.[19] Thus these cross-linked polymersomes must be considered less efficient Pickering emulsifiers than the corresponding PGMA-PS latexes. This may be due to the relatively low Hamaker constant for the former system, which necessarily reduces the attractive interaction that drives interfacial adsorption. Alternatively, the adsorbed polymersomes are likely to have a relatively low contact angle because of the more hydrophilic PHPMA core.[22] After creaming, the lower aqueous phase could be analyzed to determine the actual amount of adsorbed polymersomes. First, dynamic light scattering (DLS) studies were conducted to compare the intensity-average diameters (and polydispersities) of the polymersomes before and after their adsorption onto the oil droplets. According to Figure S3, there was no significant difference between these two polymersome size distributions. Hence it can be assumed that no size fractionation occurs during

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polymersome adsorption at the oil/water interface. This is important, since it allows the extent of adsorption of the polymersomes to be estimated by turbidimetry. Analysis of the scattering curves recorded after serial dilution of the original aqueous polymersome dispersion allowed the construction of a calibration plot of absorbance against concentration at an arbitrary absorption wavelength of 750 nm (Figure 5). This plot

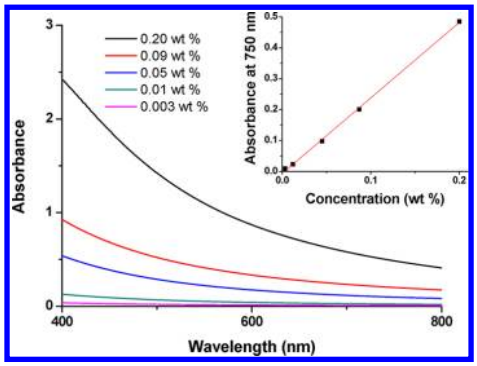

Figure 5. Visible absorption spectra for cross-linked polymersome dispersions at various concentrations. An arbitrary wavelength (750 nm) was used to construct a linear calibration plot (inset), allowing the concentration of non-adsorbed polymersomes remaining in the aqueous phase after emulsification to be determined via turbidimetry.

was used to quantify the concentration of excess (i.e., non-adsorbed) polymersomes remaining in the aqueous creamed phase after emulsification, and the extent of polymersome adsorption at the oil/water interface was calculated by difference. The polymersome adsorption efficiency was 57−78% and decreased at higher polymersome concentrations, as expected (Table S1, SI). Immediately after high-shear emulsification, some degree of foaming was observed. This suggests that the polymersomes also have some affinity for adsorption at the air/water interface. However, in contrast to the highly stable emulsion droplets, such foams usually destabilized within a few hours. In the initial stages of homogenization, there is presumably some competition between adsorption at the air/water and oil/water interfaces. As the foams subsequently destabilize, the polymersomes that were originally adsorbed at this interface re-enter the bulk aqueous phase. Thus such foaming contributes at least to some extent to the poorer emulsification efficiencies observed in the present study for $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ cross-linked polymersomes relative to the PGMA-PS latexes reported previously.

In contrast to the cross-linked polymersomes, linear $PGMA_{45}$-$PHPMA_{200}$ polymersomes exhibited distinctly different behavior when adsorbed at the *n*-dodecane/water interface. The mean droplet diameter was essentially independent of the initial polymersome concentration (Figure 4). A mean diameter of ~50 μm was achieved even at polymersome concentrations below 1.0 wt %. At 0.50 wt %, a slightly higher diameter of 67 μm was obtained, with any further reduction in concentration leading to complete demulsification. This behavior does not conform to that expected if the diblock copolymer were adsorbed onto the droplets in the form of spherical polymersomes. It seems likely that the linear polymersomes do not survive the high-shear homogenization conditions required for emulsification. Thus, the stable emulsions that are produced must be stabilized by adsorbed individual diblock copolymer chains (or possibly spherical diblock copolymer micelles) rather than intact polymersomes. In control experiments conducted *in the absence of any oil*, the aqueous polymersome dispersions remained highly turbid after high-shear homogenization. This suggests that not all of the original polymersomes are destroyed by the application of high shear. DLS studies conducted after homogenization were inconclusive, since a modest increase in the intensity-average diameter was observed along with an appreciable broadening in the size distribution (Figure S3). Although at first sight this suggests that the polymersomes were not significantly degraded, DLS is highly biased toward the presence of larger particles, which makes the detection of a minor population of much smaller micelles (or soluble copolymer chains) highly problematic. However, TEM studies conducted before and after homogenization in the absence of oil suggested at least partial polymersome degradation, since some much smaller pseudo-spherical nano-objects were observed in the final dispersion (Figure S4). If this is indeed the case, then the relatively small diblock copolymer micelles (or individual chains) would diffuse to the oil/water droplet interface and adsorb before the more slowly diffusing linear polymersomes. This also explains why there was essentially no change in the mean droplet diameter upon variation of the aqueous polymersome concentration: a significantly lower concentration of linear diblock copolymer is needed to stabilize a 50 μm *n*-dodecane droplet relative to that required for polymersomes. Calculations suggest that a linear diblock copolymer loading of only 0.024 wt % is needed to coat a 50 μm droplet assuming a surface coverage (Γ) of 2 mg m^{-2}. This concentration is well below that utilized for the formation of each of the emulsions used in this study. Control experiments ruled out the possibility that any unreacted PGMA macro-CTA could act as an emulsion stabilizer, since no stable emulsions could be obtained when this homopolymer was used. Moreover, fluorescence microscopy studies of emulsions formed using fluorescein-labeled linear polymersomes confirmed that regardless of its precise morphology, the PGMA-PHPMA diblock copolymer definitely stabilized the droplets, since the PHPMA block was tagged with the fluorescent comonomer (Figure S5).

The surface morphology of the adsorbed cross-linked and linear polymersomes was further assessed by converting the Pickering emulsions into colloidosomes. In both cases, the Pickering emulsions could be covalently stabilized using the hydroxy/diisocyanate cross-linking chemistry reported previously.[19] The PPG-TDI cross-linker was dissolved in the *n*-dodecane phase prior to homogenization at 12 000 rpm for 2 min at 20 °C. The resulting Pickering emulsions were then allowed to stand for several hours to allow the cross-linking reaction to proceed at 20 °C. In our previous study, cross-linking took place exclusively between the PPG-TDI and the PGMA stabilizer chains, as the PS core contained no reactive groups. In the present work, it is theoretically possible for either the stabilizing PGMA block or the PHPMA membrane block to react with the PPG-TDI, since they both contain the requisite hydroxyl functionality. However, the primary alcohols on the PGMA chains would be expected to react faster than the secondary alcohols on the PHPMA chains. Successful cross-linking is best judged by an alcohol challenge, which removes the internal oil phase of the Pickering emulsions. If cross-linking is not successful, then no microcapsules are observed by either OM or TEM (and this was indeed the case for control experiments conducted in the absence of any PPG-TDI). However, microcapsules were detected by these two techniques when using both the linear and cross-linked polymersomes. Figure 6 depicts typical TEM images obtained for such microcapsules in each case. The cross-linked polymersomes clearly maintained

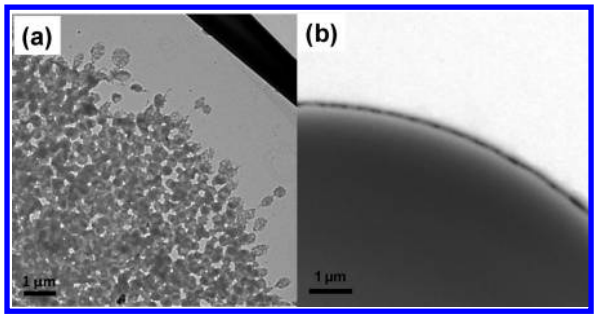

Figure 6. TEM images of cross-linked colloidosome surfaces prepared with (a) cross-linked $PGMA_{58}$-$PHPMA_{350}$-$PEGDMA_{20}$ and (b) linear $PGMA_{45}$-$PHPMA_{200}$ polymersomes. In (a), the polymersomes clearly remained intact, and part of a colloidosome shell is clearly visible; in (b), there is no evidence that the original polymersomes survived the high-shear conditions used for emulsification.

their spherical polydisperse morphology once adsorbed and covalently stabilized at the oil/water interface (Figure 6). This observation is consistent with the earlier finding that the emulsion droplet diameter can be tuned by varying the aqueous polymersome concentration (Figure 3). Therefore these microcapsules can certainly be classified as polymersome-based colloidosomes. In striking contrast, there was no evidence of any intact polymersomes within the smooth microcapsule walls when the linear polymersomes were used. It is perhaps also noteworthy that a considerably higher PPG-TDI concentration (i.e., 20.0 vs 4.0 g dm^{-3}) was required to produce stable microcapsules using linear as opposed to cross-linked polymersomes. This is presumably because, if the chains are only lightly cross-linked at the oil/water interface, then the microcapsules are more likely to disintegrate during the alcohol challenge. TEM studies confirmed that the linear polymersomes did not survive the high-shear conditions required for emulsification. Instead, they underwent partial degradation and were adsorbed as linear block copolymer chains and/or spherical micelles at the surface of the *n*-dodecane droplets, thus behaving more like a conventional surfactant than a Pickering emulsifier. The hydroxyl groups on these individual PGMA-PHPMA copolymer chains can still be cross-linked to form microcapsules that are sufficiently robust to survive an alcohol challenge. However, such polymeric superstructures cannot be described as colloidosomes, simply because the shell does not comprise colloidal particles.

In conclusion, it has been demonstrated for the first time that polymersomes can be used to form stable colloidosome microcapsules. However, it is emphasized that membrane cross-linking is essential to ensure that the polymersomes survive the high-shear homogenization conditions required to generate the precursor Pickering emulsion: linear polymersomes merely dissociate to form individual diblock copolymer chains under the same conditions.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details for the synthesis and characterization of the cross-linked and linear polymersomes, Pickering emulsions, and colloidosomes; DLS studies on the polymersomes before and after their interfacial adsorption; and visible absorption spectroscopy data for the quantification of excess polymersomes via turbidimetry. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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